News in July 2024

1. Pre-eclampsia, Placental Factors, and Offspring Congenital Heart Disease

Introduction

Congenital heart disease (CHD) impacts 0.8% of all pregnancies and is the most common birth defect. Understanding factors that may contribute to the development of CHD allows opportunities for potential early interventions to decrease CHD risk.

The fetal cardiovascular system forms early in embryogenesis and therefore is subjected to maternal factors longer than any other. There is increasing recognition that maternal conditions can be associated with the development of CHD in the fetus. Maternal conditions are wide-ranging and include socioeconomic factors to maternal health factors such as obesity, diabetes, and pre-eclampsia. In this issue of JACC: Advances, Katlaps et al1 examine the complex relationship between maternal pre-eclampsia and offspring CHD in incidents and subsequent pregnancies.

While pre-eclampsia is diagnosed after 20 weeks gestation, long after fetal cardiac structures are formed, the pathophysiologic changes of pre-eclampsia begin early in gestation. Increased levels of both soluble endoglin and fms-like tyrosine kinase 1 relative to vasculogenic placental growth factor and vascular endothelial growth factor are thought to inhibit spiral artery remodeling at the placental interface.2 Similar imbalances in these same biomarkers were recently observed in 31 fetuses with heart defects and 138 children before corrective surgery for heart defects.3 Studies suggest that angiogenic factor imbalance is predominantly found in early- but not late-onset pre-eclampsia, supporting the notion that pre-eclampsia is heterogeneous, with early and late variants. Furthermore, offspring CHD is more strongly associated with early than late preeclampsia, reinforcing the possibility that these variants differ.4

The study by Katlaps et al1 adds to our understanding of the placenta-cardiovascular axis. The investigators utilized a unique mother-infant pair database to understand more about the relationship between maternal pre-eclampsia and offspring CHD.1 The investigators leveraged a database of women who delivered in California between 2000 and 2012, a large and diverse population. They confirmed the previously reported association between pre-eclampsia and offspring CHD. In addition, they showed that that a history of pre-eclampsia is associated with an increased risk of future fetal CHD and that a history of fetal CHD is associated with an increased risk of future pre-eclampsia. The use of low-dose aspirin is used to decrease the development of pre-eclampsia, particularly in the high-risk population. As the authors also highlight, perhaps aspirin could similarly reduce the development of CHD in offspring.

This study hints at the underlying vasculogenic profile of patients with pre-eclampsia, and in the perhaps not-so independent cohort of patients who have fetuses with CHD.

2. Universal Cardiovascular Disease Risk Assessment in Pregnancy: Call to Action JACC: Advances Expert Panel

The United States has the highest maternal mortality rate among developed countries, with cardiovascular disease (CVD) being one of the leading causes of maternal deaths. Diagnosing CVD during pregnancy may be challenging as symptoms of normal pregnancy overlap with those of CVD. Delays in recognition and response to the diagnosis of CVD is a missed opportunity for timely intervention to improve maternal outcomes. Implementing universal CVD risk assessment for all pregnant and postpartum patients across clinical care settings presents a pivotal opportunity to address this issue. Integrating a validated risk assessment tool into routine obstetric care, clinicians, including obstetricians, primary care, and emergency healthcare providers, can enhance awareness of cardiovascular risk and facilitate early

CVD diagnosis. Consensus among stakeholders underscores the importance of screening and education on cardiovascular health strategies for pregnant and postpartum patients to reduce CVD-related maternal mortality. This comprehensive approach offers a pathway to identify at-risk individuals and intervene promptly, potentially saving lives and advancing maternal healthcare equity.

Highlights

- Pregnancy symptoms mimic those of cardiovascular disease and therefore diagnosis may be delayed or missed contributing to increase in maternal morbidity and/or mortality.
- Universal cardiovascular risk assessment may help identify previously undiagnosed cardiac disease and new onset cardiomyopathy during pregnancy and/or postpartum period.
- Cardiovascular risk assessment in pregnancy and/or postpartum period must be a priority in education, clinical care, research, and policy development.

The problem

The United States has the highest maternal mortality rate among the developed countries. The number continues to rise, with cardiovascular disease (CVD) contributing to one-quarter of the maternal deaths. Diagnosis of CVD is challenging during pregnancy due to the overlap of symptoms of normal pregnancy. Therefore, delays in recognition and response remain the primary drivers of adverse maternal outcomes related to CVD.

A solution

Consensus obtained through development of CVD toolkits and patient safety bundles indicate that the key step to lowering cardiovascular-related maternal mortality is the implementation of screening and clinician and patient education on cardiovascular health strategies in all care settings for

pregnant and postpartum patients. Integration of a cardiovascular risk assessment tool to routine pregnancy/postpartum care may identify patients at risk of complications allowing for timely interventions. These patients may not otherwise be alerted of their increased CVD risk or get diagnosed with underlying CVD during pregnancy, delivery, hospitalization, or during the postpartum period (**Central Illustration**).

Universal Cardiovascular Disease Risk Assessment in Pregnancy and Postpartum

The process of integrating cardiovascular disease (CVD) risk assessment begins by involving healthcare providers during the pregnancy and postpartum period to conduct and complete the risk assessment. This assessment captures patient symptom data, vital signs, physical exam data, and CVD risk factors. Based on the risk assessment output, patients could be identified as 'at risk' for CVD, and the algorithm recommends follow-up diagnostic tests and referral pathways, as well as continued patient education and counseling. EKG = electrocardiogram; ECHO = echocardiogram; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Background

The United States has the highest maternal mortality rate among developed countries despite numerous initiatives and efforts to improve maternal health.**1**,**2** A recent report by the Centers for Disease Control calls attention to the alarming increase in maternal deaths to 32.9 from 23.8 per 100,000 births in 2020. Significant racial ethnic disparities exist with non-Hispanic black patients (69.9 per 100,000) at 2.6 times risk of maternal death compared to non-Hispanic white patients. Among Hispanic women, the mortality rate increased from 12.6 to 28 per 100,000 live births from 2019 to 2021, with the highest risk observed among women aged 40 and older.**3** Advancing maternal age increases the risk with mortality rate among mothers ≥40 years of age 6.8 times higher (138.5 deaths per 100,000 live births) than those ≤25 years of age which adds to the existing disparities.

Furthermore, Pacific Islanders and Native American and Alaskan Islanders have an increased risk of maternal mortality when compared to non-Hispanic white women.**4** In fact, since 1999, Native American and Alaskan Islanders have had the largest increase in maternal mortality.**5** Cardiomyopathy accounted for 14.5% of all deaths in the population presenting as a greater proportionate cause of death than any racial group.**6** Black people, Indigenous people, and people of color are more likely to encounter perinatal medical and cardiovascular complications, despite comparable social drivers of health impacting their care and outcomes. Implicit bias of providers and perceived racial discrimination from patients impact trust in the health care system, resulting in delayed encounters for screening and reservations about research enrollment. These disparities can be largely attributed to structural and institutional racism which have resulted in social structures and barriers to care rather than biological factors.**7** Nonetheless, CVD including cardiomyopathy remains accountable for one-quarter of maternal deaths.**8** One can deduce that racisim is a risk factor for CVD.

It is estimated that two out of every three pregnancy-related deaths are preventable.**9** Comparative data of the major causes of maternal mortality indicate that most other causes of maternal deaths have declined over time; however, those due to CVD have increased.**10** The increased numbers may partly be reflective of the improved Maternal Mortality Reviews (MMR).**11** Most states in the U.S. now have organized MMR surveillance systems in place with state-wide in-depth analysis on a case-by-case basis.**12** MMR have proven to be an essential first step in understanding the gaps in healthcare and identification of improvement opportunities.**13**

Stakeholders in the U.S. from the obstetrics, cardiology, anesthesia, nursing, and public health fields contributed to the development of the Cardiovascular Disease Toolkit through California Maternal Quality Care Collaborative (CMQCC) and Cardiac Conditions in Obstetrical Care (CCOC) Patient Safety Bundle by the Alliance for Innovation on Maternal Health with a goal of improving the devastating trends.**14-16** Patient safety bundles

provide resources that align with actionable steps in an organized manner that ultimately improve system-wide processes and subsequent patient outcomes. The American Heart Association recommends preconception counseling in patients with CVD risk factors, such as diabetes, hypertension, and obesity to optimize maternal and fetal outcomes.**2** The consensus statement indicates that screening of pregnant people for cardiac conditions in all care settings is a key step to lower CVD-related maternal mortality.**15** As a result of these collaborations, a working group discussed strategies for the implementation of universal CVD risk assessment for all pregnant and postpartum people.

The challenge

Pregnancy is a state of hemodynamic overload that may lead to signs and symptoms that mimic cardiac disease in normal pregnancy.**17** It may be challenging to differentiate the common complaints of fatigue, shortness of breath, and swelling from those due to CVD. The American College of Obstetrics and Gynecology provides guidance for the evaluation of these symptoms and the urgency for additional evaluation.**18** Evidence is clear that patients with preexisting congenital and/or acquired CVD benefit through use of risk stratification models that guide management strategies.**19**,**20** Ideally, patients with known CVD should undergo preconception counseling that outlines an individualized treatment plan before pregnancy.**21** Evidence-based guidelines exist on the need for referral to the appropriate level of care for cardiac patients.**22** However, there is a paucity of literature on ways to identify pregnant and/or postpartum patients who may have unrecognized CVD or may be at risk for CVD without a known diagnosis. Reports using the CMQCC cardiovascular risk assessment algorithm and other methodologies using physical examination and electrocardiograms as screening tests for CVD detection in pregnant patients have been published to identify pregnant patients at increased risk of CVD.**23-26** Most of the existing literature focuses on postpartum CVD risk assessment in patients with adverse pregnancy outcomes as a surrogate for future CVD.**27**

Early detection and risk stratification of CVD among pregnant and postpartum patients is essential as most patients who died of CVD-related causes had underlying risk factors and had sought healthcare with CVD-related symptoms and/or had vital sign abnormities that were documented but unfortunately attributed to the normal pregnancy-related hemodynamic stress rather than “a red flag” for the presence of underling CVD. Consequently, more than half of the decedents were diagnosed with CVD only at autopsy.**17**

Pregnant patients with CVD may present with a known diagnosis or may have underlying previously unknown CVD that may manifest as onset of symptoms and/or physical examination abnormalities during pregnancy or postpartum period. The value of preconception counseling, early diagnosis, and multidisciplinary care cannot be overemphasized. People with undiagnosed unknown CVD and those with CVD index diagnosis during their pregnancy usually present in a similar manner with symptoms and abnormal vital signs, however, may not be diagnosed in time to receive guideline-recommended medical care.**17**

Often, patients for whom CVD is diagnosed for the first time in pregnancy are pediatric patients who never transitioned to adult care and may not have received well-woman examination and counseling. To complicate it further, pregnancies may be unplanned without the benefit of contraception or preconception counseling leading to delays in seeking prenatal care.**19** The other cohort are those with de novo onset of cardiomyopathy, that is, peripartum cardiomyopathy (PPCM), which typically presents with heart failure with reduced ejection fraction toward the end of pregnancy or in the first 5 months postpartum.**28** Patients who are diagnosed later in pregnancy or during the postpartum period with PPCM often enter pregnancy in their normal state of health with or without CVD risk factors and no evidence of underlying structural cardiac defect.**29**

Knowledge of the underlying cardiac condition is the key to optimize maternal outcomes in a multidisciplinary manner. The role of a “Pregnancy

Heart Team" also known as the Cardio-Obstetric Team is integral to the care of this high-risk group of patients.**18**,**30** The key team members include Maternal Fetal Medicine/Obstetrics, Cardiology (Heart Failure, Congenital Heart disease, interventional, electrophysiology specialists), Anesthesia (Obstetrics and cardiothoracic), Neonatology, Nursing Leadership, Patient Safety, Blood Bank, Perfusion Specialists, and for certain cases, Cardiothoracic Surgery.**31** Typically, the case is presented (history of present illness, physical examination, obstetric complications, and comorbidities) by the obstetrics team, cardiac diagnostic studies shared by cardiology, and the anesthesiologist outlines a safe regional anesthesia plan. Labor and delivery nursing coordinates 1:1 care of the cardiac patient and arranges for additional cardiac expertise on the labor floor as indicated. A checklist for use at these collaborative meetings helps guide members through common management questions, medications safety, and care plan through pregnancy, delivery, and postpartum care that becomes part of the patient's electronic medical record.

Unfortunately, a large proportion of maternal deaths from CVD are in patients who lack knowledge of their underlying diagnosis of CVD and those with a new diagnosis of CVD not made early enough for treatment and alter outcomes. Delays in recognition and diagnosis are the recurrent theme in mothers who died of CVD.**14**

A solution

Early recognition of CVD to allow for timely management is the key element required to lower the rates of maternal morbidity and mortality

Patients with known diagnosis of CVD and those with conventional CVD risk factors without a prior diagnosis of CVD benefit by optimizing health and multidisciplinary pregnancy care at an appropriate level of maternal care.**22** The role of preconception counseling cannot be overemphasized in this high-risk group of patients. Likewise, earlier recognition of a previously

unknown CVD or a timely diagnosis of pregnancy-associated cardiomyopathy is bound to improve maternal and fetal outcomes.**15** This scenario represents the largest gap in care of pregnant and postpartum patients that drives the CVD contribution to maternal mortality. For pregnant patients with known CVD including those with newly diagnosed PPCM, the modified World Health Organization's Risk Stratification (ESC 2018 guidelines) provides guidance on percent risk of a Maternal Cardiac Event Rate and delivery location, to help transfer or triage patients to receive the appropriate level of care. Likewise, the AIM CCOC Bundle includes a Change Package that outlines under the "R" Response a change concept: Coordinate transitions of care, especially in the "fourth" trimester, including the discharge from the birthing facility to home and transition from postpartum care to ongoing primary and specialty care along with the resources and tools for institutions to utilize and implement in various healthcare settings.**32**

We propose universal cardiovascular risk assessment in all pregnant and postpartum patients using the CVD risk assessment algorithm that stratifies pregnant and postpartum patients into the categories of "low risk" and "high risk" for CVD (**Figure 1**). The tool is based on the clinical presentation and quality improvement opportunities identified in CVD-related maternal deaths and was implemented and evaluated at major hospital systems.**33**,**34** It identifies patients at increased risk of CVD who require further assessment and cardiovascular diagnostic testing. The tool considers the common CVD medical and demographic risk factors, self-reported CVD symptoms, vital signs, and abnormal physical exam findings. The algorithm is organized in the form of four buckets shown in **Figure 1** that identifies patients who present with a cluster of variables as being at risk for CVD. One of the buckets that constitutes abnormal physical examination findings on heart or lung auscultation is considered high risk for underlying CVD, and regardless of other elements in the remainder of the buckets, further evaluation such as electrocardiogram, echocardiogram, and/or Brain

natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) is recommended.**33**,**34**

CVD Risk Assessment Algorithm

The algorithm is organized in the form of four buckets and identify patients who present with a cluster of variables as being at risk for CVD. One variable from each of the first 3 buckets or four variables from any of the first three buckets deems the patient at increased risk for CVD. The fourth bucket, that is, abnormal physical examination findings in itself identifies the patient at increased risk for CVD that requires additional cardiac work up. ∗ This is not related to biological race but secondary to structural racism and inequities in care. BNP = B-type natriuretic peptide/pro-BNP; CBC = complete blood count; CXR = chest radiograph; EKG = electrocardiogram; TSH = thyroid-stimulating Hormone.

The tool is intended for use in all pregnant and post-partum patients at their first encounter or any of the subsequent visits. Risk assessment can be repeated for patients that screen negative at any point during pregnancy or the postpartum period if there is an onset of new symptoms or other indications per the discretion of the health care provider.**35** Retrospective application of this algorithm to the 64 maternal deaths of the California MMR identified 93% of the decedents at increased risk of CVD requiring further evaluation.**14** Blumenthal et al demonstrated that prospective application of the CVD risk assessment algorithm to the general obstetrics population identified 5% of patients with cardiac conditions.**24** Further studies are under way to establish CVD risk assessment in pregnancy and postpartum as a quality measure.**36** Although cost effectiveness of such a CVD screening model in pregnancy has not been studied, overall healthcare cost has shown to be reduced by early screening and treatment for CVD with improved health outcomes in the general population.**35** Early detection of CVD through screening of pregnant and postpartum people is

recommended by the AIM CCOC bundle that allows for timely interventions. Despite this need, universal CVD risk screening using CMQCC algorithm has only been implemented as part of research in a few institutions. There is a need to develop validated CVD screening tools to bridge this gap in cardio-obstetrics. The outcome analysis of CVD diagnosed through screening in pregnancy/postpartum period and its impact on morbidity and mortality rates is currently premature. However, this is of high priority and included in next steps of analysis within the CVD screening Validation and Qualitative Improvement research projects.

Step-by step approach

Step 1: establish universal CVD risk assessment as part of routine obstetric care

The preferred option is to integrate the CVD algorithm into the electronic medical record (EMR) system at a given hospital (**Figure 2**). In limited resource clinical settings with a lack or inability to integrate into the EMR, CVD risk assessment can also be performed in a paper checklist format incorporating the elements listed in the risk assessment algorithm. Regardless, successful implementation strategy entails a group of committed individuals from various disciplines (ie, physicians, nurses, staff members, and information technology) who play a crucial role in integrating, implementing, and maintaining the process. Once CVD risk assessment is complete, the patients identified at increased risk of CVD are navigated to a smart set that include the laboratory tests, cardiac diagnostic testing, and referrals that allows the health care provider to place orders for the work up.**28**

Benefits of Universal CVD Screening

The immediate, short-term, and long-term benefits for patients identified as high risk for cardiovascular disease (CVD) during pregnancy and postpartum period. PPCM = peripartum cardiomyopathy.

Step 2: how to manage a patient identified at risk for CVD?

Once a patient is identified at increased risk of CVD or CVD risk positive, it is important to share risk assessment results with the patient along with the need for further testing for diagnosis or reassurance. Ideally, care of a patient with CVD begins in the preconception period; however, the diagnosis of CVD may not be known in some patients. The real challenge is the timely identification of previously unknown preexisting CVD or new onset cardiomyopathy in pregnancy/postpartum period. These patients constitute a vast majority of those with catastrophic outcomes. Timely diagnosis is the key as once a patient is diagnosed, ie, true positive CVD screened patients, validated risk prediction tools exist (modified WHO, CARPREG II, ZAHARA) that stratify and guide further management plan. The role of multidisciplinary teams in care for patient with CVD through all stages of care, including pregnancy, labor, delivery, and postpartum cannot be overemphasized. Patient education may include infographics regarding signs and symptoms of CVD that warrant medical attention.**31** Information regarding cardiac testing as outlined in the algorithm may include an electrocardiogram, echocardiogram, rhythm monitor, laboratory testing including BNP/NT-proBNP, thyroid function testing, and complete blood count. In general, the threshold for the measurement of BNP/NT-proBNP levels should be very low in a pregnant/postpartum patient presenting with cardiac symptoms with or without vital sign abnormalities. A BNP test is inexpensive, readily available with normal values being reassuring with a high negative predictive value for CVD. The patient should be referred to the cardiologist or maternal fetal medicine, a primary care physician, or to the cardio-obstetric clinic (if available) based on the availability of local resources for follow-up. Each health system or unit may modify the process and organize it to best fit their individual resources to make it as efficient as possible. For those persons at highest risk for morbidity and mortality and those who have barriers to healthcare such as lack of insurance or limited health literacy, expeditious evaluation in the hospital is recommended. Community Health Worker programs for patients identified to have positive

social determinants of health screening can impact and facilitate navigation of the health system.**37**,**38**

Step 3: the team: reporting and follow-up

The role of the cardio-obstetrics team members is to manage patients who are at increased risk for CVD and to assure that an appropriate work up and referral is completed. This can be done through weekly reporting on all patients with a CVD-positive risk assessment and data tracking to determine appropriate follow up. Administrative support is necessary to assist with timely scheduling to mitigate delays in diagnosis. Availability of telehealth services that were implemented in the post- COVID19 era in many parts of the country can facilitate such practice in hospitals without dedicated cardio-obstetrics teams or areas with limited access to subspecialty care.

Patient story and perceptions to cardiovascular risk assessment

A crucial part of implementing universal CVD risk assessments is to acknowledge and anticipate patients' emotional response to increased CVD risk score to help integrate this into counseling and follow-up. While reactions may vary, one of such patient's narrative illustrates how increased awareness of CVD risk impacts behaviors. Initially unfamiliar with the link between pregnancy and CVD risk, she reported "…*before I got pregnant, I didn't know that it [cardiovascular disease] was something that pregnant women would have a higher risk of, so now that I do know, I am thinking about it more*". The absence of prior conversations on this topic within her circle of friends and family contributed to her initial reaction of fear and surprise. The provider's guidance helped her navigate her newfound awareness - "…*she [the doctor] was really reassuring about what we were going to do moving forward and the options, so that made me feel like there was a game plan and ensure that I'm good to go*". Consequently, she embraced intentional change, altering her diet, increasing physical activity, and even reshaping her family's lifestyle to mitigate potential CVD risks.

This transformation extended to meticulous blood pressure monitoring, highlighting her commitment to holistic well-being. For healthcare providers, recognition of these concerns and emotions should become part of counseling and compassionate guidance with the goal of empowering patients to make informed healthcare decisions. To successfully implement universal screening strategies, it is crucial to educate the healthcare providers, ensure clinician buy-in, and integrate patient experience and risk assessment algorithm seamlessly into the standard of care, while keeping clinician's engagement by incorporating their feedback and their comfort in utilizing these strategies.

CVD risk assessment as a quality measure

We demonstrated the feasibility of implementing the CVD risk assessment algorithm for pregnant and postpartum patients into EMR at four major hospital systems.**32** The quality measure: *CVD Risk Assessment Measure–Proportion of Pregnant/Postpartum Patients that Receive CVD Risk Assessment with a Standardized Instrument* was included in the 2024 CMS Merit-based Incentive Payment Value Pathways. This will help facilitate the uptake and use in national accountability program.

The quality measure serves for quality improvement initiatives such as Plan-Do-Study-Act (PDSA) cycles. PDSA cycles may aim to improve referrals to higher levels of care and co-management of patients identified to be at risk for CVD, removal of pre-authorizations of follow-up proceedings, and improved patient education. It is important to capture the experience of utilizing the clinical decision support and quality measure in various practice settings, diverse patient demographics, and value of the CVD risk assessment tool for both quality improvement and improved diagnostic excellence purposes, ultimately identifying patients at risk for CVD who may require higher level of care during pregnancy, delivery, and and/or postpartum period.

Further development of CVD risk assessment tools

We are conducting a validation study that will provide evidence to implement universal CVD risk assessment for all pregnant/postpartum patients at the national level. The study aims to demonstrate the efficiency of the existing CVD screening tool in high-volume clinic settings and to determine the algorithm's predictive value for the total population and in racial/ethnic subsets to determine the predictive value of each individual variable. The goal is to streamline and simplify the CVD risk assessment tool/algorithm without compromising the predictive value. In the future, additional CVD risk assessment tools may be developed.

Future studies are indicated to evaluate the yield of implementing CVD screening methods as a high number of false-positive test results may put strain on the existing scarce resources. Additionally, it may overwhelm cardio-obstetrics specialists impeding care for the known high-risk CVD patients. Research should also focus on the outcomes, especially the impact on maternal morbidity and mortality due to CVD. Universal CVD screening may prove to be a cost-effective way to prevent CVD-related maternal morbidity and/or mortality.

Conclusions

Pregnancy is a window of opportunity to address CVD risk, but it is a short timeframe compared to a person's lifespan. We predict that implementation of universal CVD screening at clinical settings will allow for the identification of preexisting but previously unknown CVD, as well as diagnosis of new onset cardiomyopathy in a timely manner. The use of a CVD risk assessment quality measure and implementation of PDSA cycles allows to identify and address system and clinician barriers. Due to the late pregnancy or postpartum presentation of PPCM, it is imperative that obstetricians work together with the primary care providers, the emergency care providers, and cardiologists to best optimize the best care for pregnant and postpartum patients (**Figure 2**).**30**

Universal CVD risk assessment would expedite the diagnosis and management of pregnant and postpartum patients who are diagnosed with a cardiac condition because of CVD risk assessment. Timely diagnosis and management of CVD will mitigate their risk of adverse maternal outcomes and ultimately decrease maternal morbidity mortality in the U.S. Additionally, increased patient awareness of the modifiable CVD risk factors has the potential to improve cardiovascular and general health outcomes in birthing people with chronic medical conditions throughout their lifespan.

This is a call to action for the Society for Maternal Fetal Medicine, American College of Obstetrics and Gynecology, the American Heart Association, the American College of Cardiology, and all key stakeholders in the women's healthcare space to make cardiovascular risk assessment in pregnancy and postpartum period a priority in education, research, and policy development.

3. Semaglutide Has Similar Benefits in Women and Men With HFpEF

Among patients who have obesity-related heart failure with preserved ejection fraction (HFpEF), once-weekly semaglutide 2.4 mg (Wegovy; Novo Nordisk) induces greater weight loss in women than in men when compared to placebo. Patients of both sexes, however, derive similar benefits in terms HF-related symptoms and physical limitations, according to a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM trials.

That supports accumulating evidence, researchers say, that at least some of the positive effects of the glucagon-like peptide-1 (GLP-1) receptor agonist in this population are independent of the number of pounds shed.

Lead investigator Subodh Verma, MD, PhD (Unity Health Toronto, University of Toronto, Canada), reported the new analysis at the recent 2024 American Diabetes Association Scientific Sessions. The findings were published simultaneously online in the Journal of the American College of Cardiology.

Sex-based analyses like this one are particularly important in HFpEF, Verma told TCTMD, because the condition is more prevalent in women;

there are differences between the sexes in terms of HF pathophysiology, clinical course, prognosis, and response to certain drug therapies; and the impact of visceral adiposity in HFpEF is magnified in women.

Of note, this is the first analysis exploring potential sex differences in a clinical trial focusing on patients with obesity-related HFpEF, which is the most common phenotype in the United States. These patients tend to have a disproportionate burden of symptoms and physical limitations, and Verma said it's imperative to find therapies that not only improve prognosis, but also improve quality of life, exercise capacity, and signs and symptoms of HF.

In that context, data from the STEP-HFpEF program provide "the first insights into a potential therapy in the obesity-related HFpEF phenotype, for which we have not previously had any dedicated studies per se," he said. "It really sends a clear message that the benefit of semaglutide is entirely consistent across all of the various subgroups that we've studied, but very importantly by sex."

The STEP-HFpEF Program

For the analysis, the investigators pooled data from STEP-HFpEF in patients without diabetes and STEP-HFpEF DM in patients with type 2 diabetes. Both trials included patients with obesity-related HFpEF, defined by an LVEF of 45% or great, a body mass index (BMI) of 30 kg/m2 or higher, and a Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score below 90 points.

Of the 1,145 total patients, 49.7% were women. Compared with their male counterparts, women had a higher BMI, LVEF, and C-reactive protein level, a lower likelihood of atrial fibrillation or coronary artery disease, and worse HF symptoms and physical limitations. NT-proBNP levels were not significantly different by sex.

It really sends a clear message that the benefit of semaglutide is entirely consistent across all of the various subgroups that we've studied, but very importantly by sex.Subodh Verma

The dual primary endpoints of the analysis were the change in KCCQ clinical summary score and the percentage change in body weight, with some differences observed by sex. Women had a greater drop in body weight than did men (9.6% vs 7.2%; P = 0.006 for interaction), consistent with prior trials of GLP-1 receptor agonists. Even so, the mean increase in KCCQ score was similar in women and men (7.6 vs 7.5 points; P = 0.94 for interaction).

Also improving to a similar extent in women and men were other secondary endpoints, including 6-minute walk distance, levels of C-reactive protein and NT-proBNP, and a hierarchical composite endpoint that incorporated all-cause death, HF events, and changes in KCCQ score and 6-minute walk distance (P = NS for all interactions).

Rates of serious adverse events and serious cardiac disorders were lower with semaglutide versus placebo irrespective of sex.

Is Semaglutide a Heart Drug?

Harlan Krumholz, MD (Yale School of Medicine, New Haven, CT), incoming editor-in-chief of JACC, pointed out to TCTMD that there have been limited therapeutic options for patients with obesity-related HFpEF.

Because studies of GLP-1 receptor agonists in other contexts have shown differences in response by sex and because HFpEF disproportionately affects women, it was worth exploring within the STEP-HFpEF program whether semaglutide had differential effects by sex, he said, adding that there have also been questions about whether the drug's benefits are solely related to weight loss.

Across multiple studies now, "it seems as if there's evidence emerging that this isn't just about the weight loss, but it actually is about mechanics of

the heart and the way in which the heart functions," Krumholz said. And this analysis, showing greater weight loss in women but similar benefits across sexes, represents "more evidence that these may be heart drugs: that they're improving heart health maybe directly, not just in a way that's tracking with the weight loss but in ways that seem to be independent to some extent of the weight loss."

It seems as if there's evidence emerging that this isn't just about the weight loss.Harlan Krumholz

Krumholz said he was pleased to see that the benefits of semaglutide were similar in both women and men. "Increasingly, we're not going to be thinking about these just as anti-obesity drugs. They do treat obesity, but they're also heart health drugs and in the proper setting, they're having powerful effects on improving cardiovascular health," he said, citing the populations of patients with HFpEF and, based on SELECT, atherosclerotic cardiovascular disease.

Senior author Mikhail Kosiborod, MD (Saint Luke's Mid America Heart Institute, Kansas City, MO), said it wasn't surprising to see that women lost more weight than men considering the findings of prior trials. In addition, even though "it's fair to say that weight loss is likely an important factor behind the heart failure benefits that we see," there is emerging evidence from multiple studies that there's more to it, he added. He pointed out, for instance, that there was less weight lost in semaglutide-treated patients in STEP-HFpEF DM than in STEP-HFpEF, but that the impact on HF outcomes was similar in both trials.

"We already had a number of hints that weight loss does not explain everything and there are probably weight loss-independent effects of semaglutide at play here," Kosiborod said. "So to this question of whether it's the weight loss or the drugs, the answer is probably both are important."

For Verma, getting to the exact mechanism of benefit “is more of an academic exercise because at the end of the day, for the patient in the trenches who is really suffering with heart failure with preserved ejection faction in the context of obesity-related heart failure and is limited with symptoms and physician function, the mechanism of benefit is less relevant to them as long as it is leading to an improvement in clinical signs and symptoms.”

Increasing Adoption

Despite the positive results of trials of semaglutide and other GLP-1 receptor agonists indicating benefits beyond just weight loss, patients are still finding it difficult to access the drugs.

Krumholz said multiple factors are playing into that, including high cost, spotty insurance coverage, and drug shortages. But importantly, use of these drugs for a purpose other than weight loss is a paradigm shift, and it will take time for cardiologists to start thinking about obesity as a comorbidity that should be treated to promote cardiovascular health, he indicated. “Right now, we have to fight hard for our patients for them to be able to get it, afford it, and have it be accessible to them.”

So to this question of whether it’s the weight loss or the drugs, the answer is probably both are important.Mikhail Kosiborod

Kosiborod acknowledged that access to these medications is a challenge for both clinicians and patients, and he said one of the solutions for overcoming those obstacles is to continue building the evidence around their benefits for patients with obesity-related complications like HF or atherosclerotic CVD.

“Treating the root cause, treating that key driver of all these complications [obesity], is critically important, but we have to prove that by treating it you’re producing tangible benefits for the patients,” Kosiborod said, adding that he hopes mounting data will influence payers to make these types of drugs more available.

What is happening now, Kosiborod said, is a paradigm shift in how the medical community is thinking about HFpEF—ie, that it is a cardiometabolic disease. “I think this opens up an entirely new avenue of clinical research with various anti-obesity strategies in this patient population, which is super exciting,” he said. “It’s great news for the patients and the clinicians taking care of them, and I think it’s great news for the clinical trial community because I think we’ve discovered something absolutely fundamental about what the future treatment paradigm is going to look like for this very, very vulnerable patient population.”

4. Sex Differences in Primary Mitral Regurgitation Assessment: Highlighting the Role of Regurgitant Fraction

Introduction

Sex differences, regarding the assessment of mitral regurgitation (MR) severity and cardiac remodeling, have been scarcely addressed and notably absent in current recommendations. In fact, current guidelines propose variable cut-offs that are applied uniformly to both sexes. Studies are scarce on this regard since, in most studies, women have been under-represented and sex has not been taken into account.**1**,**2**

However, recent studies**3**,**4** have suggested that women have a delayed referral for mitral valve intervention, despite more symptomatic, with evidence of more compromised left ventricle (LV) function and likely increase in post-operative risk. This may occur because MR is more frequently diagnosed as moderate in women in spite of symptoms, and additionally, LV dysfunction and dilatation are often misdiagnosed, namely when using values without normalization for body surface area.**5** The assessment of the MR severity in women and the differences between sexes are challenging and need further focused analysis.

For acknowledging differences between sexes in regard to primary MR assessment and its impact on indication for repair, it is crucial not only to identify differences in severity criteria and to define cut-offs for proposing timely management but also to understand the pathophysiology behind those differences.

Women with moderate to severe and severe MR were found to have significantly smaller LV and stroke volumes than men.**6** Also, in patients with organic MR,**7**,**8** women in comparison with men were found to have smaller end-diastolic and end-systolic LV dimensions and lower regurgitant volume. However, these findings were related with the features of advanced disease, such as higher pulmonary pressure, more atrial fibrillation, and heart failure symptoms. The ensuing valve surgery is often delayed by the classification of MR as moderate as based in conventional cut-offs for regurgitant volumes.

In the current study,**9** the authors aimed to evaluate the phenotypes of primary MR by mitral valve prolapse, according to sexes. Additionally, they aimed comparing men and women regarding the relationship between regurgitation severity and cardiac remodeling with hallmarks of advanced disease such as functional class, LV dilatation, left atrial (LA) dilatation, and pulmonary hypertension. In a large cohort of patients with moderate to severe and severe MR due to valve prolapse referred for MV intervention, the authors analyzed retrospectively data from patients that underwent both echocardiography and cardiovascular magnetic resonance (CMR) for MR severity and cardiac remodeling assessment. In this cohort, women were older than men, had higher NYHA functional class, and larger indexed LA volumes, all hallmarks of clinical severity, despite showing lower MR effective regurgitant orifice area (EROA), regurgitant volumes, as well as ventricular volumes than men. The optimal threshold values for the regurgitant volume and EROA associated with abnormally increased LV size (according to reference) were consistently lower in women than in men. Moreover, for the same regurgitant fraction, regurgitant volumes in women were significantly lower. Regurgitant fraction, in contrast to regurgitant

volume, was consistently associated with clinical adverse manifestations such as NYHA functional class III/IV, severe LA dilatation, or pulmonary hypertension, in both sexes. Importantly, optimal cut-offs for regurgitant fraction regarding clinical adverse features were similar in both sexes, while regurgitant volumes were different according to sex even when indexed to body surface area.

A previous study by House et al**10** using CMR described that a regurgitant fraction of 40% correlated with different regurgitant volumes according to sex, with smaller volumes in women, suggesting a gender-independent value for the regurgitant volume in the assessment for MR. In the current study, Altes et al go further, showing that regurgitant fraction had a consistent association with the hallmarks of adverse clinical outcomes with similar cutoffs in both sexes, in contrast with RV even after indexing to body surface area.

The authors discuss elegantly the findings and raise appropriate hypothesis for justifying the pathophysiology underlying the smaller regurgitant volume in women even when indexed to body surface area. It is conceivable that a more restrictive physiology in women probably related to the smaller heart size and a more advanced myocardial disease, with more fibrosis in advanced age, may have had impact on the LV volumes and cut-offs of severity using this parameter. A recent study on organic MR referred for intervention**11**; women presented evidence of more raised LA stiffness than men, suggesting more advanced cardiac disease. On the other side, indexing the regurgitant volume to the LF total stroke volume seems to provide a more robust index that also takes into account the LV size, providing a unified parameter for severity assessment.

This study represents in advance in knowledge regarding sex-related differences in the clinical and imaging phenotypes of primary MR using state-of-art imaging modalities like CMR and echocardiography. This suggests that using a single EROA or regurgitant volume cut-off values as recommended for grading MR severity in women would place MR severity in

the range of moderate, despite the underestimate on the impact of the LV remodeling and delay the referral to mitral valve repair.

Further prospective studies should be undertaken for confirmation of findings, which are promising and with substantial support from an appropriate design and robust methods. First, lower regurgitant volumes and EROA cut-offs for MR severity may be more appropriate from the pathophysiological point of view. Second, regurgitant fraction seems a more robust and independent parameter of severity for both sexes. As also suggested by the authors, this parameter should also be assessed against long-term follow-up for appropriate prognostic purposes and better therapeutic decisions.

Of note, an important issue regards the limitation for echocardiography in challenging cases of primary mitral valve such as late systolic MR or multiple jets in organic MR where concordance between echo and CMR is poor and where regurgitant volume by CMR has been shown to be stronger predictor for mortality or indication for surgery in comparison to echo.**12**

The authors should be congratulated for this nicely designed study that explores the assessment of severity of primary MR in women, a recently identified gap in knowledge that opens new avenues for increased precision in the diagnosis of this valve heart disease.

5. Impact of Sex on Severity Assessment and Cardiac Remodeling in Primary Mitral Regurgitation

Abstract

Background

Women with severe primary mitral regurgitation (MR) have lower surgery rates than men and could suffer from delayed referral for mitral valve (MV) intervention, exposing them to an increased risk of postoperative adverse outcomes.

Objectives

The purpose of this study was to assess the sex-based differences in patients with primary MR.

Methods

The study sample consisted of 420 patients (median age: 62 years, 26% women) with primary MR due to valve prolapse referred for preoperative assessment who underwent transthoracic echocardiography (TTE) and cardiac magnetic resonance (CMR) imaging. Multiple endpoints (abnormally increased left ventricular size, NYHA functional class III/IV, severe left atrial [LA] dilatation, pulmonary hypertension) were studied using areas under the curves and logistic regression models.

Results

Women were older than men, had higher NYHA functional class and larger indexed LA volumes (all $P \leq 0.031$), despite displaying lower MR effective regurgitant orifice area, regurgitant volumes (RegVol), and ventricular volumes than men (all $P \leq 0.002$). The optimal cut-off values of RegVol associated with abnormally increased left ventricular size according to reference normal values were lower in women (TTE: 67 ml, CMR: 50 ml) than in men (TTE: 77 ml, CMR: 65 ml). MR regurgitant fraction, but not RegVol, was associated in women and men with NYHA functional class III/IV, severe LA dilatation, and pulmonary hypertension (all areas under the curves, $P \leq 0.024$).

Conclusions

Despite having hallmarks of more advanced valvular heart disease, women with significant primary MR demonstrate lower mitral RegVol and ventricular volumes than men. In contrast, the systematic calculation of MR regurgitant fraction could standardize MR quantification irrespective of sex.

Introduction

Chronic significant mitral regurgitation (MR) causes left ventricular (LV) volume overload and dilatation, eventually progressing to LV dysfunction.**1** Currently, the grading of MR severity is based primarily on absolute mitral regurgitant volume (RegVol) and effective regurgitant orifice area (EROA).**2**

However, normal LV and cardiac stroke volumes depend on body size and are influenced by gender and age.**3**,**4** Also, the clinical and morphological cardiac response to a fixed RegVol varies between patients due to comorbidities, LV and left atrial (LA) function, and the timing and duration of the volume overload.**5**,**6** Therefore, a given amount of MR RegVol is likely to impact LV remodeling and hemodynamics differently depending on these factors. Hence, the idea of a unique RegVol cut-off value for grading MR severity in every patient is debatable.**7** Likewise, previous studies suggested that sex could influence the quantification of primary MR and the degree of cardiac remodeling in response to volume overload.**8**,**9**

Degenerative mitral valve (MV) disease is more common in women, but they have lower surgery rates than men and suffer from delayed referral for MV intervention.**10**,**11** This leads to a worse clinical presentation and an increased risk of postoperative cardiovascular morbi-mortality.**12-14** Understanding why women are likely to undergo MV surgery less and later than men and how to address this situation and ensure that both sexes receive equivalent care is of utmost importance. Indeed, the current recommended echocardiographic threshold values for MR quantitative parameters (EROA, RegVol) and LV remodeling in primary MR (LV end-systolic diameter [ESD]) are not sex-specific and have been based on epidemiological studies where women were underrepresented.**10**,**15**,**16**

Since the evidence regarding the influence of sex on primary MR quantification and cardiac remodeling in contemporary practice remains limited, we investigated whether there are sex-based differences in the clinical and imaging phenotypes of patients with significant primary MR managed in contemporary practice. We specifically aimed at making use of

the advantages of cardiac magnetic resonance (CMR) imaging to precisely evaluate LV remodeling and hemodynamics.**17** We thus evaluated relations between MR severity and cardiac remodeling using echocardiography and CMR in a large cohort of patients with significant primary MR due to valve prolapse referred to tertiary centers for MV intervention.

Methods

Study sample

This study involved patients with primary chronic primary MR due to prolapse referred for MV intervention in 3 heart valve centers (Brussels, Lille, and Monaco) between January 2005 and December 2022 who had undergone a comprehensive transthoracic echocardiography (TTE) and a CMR within 3 months. Inclusion criteria were patients at least 18 years of age with significant (moderate-to-severe or severe according to American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines) primary MR who underwent MV intervention within 6 months after baseline CMR (99% of patients underwent MV surgery and 1% transcatheter mitral edge-to-edge repair).**15**,**16** Exclusion criteria were: acute MR, MR from another etiology than prolapse, prior cardiac surgery, more than mild another left valvular heart disease; prosthetic valve or intracardiac shunt; pregnancy; standard contraindication for CMR; poor TTE image quality; refusal to participate in the study; and evidence of ischemic myocardial scar.

In each center, patients were prospectively invited to undergo CMR during hospitalization for preoperative work-up of primary MR. Doppler-echocardiography and CMR data were prospectively entered into an electronic database in each center and pooled retrospectively. Clinical data were obtained by chart review. The Logistic EuroSCORE II was calculated for all patients.**18** Coronary artery disease was considered >50% epicardial stenosis. The present study had been approved by local institute independent ethics committees and was conducted in accordance with

institutional policies, national legal requirements, and the revised Declaration of Helsinki. Authorization for research participation was obtained for all patients.

Echocardiography

All patients had comprehensive Doppler-echocardiographic exams performed using commercially available ultrasound systems by experienced echocardiographers and analyzed locally in each center by the different investigators according to European Association of Cardiovascular Imaging/American Society of Echocardiography guidelines.**4** MR severity was graded according to a multiparametric approach, as recommended by guidelines, and MR-EROA and regurgitant volume (Echo-RegVol) values were computed by the proximal isovelocity surface area technique without correction for constraint.**19** Details regarding the echocardiographic assessment of the MV are provided in the **Supplemental Appendix**.

Cardiac magnetic resonance imaging

Details regarding the CMR assessment are provided in the **Supplemental Appendix**. Briefly, CMR studies were performed on clinical scanners and analyzed locally by experienced operators blinded to the echocardiographic data of the patient. LV and right ventricular (RV) end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) were assessed from consecutive short-axis cine steady-state free precession pulse images covering the entire LV from the mitral plane to the apex. The LV total stroke volume (LVTSV) was obtained by subtracting the LVESV from the LVEDV. Aortic stroke volume was derived from quantitative through-plane phase-contrast measurement performed at the level of the sino-tubular junction perpendicular to the aorta.**20** Mitral regurgitant volume (CMR-RegVol) was calculated by subtracting the aortic stroke volume from the total LVTSV. Mitral regurgitant fraction (CMR-RegFrac) was defined as CMR-RegVol divided by the LVTSV, expressed as a percentage.

Statistical analysis

Multiple endpoints were used in the present study.

- LV dilatation according to CMR-indLVEDV either as a continuous covariate or according to age and sex-stratified upper reference limit normal values from the CMR UK Biobank study (women <55 years: 101 ml/m2, 55-64 years: 94 ml/m2, ≥65 years: 96 ml/m2; men <55 years: 112 ml/m2, 55-64 years: 117 ml/m2, ≥65 years: 110 ml/m2).**3**
- Severe LA dilatation is defined as Echo-indLAV ≥60 ml/m2
- Pulmonary hypertension is defined as an RV peak pressure gradient of ≥50 mm Hg
- Heart failure symptoms are defined as NYHA functional class III-IV.

These endpoints were used to compare between women and men with significant primary MR referred for preoperative assessment: 1/baseline differences in the clinical and imaging (Echo, CMR) characteristics 2/MR quantitative parameters (MR-EROA, Echo-RegVol, CMR-RegVol, and CMR-RegFrac).

Data were analyzed with R version 4.1.1 (R Foundation for Statistical Computing) and GraphPad Prism (GraphPad Software). Quantitative data are reported as median (25th-75th percentile), while qualitative data are presented as absolute numbers (percentages). Patients were stratified by sex. Associations between sex and baseline categorical variables were examined using either the Pearson chi-square statistic or Fisher's exact test. Individual differences for continuous variables were compared using Mann-Whitney U tests. Multivariable logistic regression models were employed to assess the relationship between MR quantitative parameters, cardiac remodeling, and sex while controlling for age, body surface area (BSA), and NYHA functional class. Receiver operating characteristic (ROC) curves were used to evaluate the association according to sex between MR quantitative parameters and abnormally increased LV size, defined as a value of indLVEDV greater than age and sex-stratified upper reference limit normal

values.**3** Optimal threshold values of MR quantitative parameters associated with abnormally increased indLVEDV were determined separately for each sex by selecting the point on the ROC curve closest to the top-left corner. Linear regression analyses were performed to model the relationship between CMR-RegFrac and indLVEDV in women and men and compared by analysis of covariance. The relationship between MR-EROA, Echo-RegVol, CMR-RegVol, CMR-RegFrac, and NYHA functional class III/IV, Echo-indLAV ≥60 ml/m2, RV peak pressure gradient ≥50 mm Hg, stratified by sex, was assessed using areas under the curves and logistic regression models. All analyses considered a 2-tailed *P* value of <0.05 as statistically significant.

Results

Clinical and echocardiographic characteristics of patients with significant primary MR according to sex

We first describe the differences in clinical and imaging characteristics between women and men with significant primary MR referred for preoperative assessment (**Tables 1** and **2**). Among the 420 patients included, 26% (n = 108) were women. Women were older than men (*P* < 0.001) and more symptomatic (NYHA functional class III-IV; 33% vs 22%, *P* = 0.031) (**Central Illustration**).

Table 1Baseline Clinical and Echocardiographic Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
Clinical and biological parameters				
Age (y)	62 (53-71)	67 (59-73)	61 (51-69)	**<0.001**

Table 1Baseline Clinical and Echocardiographic Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
Height (cm)	175 (167-180)	164 (158-168)	178 (172-183)	**<0.001**
Weight (kg)	75 (66-84)	62.5 (55-70)	78 (72-86)	**<0.001**
BSA (m2)	1.91 (1.77-23)	1.68 (1.58-1.78)	1.96 (1.86-2.07)	**<0.001**
BMI (kg/m2)	24.6 (22.6-26.9)	23.5 (20.7-27)	24.8 (23.1-26.9)	**0.001**
Hypertension	148 (35%)	36 (33%)	112 (36%)	0.716
Dyslipidemia	103 (24%)	25 (23%)	78 (25%)	0.798
Coronary artery disease	58 (14%)	6 (6%)	52 (17%)	**0.006**
EuroSCORE II (%)	1.04 (0.70-1.86)	1.52 (0.99-2.48)	0.96 (0.67-1.56)	**<0.001**
History of atrial fibrillation	87 (21%)	21 (19%)	66 (21%)	0.810
NYHA functional class				**0.031**
I	159 (38%)	31 (29%)	128 (41%)	

Table 1Baseline Clinical and Echocardiographic Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
II	158 (38%)	42 (39%)	116 (37%)	
III-IV	103 (24%)	35 (32%)	68 (22%)	
Serum creatinine level (mg/dl)	0.92 (0.83-1.06)	0.81 (0.72-0.91)	0.96 (0.87-1.10)	**<0.001**
eGFR (ml/m2)	83 (63-105)	63 (52-85)	88 (69-109)	**<0.001**
Echocardiographic parameters				
LVEDD (mm)	59 (55-62)	55 (51-60)	59 (56-63)	**<0.001**
LVESD (mm)	35 (31-40)	33 (29-38)	36 (32-40)	**<0.001**
indLVEDD (mm/m2)	31 (29-33)	33 (29.5-36)	30 (28-33)	**<0.001**
indLVESD (mm/m2)	19 (16-21)	19 (17-22)	18 (16-21)	**0.006**
Echo-LVEDV (ml)	190 (160-	146 (122-	200 (179-	**<0.001**

Table 1Baseline Clinical and Echocardiographic Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
	219)	172)	226)	
Echo-LVESV (ml)	64 (49-81)	46.0 (37-59)	71.5 (57-85)	**<0.001**
Echo-indLVEDV (ml/m2)	99 (86-110)	88 (76-100)	103 (90-114)	**<0.001**
Echo-indLVESV (ml/m2)	34 (27-41)	28 (22-34)	36 (29-42)	**<0.001**
Echo-LVEF (%)	65 (61-71)	68 (63-72)	64 (60-70)	**0.001**
indLAV (ml/m2)	56 (45-73)	61 (47-82)	55 (44-71)	**0.009**
RV peak pressure gradient (mm Hg) (n = 360)	27 (22-37)	31 (22-42)	27 (22-35)	0.058
MR EROA (mm2)	47 (35-62)	40 (30-50)	51 (39-65)	**<0.001**
Echo-RegVol (ml)	74 (58-89)	68 (50-81)	76 (62-91)	**0.002**
MR prolapse				**0.041**

Table 1Baseline Clinical and Echocardiographic Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
localization				
Anterior	30 (7%)	8 (7%)	22 (7%)	
Posterior	294 (70%)	66 (61%)	228 (73%)	
Bi-leaflet	96 (23%)	34 (32%)	62 (20%)	
Flail leaflet	173 (41%)	39 (36%)	134 (43%)	0.258
Mitral annulus disjunction	102 (24%)	30 (27%)	73 (23%)	0.554

Values are median (IQR) or n (%). *P* values in **bold** are below the 0.05 threshold.

BMI = body mass index; BSA = body surface area; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; ESD = end-systolic diameter; ESV = end-systolic volume; LAV = left atrial volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitant; RegVol = regurgitant volume; RV = right ventricular.

Table 2Baseline CMR Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
CMR-LVEDV (ml)	214 (180-255)	173 (143-198)	229 (196-264)	**<0.001**

Table 2Baseline CMR Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
CMR-LVESV (ml)	77 (59-99)	57 (42-73)	84 (64-103)	**<0.001**
CMR-indLVEDV (ml/m2)	113 (96-130)	100 (90-116)	118 (101-133)	**<0.001**
CMR-indLVESV (ml/m2)	40 (32-51)	35 (25-43)	42 (33-52)	**<0.001**
LV mass (g)	148 (125-172)	114 (99-131)	159 (140-181)	**<0.001**
indLV mass (g/m2)	78 (67-87)	67 (58-77)	81 (71-92)	**<0.001**
CMR-LVEF (%)	64 (58-70)	67 (61-72)	63 (57-68)	**<0.001**
LV sphericity index	0.61 (0.56-0.66)	0.64 (0.59-0.71)	0.60 (0.55-0.64)	**<0.001**
LV fibrosis, (n = 358)	61 (17%)	16 (17%)	45 (17%)	1.00
Aortic forward volume (ml)	70 (57-84)	57 (46-73)	74 (62-87)	**<0.001**
Ind-Aortic forward volume (ml/m2)	37.5 (30-44)	35 (27-42)	38 (32-44)	**0.010**
CMR-RegVol (ml)	60 (46-85)	52 (40-63)	64 (50-92)	**<0.001**
indCMR-RegVol (ml/m2)	32 (24-45)	30 (23-39)	33 (25-46)	**0.030**
CMR-RegFrac (%)	48 (38-57)	48 (38-	49 (38-	0.736

Table 2Baseline CMR Characteristics of the Study Sample According to Sex	**All Patients (N = 420)**	**Women (n = 108, 26%)**	**Men (n = 312, 74%)**	**Overall *P* Value**
		55)	57)	
RVEDV (ml)	142 (117-170)	114 (92-139)	152 (130-177)	**<0.001**
RVESV (ml)	66 (52-88)	52 (35-66)	73 (58-94)	**<0.001**
indRVEDV (ml/m2)	76 (64-89)	69 (57-81)	78 (66-90)	**<0.001**
indRVESV (ml/m2)	35 (28-45)	31 (22-40)	37 (29-46)	**<0.001**
RVEF (%)	52 (47-58)	54 (47-62)	52 (46-57)	**0.011**

Values are median (IQR) or n (%). *P* values in **bold** are below the 0.05 threshold.

CMR = cardiac magnetic resonance imaging; ind = indexed to body surface area; RegFrac = regurgitant fraction; other abbreviations as in **Table 1**.

Impact of Sex on Severity Assessment and Cardiac Remodeling in Primary Mitral Regurgitation

For continuous variables, IQRs are displayed in bar plots. Differences for age, RV peak pressure, indLAV, and NYHA class are displayed above, while those for MR EROA, Echo-RegVol, CMR-RegVol, CMR-indLVEDV, and CMR-RegFrac are displayed below. BSA = body surface area; EDV = end-diastolic volume; EROA = effective regurgitant orifice area; ind = indexed to BSA; LAV = left atrial volume; LV = left ventricular; RegFrac = regurgitant fraction; RegVol = regurgitant volume; RV = right ventricular.

Women had more bileaflet prolapse than men (32% vs 20%, *P* = 0.041). The proportion of flail leaflet was similar between women and men (*P* = 0.258). MR-EROA (40 [30-50.5] mm2 vs 51 [39-65] mm2, *P* < 0.001) and Echo-RegVol (68 [50-81] mL vs 76 [62-91] mL, *P* = 0.002) were lower in women than in men (**Central Illustration**). Accordingly, women had more often moderate-to-severe (defined as MR-EROA <40 mm2 and Echo-RegVol <60 mL) rather than severe MR (25% vs 13%, *P* = 0.007) (**Figure 1**). Yet women had a larger indLAV than men (61 [47-84] mL/m2 vs 55 [43-70] mL/m2, *P* = 0.009).

Relationship Between MR Severity, LV Dysfunction, and LA Dilatation Stratified by Sex in Primary MR

Bar graphs show the proportion of women and men with primary MR regarding MR severity grading (moderate-to-severe or severe), LV dysfunction (LVEF <60%, LVESD ≥40 mm) and severe LA dilatation (indLAV ≥60 ml/m2). EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LAV = left atrial volume; LV = left ventricular; MR = mitral regurgitant/regurgitation.

Absolute LV diameters were smaller, while indexed LV diameters were larger in women than in men (**Table 1**). However, both absolute and indexed LV volumes were lower in women (*P* < 0.001 for all). Median LVEF values were higher for women compared to men (*P* = 0.001), but the proportion of patients with LVEF <60% was similar in women and men (16% vs 21%, *P* = 0.332). Women less commonly presented with absolute LVESD ≥40 mm (18% vs 31%, *P* = 0.012) but more frequently had severe LA dilatation than men (55% vs 40%, *P* = 0.013) (**Figure 1**). After adjusting for age, BSA, and symptoms, the differences in MR-EROA, Echo-RegVol, and indexed LV volumes persisted between women and men (**Figure 2A**).

Relationship Between MR Quantitative Parameters, Cardiac Remodeling, and Sex

Relationship between (A) echocardiographic and (B) CMR MR quantitative parameters (MR-EROA, Echo-RegVol, CMR-RegVol) or cardiac remodeling (LVESD, indLVESD, indLVEDV, indLVESV, indRVEDV, LVSI) or function (LVEF, RVEF) characteristics and sex, while controlling for age, BSA, and NYHA functional class. Multivariable logistic regression models were used for each imaging characteristic tested, adjusting for age, BSA, and NYHA functional class. In each analysis conducted, the dependent variable was being male or being female, while the independent covariables included age, BSA, NYHA functional class, and each of the imaging characteristics sequentially. Adjusted ORs were calculated for a 1-SD increase in each imaging characteristic. The forest plots depict the adjusted OR (represented by circles) along with their corresponding 95% CIs (horizontal line). The vertical dashed line at an OR of 1.00 indicates no relationship between the analyzed imaging characteristic and sex after adjusting for age, BSA, and NYHA functional class. Adjusted OR and their 95% CI on the left side of the vertical line suggest imaging characteristics are more likely to be associated with primary MR male patients with increased values. Conversely, adjusted OR and their 95% CI on the right side of the vertical line suggest imaging characteristics are more likely to be associated with primary MR female patients with increased values. BSA = body surface area; CMR = cardiac magnetic resonance imaging; EDV = end-diastolic volume; EF = ejection fraction; EROA = effective regurgitant orifice area; ESD = end-systolic diameter; ESV = end-systolic volume; ind = indexed to BSA; LAV = left atrial volume; LV = left ventricular; MR = mitral regurgitant; RegFrac = regurgitant fraction; RegVol = regurgitant volume; RV = right ventricular; SI = sphericity index.

CMR characteristics of patients with significant primary MR according to sex

CMR-assessed LV volumes were lower in women than in men (all $P < 0.001$) (**Table 2**). Women had a lower median CMR-RegVol than men (52 [40-64] mL vs 64 [50-92] mL, $P < 0.001$), and this difference persisted when indexing for BSA. In contrast, CMR-RegFrac values were similar between

sexes (P = 0.736) (**Central Illustration**). The proportion of patients with CMR-RegFrac ≥40% was similar between sexes (71% vs 70%, P = 1.00). LV shape was more spherical in women than in men (LV sphericity index: 0.64 [0.59-0.71] vs 0.60 [0.55-0.64], P < 0.001). After adjusting for age, BSA, and symptoms, the differences in CMR-RegVol, indexed LV, and RV volumes persisted between women and men (**Figure 2B**).

After excluding patients with coronary artery disease, similar differences in the phenotypic presentation of women and men with primary MR were found (**Supplemental Table 1**). Excluding patients with atrial fibrillation at the time of echocardiography and CMR (n = 27, 6%) yielded similar results (**Supplemental Table 2**).

Relationship between MR quantitative parameters and abnormal LV remodeling according to sex

We examined the relationship between MR quantitative parameters (MR-EROA, Echo-RegVol, and CMR-RegVol) and LV dilatation based on indLVEDV. **Figure 3** shows ROC curves evaluating the relationship between MR-EROA, Echo-RegVol, and CMR-RegVol and abnormal LV remodeling (indLVEDV greater than age and sex-stratified upper reference limit normal values). Optimal thresholds of MR-EROA (women: 40 mm2, men: 53 mm2), Echo-RegVol (women: 67 ml, men: 77 ml), and CMR-RegVol (women: 50 ml, men: 65 ml) associated with abnormally increased indLVEDV were consistently lower in women than in men.

Relationship Between MR Quantitative Parameters and Abnormally Increased Indexed LV End-Diastolic Volume Stratified by Sex

ROC curves display the relationship stratified by sex (A, women; B, men) between MR-EROA, Echo-RegVol, CMR-RegVol, and abnormally increased LV size (defined as values of CMR-assessed indLVEDV >95% upper limit age- and sex-stratified normal reference values). CMR = cardiac magnetic resonance imaging; EROA = effective regurgitant orifice area; LV = left

ventricular; MR = mitral regurgitant; RegVol = regurgitant volume; ROC = receiver operating characteristic.

Figure 4 shows the relationship between CMR-RegFrac and indLVEDV stratified by sex. The slope of the regression lines for women and men were similar (*P* for interaction = 0.613), but the intercept was smaller in women (*P* for intercept <0.001), showing that for a similar RegFrac value, women had smaller indLVEDV than men.

Relationship Between MR Regurgitant Fraction and Indexed LV End-Diastolic Volume (indLVEDV) Stratified by Sex

Dashed red and blue lines display the upper limit reference values of indLVEDV in women (101 mL/m2) and men (117 mL/m2), respectively. LV = left ventricular; MR = mitral regurgitant.

Relationship between MR quantitative parameters, symptoms, LA remodeling, and pulmonary pressures according to sex

We assessed the relationship between MR quantitative parameters (MR-EROA, Echo-RegVol, CMR-RegVol, and CMR-RegFrac) and known features of postoperative adverse outcome in primary MR: NYHA functional class III-IV, severe LA dilatation, and pulmonary hypertension. **Table 3** summarizes the ROC analysis of MR quantitative parameters associated with NYHA functional class III/IV, indLAV ≥60 ml/m2, and RV peak pressure gradient ≥50 mm Hg. Unlike MR-EROA, Echo-RegVol, or CMR-RegVol, CMR-RegFrac was consistently associated with NYHA functional class III/IV, indLAV ≥60 ml/m2, and RV peak pressure gradient ≥50 mm Hg in both sexes. The optimal thresholds of CMR-RegVol associated with indLAV ≥60 ml/m2 and RV peak pressure gradient ≥50 mm Hg were consistently lower in women than in men. By opposition, those of CMR-RegFrac were similar between women and men.

AUC = area under the curve; LA = left atrial; other abbreviations as in **Tables 1** and **2**.

Table 4 shows the age-adjusted OR for MR-EROA, Echo-RegVol, CMR-RegVol, and CMR-RegFrac associated with NYHA functional class III/IV, indLAV ≥60 ml/m2, and RV peak pressure gradient ≥50 mm Hg, stratified by sex. Only CMR-RegFrac was consistently associated with each of these hallmarks of adverse outcomes in primary MR in both sexes.

Discussion

In this large contemporary cohort of patients with significant primary MR due to valve prolapse referred to tertiary centers for preoperative assessment, we demonstrated significant sex-related differences in the clinical and imaging phenotypes of MR using echocardiography and CMR. The salient findings of our study were:

1) Despite having hallmarks of more advanced valve disease including more severe symptoms and larger indLAV, women had lower mitral RegVol and ventricular volumes than men, even after adjusting for confounders such as age or BSA (**Central Illustration**).

2) The optimal cut-off values of EROA and RegVol associated with abnormally increased LV size according to age and sex-stratified normal reference values were consistently lower in women than in men. This suggests that using a single EROA or RegVol cut-off value for grading MR severity in all patients, regardless of sex, could underestimate the impact of the valvular load on LV remodeling in women.

3) In contrast to CMR-RegVol, similar values of CMR-RegFrac were found between women and men. Furthermore, CMR-RegFrac, but not MR-EROA, Echo-RegVol, or CMR-RegVol, was consistently associated with NYHA functional class III/IV, severe LA dilatation, or pulmonary hypertension in women and men, even accounting for age and with similar optimal threshold values. These findings support the routine use of CMR-RegFrac to normalize RegVol to LV total stroke volume and reconcile, at least in part, the differences in MR quantification and its consequences on adverse cardiac remodeling between women and men.

Clinical implications of the differences in MR quantification between women and men

Our research extends upon prior studies that have suggested that women with significant primary MR experience delays in diagnosis and initial specialist assessment, resulting in a worse postoperative outcome compared to men.**13**,**14** Indeed, despite being older at presentation, reporting more symptoms, and having larger indexed left atrial volumes, women in our study had lower mitral EROA, RegVol, and ventricular volumes than men, resulting in MR being classified more often as "moderate-to-severe" rather than severe, consistent with the previous study by Enriquez-Sarano et al,**21** where only 18% of patients with an MR EROA >40 mm2 were women. Likewise, another study from the same group demonstrated that long-term excess mortality could appear since the "moderate" range of MR grading severity.**22** Similar to previous findings, women in our cohort presented with more bi-leaflet prolapse.**13** Previous studies showed that the severity of MR could be underestimated by MR-EROA or Echo-RegVol compared with CMR in bi-leaflet prolapse.**23**,**24** Interestingly, we found that the CMR-RegVol assessed by the volumetric method, valid in patients with bi-leaflet prolapse, was still lower in women. Uretsky et al showed that patients with CMR-RegVol values within the "intermediate" range (30-60 mL) could exhibit true features of severe MV disease.**25** In practice, CMR-RegVol values below the 60 ml threshold retained by guidelines are frequently found for women despite clear resolution of symptoms after MV surgery. Therefore, it is likely that many women with MR initially graded as "moderate-to-severe" actually have true severe MR, since their EROA and RegVol values can be lower than those of men despite similar or even higher degrees of symptoms or adverse cardiac consequences.

Clinical implications of the differences in LV remodeling between women and men in primary MR

Both American and European guidelines indicate that patients with asymptomatic, significant primary MR and LV dysfunction should be

promptly referred for MV surgery.**15**,**16** However, LV dimensions are influenced by body size and sex.**3**,**4** In our study, women had a lower prevalence of LVESD ≥40 mm compared to men, consistent with the original Mitral Regurgitation International Database study.**26** Indexing LV diameters to BSA has been suggested to correct for the discrepancies in LV remodeling according to sex in primary MR.**8** However, in our cohort, even after indexing for BSA, women exhibited lower smaller LV volumes than men, while this finding was not captured by the sole assessment of indexed LV diameters. The differences in LV size between women and men with primary MR extend beyond body size and reflect physiological variations. Women could present with more restrictive physiology, particularly at older ages, resulting in a milder degree of RegVol and LV dilatation before symptom onset. On the other hand, the LA volume is a strong predictor of outcome in primary MR, which should be particularly considered in women who are likely to present with markedly enlarged LA despite normal or mildly enlarged LV.**27**

The importance of assessing MR regurgitant fraction

We observed that the optimal cut-off values of EROA and RegVol associated with abnormally increased age- and sex-stratified indLVEDV were consistently lower in women than in men. This underscores the risk of underestimating MR severity in women when relying solely on RegVol, as they tend to have smaller LV cardiac volumes. It is not surprising that the strength of this association was better with CMR-RegVol than MR-EROA or Echo-RegVol, as both of the latter measures are poorly related to LV size.**24** Also, our data indicate that merely correcting for body size could not sufficiently account for the differences between women and men when quantifying MR. Indeed, women demonstrated a slight but significant lower indexed CMR-RegVol compared to men, while no difference was observed for CMR-RegFrac. From a hemodynamic perspective, it is more accurate to relate the RegVol to LV rather than body size. Indeed, a fixed mitral RegVol for a given LV volume in 1 patient could not have the same clinical implications compared with another one with the same RegVol but a smaller

or larger LV, irrespective of body size. Consequently, the mitral RegFrac, which accounts for LV size rather than BSA, could be more reliable to grade MR severity.**9** In our study, CMR-RegFrac was the sole MR quantitative parameter consistently associated with NYHA functional class III/IV, significant LA dilatation, and pulmonary hypertension, even accounting for age, and with similar optimal threshold values between women and men. These findings underscore the importance of assessing RegFrac to standardize MR quantification, irrespective of sex.

Study limitations

Although the clinical, echocardiographic, and CMR data were prospectively collected in each of the centers, the present analysis is of a retrospective nature and is thus subject to inherent limitations related to such design. We focused on a homogeneous sample of patients with chronic primary MR due to prolapse; therefore, we could not assess the differences between women and men in other MR etiologies. We included patients with at least moderate-to-severe primary MR undergoing TTE and clinically indicated CMR; therefore, we could not assess the potential differences between women and men presenting with milder grades of MR. Yang et al recently showed that women with less than moderate primary MR may exhibit early LA and LV remodeling.**28** This finding reinforces the hypothesis that current thresholds for MR quantitative parameters underestimate the severity of MR in women. CMR and TTE studies were not performed simultaneously for the whole study sample. However, we believe that this point did not impact our findings, since our objective was not to compare the diagnostic value of TTE vs CMR stratified by sex but rather to examine the differences between women and men with primary MR using complementary imaging modalities. Late gadolinium enhancement analysis by CMR was not performed in all patients. Myocardial T1 mapping and extracellular volume quantification emerged in last years as promising risk markers in primary MR but were not available for the vast majority of this study sample.**29** This study involves a Caucasian sample of patients with primary MR. Further research is required to specifically assess the differences in phenotypes between women and men

with primary MR from other ethnicities such as Afro-Caribbean or Asian. Unlike CMR-RegFrac, RegFrac assessed by 2D-echocardiography was not prospectively and systematically assessed in all patients. The vast majority of patients (94%) were in sinus rhythm at the time of assessment; hence, our findings cannot apply to those with atrial fibrillation during examination since the volumetric quantification of MR in patients with arrythmia can be cumbersome and require averaging multiple beats. Finally, due to the study's design, we were unable to conduct survival analyses upstream of the intervention. We believe that our findings would pave the way for investigating whether absolute MR quantitative parameters (MR-EROA, Echo-RegVol, or CMR-RegVol) in women might necessitate lower threshold values than those in men for prognostic considerations. Additionally, we acknowledge the importance of investigating whether using a uniform threshold value for CMR-RegFrac irrespective of sex would yield similar clinical outcomes between women and men both before and after MV intervention.

Conclusions

Despite the clear hallmarks of more advanced valvular heart disease, women with significant primary MR due to valve prolapse demonstrate lower MR volumes and ventricular volumes compared to men. Our results support the finding that women face a risk of delayed referral for MV intervention due to the underestimation of both MR severity and its impact on cardiac remodeling when relying solely on LV size assessment. Accounting for LV size and calculating the MR fraction could help address these sex-related differences and improve MR assessment accuracy in women. These findings provide valuable insights for further research to establish sex-specific criteria for quantitative MR assessment and optimal timing for intervention.

7. Coronary Artery Bypass Graft Failure in Women: Incidence and Clinical Implications

Abstract

Background

Women have worse outcomes after coronary artery bypass surgery (CABG) than men.

Objectives

This study aimed to determine the incidence of CABG graft failure in women, its association with cardiac events, and whether it contributes to sex-related differences in outcomes.

Methods

A pooled analysis of individual patient data from randomized clinical trials with systematic imaging follow-up was performed. Multivariable logistic regression models were used to assess the association of graft failure with myocardial infarction and repeat revascularization between CABG and imaging (primary outcome) and death after imaging (secondary outcome). Mediation analysis was performed to evaluate the effect of graft failure on the association between female sex and risk of death.

Results

Seven randomized clinical trials (N = 4,413, 777 women) were included. At a median imaging follow-up of 1.03 years, graft failure was significantly more frequent among women than men (37.3% vs 32.9% at the patient-level and 20.5% vs 15.8% at the graft level; $P = 0.02$ and $P < 0.001$, respectively). In women, graft failure was associated with an increased risk of myocardial infarction and repeat revascularization (OR: 3.94; 95% CI: 1.79-8.67) and death (OR: 3.18; 95% CI: 1.73-5.85). Female sex was independently associated with the risk of death (direct effect, HR: 1.84; 95% CI: 1.35-2.50)

but the association was not mediated by graft failure (indirect effect, HR: 1.04; 95% CI: 0.86-1.26).

Conclusions

Graft failure is more frequent in women and is associated with adverse cardiac events. The excess mortality risk associated with female sex among CABG patients is not mediated by graft failure.

8. Sex Differences in Ventricular Arrhythmias and Outcomes After AMI

Study Questions:

What are the sex differences in the incidence and in-hospital outcomes of patients with acute myocardial infarction (AMI) and ventricular arrhythmias (VAs)?

Methods:

VAs are a common cause of death in patients with AMI. Studies have shown sex differences in the incidence, presentation, and outcomes of AMI. However, less is known about sex differences in patients with AMI who develop VA. Using the National Inpatient Sample (NIS) 2016–2020, the authors conducted a retrospective analysis of patients admitted for AMI with a secondary diagnosis of VA. Multivariable logistic regression was performed to estimate the sex-specific differences in the rates and in-hospital outcomes of VAs post-AMI. The NIS is the largest publicly available all-payer inpatient database in the United States and is maintained by the Agency for Healthcare Research and Quality, it is designed as a stratified probability sample of discharges representing nonfederal acute care hospitals nationwide. Samples from these hospitals are recorded and then weighted to ensure that they are nationally representative.

The study population included patients who had type 1 AMI and were admitted to the hospital for management. The sociodemographic variables

and presentation were compared between the two groups. The primary endpoint of this study was to determine the sex differences in the rates of VA among patients with AMI, while the secondary outcomes were sex differences in rates of in-hospital mortality, cardiogenic shock, cardiac arrest, implantable cardiac defibrillator (ICD) insertion, palliative care consultation, catheter ablation, and length of hospitalization.

Results:

Of the 1,543,140 patients admitted with AMI, 11.3% of patients had VA after AMI. The odds of VA after AMI were higher among men (12.6 vs. 8.8%, adjusted odds ratio [aOR], 1.72; 95% confidence interval [CI], 1.67–1.78). Women had significantly higher odds of in-hospital mortality (aOR, 1.32; 95% CI, 1.21–1.42; $p < 0.001$), cardiogenic shock, and cardiac arrest, and were less likely to receive an ICD and undergo catheter ablation.

Conclusions:

The authors report there are significant sex- and gender-based differences in patients with AMI and VAs. Women were less likely to have VAs after AMI but those who did were less likely to receive an ICD and had worse outcomes in terms of cardiogenic shock, cardiac arrest, and sudden death.

Perspective:

VAs including ventricular tachycardias (VTs) occur in about 10-20% of the population with AMI. These patients tend to have worse outcomes such as cardiogenic shock, cardiac arrest, and decompensated heart failure. Previous studies have explored sex differences but this study from NIS explores these data from a large, nationally represented dataset and sex differences were explored in detail. Despite less likely presentation of VA after type 1 AMI in women, they were less likely to receive ICD placement and had worse outcomes. This study highlights that while ICD placement continues to be standard of care as secondary prevention in VT in those with AMI, women are less likely to receive this evidence-based treatment.

Future studies need to explore the contributions as to why women are less likely to have VAs than men and address gaps in care.

9. The Role of Psychosocial Stress on Cardiovascular Disease in Women: *JACC* State-of-the-Art Review

Abstract

Psychosocial stress can affect cardiovascular health through multiple pathways. Certain stressors, such as socioeconomic disadvantage, childhood adversity, intimate partner violence, and caregiving stress, are especially common among women. The consequences of stress begin at a young age and persist throughout the life course. This is especially true for women, among whom the burden of negative psychosocial experiences tends to be larger in young age and midlife. Menarche, pregnancy, and menopause can further exacerbate stress in vulnerable women. Not only is psychosocial adversity prevalent in women, but it could have more pronounced consequences for cardiovascular risk among women than among men. These differential effects could reside in sex differences in responses to stress, combined with women's propensity toward vasomotor reactivity, microvascular dysfunction, and inflammation. The bulk of evidence suggests that targeting stress could be an important strategy for cardiovascular risk reduction in women.

Highlights

- Psychosocial stress contributes to cardiovascular disease through multiple pathways, and young and midlife women, especially those from marginalized groups, are particularly vulnerable to the adverse effects of psychosocial stress.
- A multipronged approach to psychosocial adversity at the individual and community levels is needed to reduce the impact of stress on women's

cardiovascular health.

- Clinical trials should explore the benefits of targeting psychosocial stress to improve women's cardiovascular health.

10. Improving Care of Patients With Hypertensive Disorders of Pregnancy

As the field of reproductive and maternal health has grown, awareness about the impact of hypertension during and after pregnancy on future cardiovascular health has also increased.

Hypertensive disorders of pregnancy (HDP) affect about 8% to 10% of pregnant individuals and includes hypertension that occurs during and after pregnancy, such as chronic hypertension, gestational hypertension, preeclampsia, eclampsia and postpartum hypertension. Individuals who are Black, over the age of 35 years, and those with obesity, a BMI >30 and diabetes are at higher risk.

To help increase awareness of HDP and bridge gaps in care, a new Postpartum Hypertension Clinic Development Toolkit, created jointly by the ACC's Prevention of Cardiovascular Disease Member Section and the Reproductive Health and Cardio-Obstetrics Member Section in collaboration with the ACC Pennsylvania Chapter and others, offers guidance for developing postpartum hypertension clinics and best practices for transitions in care.opulation and how to achieve them.

The toolkit is geared for all members of the care team: ob-gyn specialists, cardiologists, APPs, NPs and PAs and more, and recognizes the need for multidisciplinary care.

"There was a real need to create something that helps guide clinicians from different systems, not just academic tertiary care centers, but also clinicians in more rural locations and nonacademic centers who are taking care of

individuals with HDP and want to build an HDP clinic or remote blood pressure monitoring programs," says **Malamo Countouris, MD, AACC**, the toolkit's lead creator and writer.

Toolkit Components

The toolkit consists of seven parts and can be downloaded as a whole or as individual sections.

- Part I discusses how to start a postpartum hypertension clinic for individuals with HDP, from conceptualizing the clinic to reviewing administrative logistics and coding.
- Part II focuses on clinical models and framework for the clinic, including clinical models and operations, clinic activities, and coding and billing.
- Parts III and IV focus on obstetric considerations after HDP and managing blood pressure postpartum.
- Parts V-VII provide clinic example documents and other materials, patient education resources, and appendices and references.

Although the toolkit provides information on how to start a clinic, the information is also valuable for clinicians who are not looking to start a clinic but want to improve how they provide care to their patients with HDP, perhaps through telehealth or remote blood pressure monitoring.

Countouris notes there are currently no standard guidelines for following patients with HDP, particularly after six weeks postpartum when they typically have their last visit with their obstetric clinician. At this point, she says about 40% of individuals still have hypertension and ideally should be transitioned from their obstetric clinician to their primary care clinician or cardiologist.

The toolkit aims to establish structured postpartum care for patients with HDP to help care teams follow up on necessary antihypertensive medication,

screen for cardiovascular risk factors and talk to patients about long-term cardiovascular risk.

The toolkit also provides information on a "baseline" knowledge of treatment that all members of the care team should have. "Talking about contraception and breastfeeding are important in this population, and this toolkit helps cardiologists with these conversations," she says.

11. Excess Mortality in Women Undergoing CABG Not Mediated By Graft Failure

The incidence of graft failure in CABG is higher among women than men, and is associated with adverse cardiac events; however, the excess mortality risk in women was not mediated by graft failure, according to a study published July 1 in JACC.

Sigrid E. Sandner, MD, MSCE, et al., conducted a pooled analysis of individual patient data from randomized clinical trials with systematic imaging follow-up to examine the incidence of CABG graft failure in women, its association with cardiac events, and its potential impact on sex differences in clinical outcomes. Seven randomized clinical trials including 4,413 total patients – 777 of whom were women – were included in the analysis. The primary outcome was the association of graft failure with myocardial infarction and repeat revascularization between the initial CABG procedure and follow-up imaging. Death after imaging was a secondary outcome.

The authors found that at the median imaging follow-up of 1.03 years, graft failure was more frequent among women vs. men (37.3% vs. 32.9% at the patient-level and 20.5% vs. 15.8% at the graft level; $p=0.02$ and $p<0.001$, respectively). An association was observed for both the primary and secondary outcome in women (odds ratio [OR], 3.94; 95% CI, 1.79-8.67 and OR, 3.18; 95% CI, 1.73-5.85, respectively).

Although female sex was independently associated with risk of death (direct effect HR, 1.84; 95% CI, 1.35-2.50), the association was not mediated by graft failure (indirect effect HR, 1.04; 95% CI, 0.86-1.26).

“Our data showed that graft failure did not mediate the excess risk of death associated with female sex,” state the authors. “This highlights the need to address other disparities in the diagnosis and treatment of coronary disease in women to reduce the gap in CABG outcomes between sexes.”

In an accompanying editorial comment, **Amy A. Sarma, MD**, and **Jared A. Spitz, MD, FACC**, add: “… it is time to move beyond simply describing these disparities and develop evidence-based strategies for ensuring delivery of optimal preventive therapy, improving enrollment and engagement with cardiac rehabilitation programs, and better understanding of nonatherosclerotic contributors to risk among women, including endothelial dysfunction.”

12. Heat Exposure–Induced Risks of Preterm Birth Mediated by Maternal Hypertension

Heat exposure is associated with an increased risk of preterm birth (PTB), with previous work suggesting that maternal blood pressure may play a role in these associations. Here we conducted a cohort study of 197,080 singleton live births across 8 provinces in China from 2015 to 2018. The study first estimated the associations between heat exposure, maternal hypertension and clinical subtypes of PTB, and then quantified the role of maternal hypertension in heat and PTB using mediation analyses. We show that heat exposure (>85th, 90th and 95th percentiles of local temperature distributions) spanning from conception to the 20th gestational week was associated with a 15–21% increase in PTB, and a 20–22% increase in medically indicated PTB. Heat exposure is likely to increase the risk of maternal hypertension and elevated blood pressure. Maternal hypertension mediated 15.7% and 33.9% of the effects of heat exposure (>90th percentile) on PTB and medically indicated PTB, respectively. Based on this large-

population study, we found that exposure to heat in early pregnancy can increase the risk of maternal hypertension, thereby affecting the incidence of PTB.

13. **Ideal Aspirin Dose in Secondary Prevention Doesn't Differ Much by Sex**

oth women and men with atherosclerotic cardiovascular disease (ASCVD) who take aspirin as secondary prevention fare just as well, for the most part, whether they're on 81 mg or 325 mg daily, according to sex-specific analyses from the ADAPTABLE randomized trial.

Catherine P. Benziger, MD (Essentia Health, Duluth, MN), lead author of the study, which was published online Wednesday in JAMA Cardiology, said they were curious to see if the known differences in aspirin metabolism by sex might have an impact on safety and effectiveness. "Aspirin, to me, is the least controversial of the meds for secondary prevention" and taken widely, so it's an area ripe for further study, she explained.

Aspirin works through multiple mechanisms: by inhibiting cyclooxygenase 1 (COX-1) pathways as well as COX-1–independent pathways. Prior research has shown the latter are inhibited to a lesser extent in women. And while aspirin does appear to have a differential effect for male versus female patients as primary prevention (where its use has since fallen out of favor in clinical guidelines thanks to the negative ASPREE, ARRIVE, and ASCEND trials), these sex discrepancies have yet to be explored in the realm of secondary prevention.

The ADAPTABLE trial is unique, said Benziger, in that it was able to enroll a sizeable proportion of women—31%—thanks to its roots in the Patient-Centered Outcomes Research Institute (PCORI) clinical research network (PCORnet).

"Traditionally in clinical trials, women are underrepresented," she observed. "Women are undertreated for both primary and secondary prevention: we're

not as aggressive at treating their blood pressure, treating their lipids, and once they have a heart attack, we don't get them as aggressively on dual antiplatelet therapy, get their cholesterol down, [etc].” Some of this undertreatment is thanks to bias in medicine and some of it is due to the fact that “a lot of our research has been largely done on men, and [it’s possible] women don't react the same way to some of the medications and things,” Benziger commented.

Similar Effectiveness but an Unusual Safety Outcome

ADAPTABLE's main results, published in the New England Journal of Medicine in 2021, showed that 81 mg aspirin is just as effective as 325 mg at preventing major cardiovascular events, and both doses are associated with a very low rate of bleeding.

The trial enrolled 15,076 participants with established ASCVD across 40 centers and one health plan. Slightly less than half (48.8%) of the trial’s 4,724 women were randomized to an aspirin dose of 81 mg and the rest to 325 mg. Notably, though, adherence to the assigned study drug was spotty—13.4% of women and 10.3% of men originally in the 81-mg group switched or discontinued their dose, as did 41.8% and 42.4%, respectively, of those originally in the 325-mg dose.

Female participants tended to be younger than those who were male and were less likely to self-identify as white, more likely to smoke, and more often had a history of peripheral arterial disease.

Over a median follow-up of 26.2 months, there was no interaction by sex for the study’s primary endpoint—all-cause death and hospitalization for MI or stroke—between women and men (8.1% vs 7.1%, respectively; P for interaction = 0.74). While the rates of all-cause death and hospitalization for MI were similar for the two sexes, women were more likely to be hospitalized for stroke than men (1.94% vs 0.97%; P for interaction < 0.001) and were less likely to undergo revascularization with PCI or CABG (4.98% vs 6.60%; P for interaction = 0.002).

Women assigned to the 81-mg dose, compared with the 325-mg dose, had a slightly lower likelihood of dying (adjusted HR 0.73; 95% CI 0.55-0.99) but no difference in the primary endpoint. For men, the dose did not appear to influence effectiveness.

Rates of major bleeding, the study's primary safety outcome, were similar between women and men (0.69% vs 0.60%). Yet major bleeding, counterintuitively, was slightly more common in women assigned to 81 mg aspirin versus 325 mg (0.83% vs 0.52%; adjusted HR 2.21; 1.04-4.70). Again, men saw no difference by dose.

Benziger said the finding of more bleeding among women at the lower dose can likely be explained by background medication use. Patients could not be on anticoagulation when they enrolled, but if they developed atrial fibrillation or another indication during the study, they could begin to take it at a later date—this combination of anticoagulant and antiplatelet therapy would affect bleeding risk, so many patients originally randomized to receive 325 mg would have likely switched to the 81 mg.

Unfortunately, there's a lack of data tracking either this or the use of dual antiplatelet therapy, she added. "So to me, the higher bleeding rate is likely not because of the aspirin, but probably because of other factors that were not adequately captured in our data collection of the pragmatic trial."

Practice is "a huge mix," for both men and women, when it comes to aspirin dosing in secondary prevention, Benziger said. Indeed, as the paper notes, "none of the primary or secondary prevention guidelines provide sex-specific recommendations on aspirin use or dosage but encourage shared decision-making between patient and clinician."

In today's world, as it has been for decades, "aspirin is still very much a mainstay," she noted. But the search for an optimal dose may become less relevant as antithrombotic regimens evolve and the implications for particular subgroups, such as patients with atrial fibrillation or diabetes, are better understood.

Based on their findings, “at this point, [it seems] whatever aspirin dose you were on was probably fine, Benziger specified. “If you asked my opinion, probably I would go with the 81 milligram now, but [with the caveat that] for women there seemed to be a slightly higher risk of bleeding. Now, is that related to the 81 milligrams? Probably not.”

14. Large-Scale Proteomics and Hypertensive Disorders of Pregnancy

Study Questions:

Can proteome assessment of first-trimester blood samples be used to predict the development of hypertensive disorders of pregnancy (HDP)?

Methods:

This was an ancillary study of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), a multicenter observational study at eight academic US medical centers. Clinical data and first trimester plasma samples (collected from 2010–2013) were analyzed. HDP included gestational hypertension and pre-eclampsia. Controls were selected from participants who delivered at 37 weeks or later without any HDP, preterm birth, or small-for-gestational age infant. The aptamer-based proteomics panel included 6,481 unique human proteins.

Results:

Of 1,850 participants with analyzable proteomic assay results, 753 had HDP and 1,097 were controls. Overall, the mean age was 26.9 years. Analysis was performed with the elastic net model, allowing for forced inclusion of prespecified covariates. No proteins were selected to augment the clinical and demographic covariates. Predictive models showed only modest discriminative results: The area under the receiver operating characteristic

curve (AUC) was 0.64 (95% confidence interval [CI], 0.61-0.67) in a training set, and 0.62 (95% CI, 0.56-0.68) in a test set.

Conclusions:

The authors conclude that an aptamer-based proteomics panel did not improve prediction of HDP over and above routine clinical and demographic factors.

Perspective:

HDP complicate 10-15% of first pregnancies and, in addition to immediate high-risk consequences, are associated with long-term increased risk of future cardiovascular disease. The ability to predict which patients are at highest risk for HDP would potentially help prevent the associated complications. Several prior studies have explored various biomarkers but have been unable to provide predictive ability. This study explored a large-scale proteomics panel; however, no protein out of >6,000 unique human proteins was found to be effective in predicting HDP, nor was any predictive model that included clinical and demographic variables. This well-designed large study suggests that other approaches may be needed in order to better predict HDP, and investigators should continue to seek ways to improve care for these patients.

15. Patient Sex, Familial Hypercholesterolemia, and Long-Term Cardiovascular Risk Factor Management 5 Years After an Acute Coronary Syndrome

BACKGROUND

Long-term control of cardiovascular risk factors after acute coronary syndrome (ACS) is the cornerstone for preventing recurrence. We investigated the extent of cardiovascular risk factor management in males and females with and without familial hypercholesterolemia (FH) 5 years after ACS.

METHODS

We studied patients hospitalized for ACS between 2009 and 2017 in a Swiss multicenter prospective cohort study. FH was defined based on clinical criteria from the Dutch Lipid Clinic Network and Simon Broome definitions. Five years post-ACS, we assessed low-density lipoprotein-cholesterol (LDL-c) levels, lipid-lowering therapy (LLT), and other cardiovascular risk factors, comparing males to females with and without FH using generalized estimating equations.

RESULTS

A total of 3139 patients were included; mean age was 61.4 years (SD, 12.1), 620 (19.8%) were female, and 747 (23.5%) had possible FH. Compared with males at 5-years post-ACS, females were more likely to not use statins (odds ratio, 1.61 [95% CI, 1.28–2.03]) and less likely to have combination LLT (odds ratio, 0.72 [95% CI, 0.55–0.93]), without difference between patients with FH and without FH. Females in both FH and non-FH groups less frequently reached LDL-c values ≤1.8 mmol/L (odds ratio, 0.78 [95% CI, 0.78–0.93]). Overall, patients with FH were more frequently on high-dose statins compared with patients without FH (51.0% versus 42.9%; P=0.001) and presented more frequently with a combination of 2 or more LLT compared with patients without FH (33.8% versus 17.7%; P<0.001), but less frequently reached LDL-c targets of ≤1.8 mmol/L (33.5% versus 44.3%; P<0.001) or ≤2.6 mmol/L (70.2% versus 78.1%; P=0.001).

CONCLUSIONS

Five years after ACS, females had less intensive LLT and were less likely to reach target LDL-c levels than males, regardless of FH status. Males and females with FH had less optimal control of LDL-c despite more frequently taking high-dose statins or combination LLT compared with patients without FH. Long-term management of patients with ACS and FH, especially females, warrants optimization.

16. Perinatal Depression and the Risk of Maternal CVD

BACKGROUND AND AIMS

Increasing evidence suggests that some reproductive factors/hazards are associated with a future risk of cardiovascular disease (CVD) in women. While major (non-perinatal) depression has consistently been associated with CVD, the long-term risk of CVD after perinatal depression (PND) is largely unknown.

METHODS

A nationwide population-based matched cohort study involving 55 539 women diagnosed with PND during 2001–14 in Sweden and 545 567 unaffected women individually matched on age and year of conception/delivery was conducted. All women were followed up to 2020. Perinatal depression and CVD were identified from Swedish national health registers. Using multivariable Cox models, hazard ratios (HR) of any and type-specific CVD according to PND were estimated.

RESULTS

The mean age at the PND diagnosis was 30.8 [standard deviation (SD) 5.6] years. During the follow-up of up to 20 years (mean 10.4, SD 3.6), 3533 (6.4%) women with PND (expected number 2077) and 20 202 (3.7%) unaffected women developed CVD. Compared with matched unaffected women, women with PND had a 36% higher risk of developing CVD [adjusted HR = 1.36, 95% confidence interval (CI): 1.31–1.42], while compared with their sisters, women with PND had a 20% higher risk of CVD (adjusted HR = 1.20, 95% CI 1.07–1.34). The results were most pronounced in women without a history of psychiatric disorder (P for interaction < .001). The association was observed for all CVD subtypes, with the highest HR in the case of hypertensive disease (HR = 1.50, 95% CI: 1.41–1.60), ischaemic heart disease (HR = 1.37, 95% CI: 1.13–1.65), and heart failure (HR 1.36, 95% CI: 1.06–1.74).

CONCLUSIONS

Women with PND are at higher risk of CVD in middle adulthood. Reproductive history, including PND, should be considered in CVD risk assessments of women.

17. Implementation of First-Trimester Screening and Prevention of Preeclampsia

BACKGROUND

This trial aimed to assess the efficacy, acceptability and safety of a first-trimester screen-and-prevent strategy for preterm preeclampsia (PE) in Asia.

METHODS

Between 1st August 2019 and 28th February 2022, this multicenter stepped wedge cluster randomized trial included maternity/diagnostic units from ten regions in Asia. The trial started with a period where all recruiting centers provided routine antenatal care without study-related intervention. At regular six-week intervals, one cluster was randomized to transit from non-intervention phase to intervention phase. In the intervention phase, women underwent first-trimester screening for preterm PE using a Bayes theorem-based triple-test. High-risk women, with adjusted risk for preterm PE ≥ 1 in 100, received low-dose aspirin from <16 weeks until 36 weeks.

RESULTS

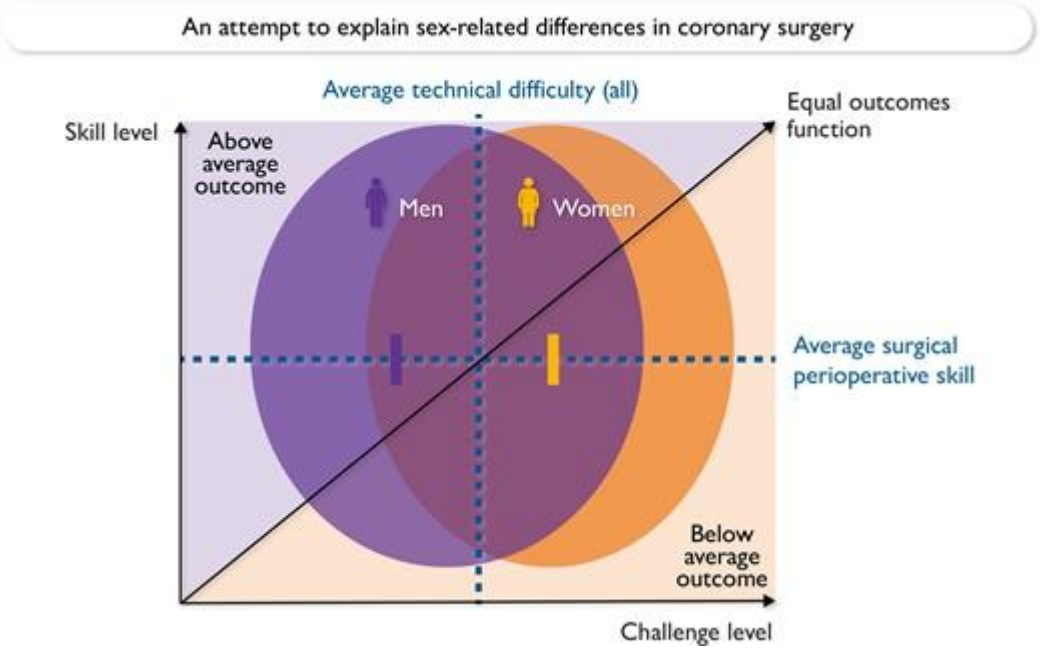
Overall, 88.04% (42,897/48,725) of women agreed to undergo first-trimester screening for preterm PE. Among those identified as high-risk in the intervention phase, 82.39% (2,919/3,543) received aspirin prophylaxis. There was no significant difference in the incidence of preterm PE between the intervention and non-intervention phases (adjusted odds ratio [aOR] 1.59; 95% confidence interval [CI] 0.91 to 2.77). However, among high-risk women in the intervention phase, aspirin prophylaxis was significantly associated with a 41% reduction in the incidence of preterm PE (aOR 0.59; 95%CI 0.37 to 0.92). Additionally, it correlated with 54%, 55% and 64%

reduction in the incidence of PE with delivery at <34 weeks (aOR 0.46; 95%CI 0.23 to 0.93), spontaneous preterm birth <34 weeks (aOR 0.45; 95%CI 0.22 to 0.92) and perinatal death (aOR 0.34; 95%CI 0.12 to 0.91), respectively. There was no significant between-group difference in the incidence of aspirin-related severe adverse events.

CONCLUSIONS

The implementation of the screen-and-prevent strategy for preterm PE is not associated with a significant reduction in the incidence of preterm PE. However, low-dose aspirin effectively reduces the incidence of preterm PE by 41% among high-risk women. The screen-and-prevent strategy for preterm PE is highly accepted by a diverse group of women from various ethnic backgrounds beyond the original population where the strategy was developed. These findings underpin the importance of the widespread implementation of the screen-and-prevent strategy for preterm PE on a global scale.

18. **Challenge–skill balance in cardiac surgery: an attempt to explain sex-related differences in coronary surgery**



19. **Multiple arterial vs. single arterial coronary artery bypass grafting: sex-related differences in outcomes**

Abstract

Background and Aims

Uncertainty exists over whether multiple arterial grafting has a sex-related association with survival after coronary artery bypass grafting. This study aims to compare the long-term survival of using multiple arterial grafting vs. single arterial grafting in women and men undergoing coronary artery bypass grafting.

Methods

The retrospective study used the Australian and New Zealand Society of Cardiothoracic Surgical Database with linkage to the National Death Index. Patients from 2001 to 2020 were identified. Sex-stratified, inverse probability weighted Cox proportional hazard model was used to facilitate survival comparisons. The primary outcome was all-cause mortality.

Results

A total number of 54 275 adult patients receiving at least two grafts in primary isolated bypass operations were analysed. The entire study cohort consisted of 10 693 (19.7%) female patients and 29 711 (54.7%) multiple arterial grafting procedures. At a median (interquartile range) postoperative follow-up of 4.9 (2.3–8.4) years, mortality was significantly lower in male patients undergoing multiarterial than single arterial procedures (adjusted hazard ratio 0.82; 95% confidence interval 0.77–0.87; $P < .001$). The survival benefit was also significant for females (adjusted hazard ratio 0.83; 95% confidence interval 0.76–0.91; $P < .001$) at a median (interquartile range) follow-up of 5.2 (2.4–8.7) years. The interaction model from Cox regression suggested insignificant subgroup effect from sex ($P = .08$) on the observed survival advantage. The survival benefits associated with multiple arterial grafting were consistent across all sex-stratified subgroups except for female patients with left main coronary disease.

Conclusions

Compared to single arterial grafting, multiple arterial revascularization is associated with improved long-term survival for women as well as men.

20. Atherosclerotic plaque-specific methylation biomarkers in plasma cell-free DNA of female and male patients with coronary artery disease

The atherosclerotic plaques causing myocardial infarctions

Identifying the vulnerable plaque has long been one of the holy grails in cardiology. The underlying theory is promising: if the plaque is causing the myocardial infarction, then its early identification provides an opportunity for preemptive treatment, potentially preventing future myocardial infarction, subsequent arrhythmias, and sudden death. Despite decades of research, predicting which atherosclerotic lesions will become symptomatic remains challenging.

The classic concept of the ‘vulnerable plaque’, which identifies plaque rupture as the primary pathological factor in type 1 myocardial infarction, originated in the 1980s from observations of patients who had died from

myocardial infarction.1 Later, two main mechanisms were conceptualized: plaque rupture and plaque erosion.2–4 Plaque rupture results from macrophage infiltration and matrix degradation and is associated with hypercholesterolaemia. Plaques that cause complications by erosion, on the other hand, are characterized by a strong extracellular matrix, limited lipid cores, and a thick fibrous cap. The less common mechanism, plaque erosion, is not associated with elevated cholesterol and is the prime cause of coronary thrombosis in premenopausal women.5 While our understanding on the mechanisms of plaque rupture has grown over the years, our knowledge on fibrous plaques and plaque erosion remains limited, despite its role in sudden cardiac death.

Over the last years, we and others have made significant progress in describing the molecular networks of fibrous plaques that are common in atherosclerosis obtained from women. We have uncovered an important role of smooth muscle and endothelial cell plasticity within symptomatic plaques in women.6,7

Notably, cell plasticity and differentiation go hand in hand with dynamic DNA methylation patterns that can regulate tissue-specific gene transcription.8 Unstable diseased vascular tissue, such as atherosclerotic plaque, likely releases DNA fragments into the circulation. If originating from atherosclerotic plaque, these DNA fragments may carry methylation marks which encode the biological processes unique to the cells they originate from, including some of these cell plasticity properties unique to plaque (*Figure 1*).

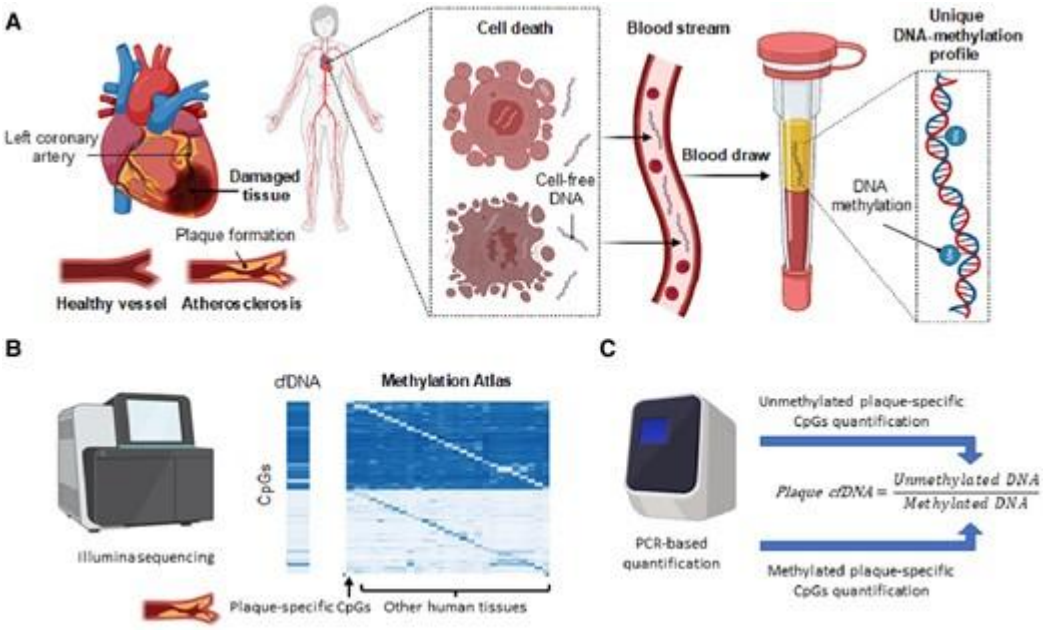


Figure 1

U-BiomarCARE, the use of cell-free DNA methylation patterns to detect atherosclerotic plaque from blood. (*A*) The concept of cell-free DNA in the detection of high-risk atherosclerotic plaque. (*B*) Current methodology used for identification of plaque-specific CpGs using expensive sequencing technologies. The plaque-specific signals are derived from a tissue DNA methylation atlas, incorporating genome-wide plaque methylomes to identify plaque-specific CpGs. (*C*) Proposed solution with the development of a PCR-based quantification assay to measure methylation at plaque-specific CpG sites. Figure is made with BioRender

In recent years, plasma cell-free DNA methylation (cfDNAme) has emerged as a potential non-invasive and tissue-specific biomarker which has been proven useful, especially in the cancer field. Also, in the cardiovascular field, the first applications of cfDNAme are emerging.9 We hypothesized that vulnerable plaques release cell-free DNA into the circulation that carries plaque-specific methylation signatures. These signatures could be detected in patients at risk for myocardial infarction, offering a measurable biomarker for early intervention. Therefore, we set out to identify plaque-specific DNA methylation marks that are hypo- or hypermethylated in atherosclerotic plaque tissue, and not in any other tissue-type. Our next

goal is to determine whether these plaque-tissue-specific methylation signals differ in plasma cfDNA between patients with vs. without coronary artery disease.

Integration of plaque-based biomarkers into clinical practice

Current state-of-the-art techniques to identify patients at high risk for myocardial infarction rely on imaging techniques such as coronary computed tomography angiography (CCTA) and coronary angiography (CAG). Both imaging modalities may be used sequentially to provide a comprehensive assessment of the degree of atherosclerosis in the coronary arteries. The primary choice between CCTA and CAG depends on various factors, including the clinical presentation, the need for intervention, existing co-morbidities, and local expertise. Some of these factors are not directly related to a patient's risk, but rather to the facilities at hand. U-BiomarCARE was recently funded by the European Research Council to develop an innovative method to tackle the major challenge of identifying plaque-based biomarkers predictive of symptomatic plaques in the circulation.

Our two-staged strategy is as follows: first, we will identify relevant biomarkers selected from whole genome methylation sequencing of plasma cell-free DNA. This allows us to detect genomic regions that best reflect atherosclerotic plaque presence in cfDNA. Second, we plan to develop a prototype for polymerase chain reaction (PCR)-based quantification of cfDNA methylation and assess its performance as compared to whole genome methylation.

A blood-based point-of-care biomarker that predicts the risk of an atherosclerotic plaque becoming symptomatic may complement, or even replace current imaging strategies. Therefore, this test may be evaluated in various clinical scenarios. First, it may be useful to identify high-risk plaques in patients who have symptoms. We anticipate that the risk assessment provided by the cfDNA profile will guide clinical decisions and

assist in determining which patients require further testing, potentially lowering healthcare costs. Second, considering that a significant number of patients do not exhibit symptoms before an acute myocardial infarction or sudden cardiac death, a straightforward and economically viable blood-based assay could enable cost-effective population-based screening for high-risk plaques. This approach, together with existing blood-based markers like lipid profiles, could offer a more direct and efficient risk detection strategy, significantly enhancing cardiovascular risk management.

In recent years, the potential of epigenetic biomarkers for clinical applications has gained increasing interest, spurred by advancements in technologies that allow for large-scale epigenetic data analysis. Following the current trends of developing point-of-care strategies and a drive towards miniaturization of techniques, we aim to translate our whole methylome patterns into a more accessible quantitative polymerase chain reaction (qPCR)-based assay. This goal is particularly feasible following the recent COVID-19 pandemic, which necessitated the widespread establishment of qPCR infrastructures across clinical diagnostics laboratories worldwide.10 This accelerated the development of qPCR-based testing and contributed to the establishment of multiplexed assays, which enables the simultaneous testing of samples for various conditions. Therefore, qPCR-based platform fits current diagnostic infrastructures.

Conclusions

Taken together, a plaque biomarker may guide risk stratification of patients. The cell- and tissue-specificity of cfDNA methylation patterns has the potential to provide precise and timely insights into the state of atherosclerotic plaques. The successful implementation of such a biomarker could significantly impact the healthcare sector by enabling the targeted detection of dangerous atherosclerotic plaques in both men and women.

21. **Hypertension in pregnancy—what's new in the 2023 ESH Guidelines for the management of arterial hypertension**

Extract

The new European guidelines on hypertension were published in the December issue of the Journal of Hypertension.1 It is an extensive document covering 119 pages containing more than 1700 references. It is a collaborative work by 59 authors. The subchapter on hypertension in pregnancy has been updated quite substantially. The major pieces of novelty can be summarized as follows (Table 1):

The definition of pre-eclampsia

The 2023 ESH Guidelines adopted the definition of pre-eclampsia introduced by the International Society for the Study of Hypertension in Pregnancy in 2018, which no longer insists on the presence of proteinuria (defined as urinary albumin excretion in a 24 h urine sample >0.3 g/day or urinary albumin to creatinine ratio >30 mg/mmol, i.e. 0.3 mg/mg in both guidelines), but instead also includes other maternal organ or uteroplacental dysfunction2:

...

Transient gestational hypertension

This is usually detected in the clinic and settles itself over several hours, which has been documented by repeated blood pressure measurements. However, there is a 40% risk of developing true gestational hypertension or pre-eclampsia for the remainder of the pregnancy. Therefore, careful follow-up is recommended. This will hopefully improve the outcome.

22. Hypertension Before Pregnancy Reduces Live Birth Rates in ART

Previous research findings demonstrate a link between pre-existing hypertension among patients undergoing ART. Although optimal blood pressure targets may differ for patients seeking reproductive assistance, blood pressure guidelines do not reflect female reproductive health.

To assess the impact of blood pressure on live birth rate, researchers conducted a retrospective cohort study comprising women who underwent ART at the Reproductive and Genetic Hospital of CITIC-Xiangya in China between 2016 and 2020. Participants (N=104,721) had 3 consecutive blood pressure measurements taken no more than 6 months before ART.

The primary outcome was live birth rate, whereas secondary outcomes included clinical pregnancy, ectopic pregnancy, gestational diabetes, gestational hypertension, and good birth outcome (live birth after 37 weeks' gestation with a birth weight between 2500 and 4000 g without major congenital abnormalities). Hypertension was defined as an average systolic blood pressure of 140 mmHg or greater or diastolic blood pressure of 90 mmHg or greater.

The study population comprised normotensive women (n=70,545), women meeting the criteria for hypertension (n=2544), and women receiving anti-hypertensive treatment (n=373).

Participants who had a live birth were more likely to be younger, whereas those who did not have a live birth were more likely to have secondary infertility, uterine adhesions, and leiomyoma.

[O]ur findings on blood pressure and [live birth rate] after infertility treatment align with general population data on cardiovascular outcomes.

Among the 73,462 total transfer cycles, 55.3% resulted in a live birth. The live birth rate was significantly higher among normotensive women (55.5%) than those with hypertension (48.1%; adjusted risk ratio [aRR], 0.919; 95%

CI, 0.885-0.955; P <.001) but not those receiving anti-hypertensive treatment (48.5%; aRR, 0.952; 95% CI, 0.863-1.049; P =.320).

With every 10-mmHg increase in systolic blood pressure, the likelihood of achieving a live birth decreased among patients with normotension (aRR, 0.988; 95% CI, 0.981-0.995; P =.001) and hypertension (aRR, 0.946; 95% CI, 0.907-0.986; P =.009).

Among the women with normal blood pressure, first trimester miscarriage risk increased with every 10-mmHg increase in systolic (aRR, 1.052; 95% CI, 1.022-1.082; P <.001) and diastolic (aRR, 1.051; 95% CI, 1.013-1.091; P =.009) blood pressure.

The researchers observed no associations between blood pressure and pregnancy duration, birth weight, or Z-scores.

In sensitivity analyses that used the stricter American College of Cardiology and American Heart Association guidelines, the results were consistent with the main analysis.

In a subgroup analysis, the association between systolic blood pressure and live birth rate was not significant among:

- Participants aged more than 40 years;
- Participants with a body mass index (BMI) greater than 24 kg/m2; and,
- Participants who underwent ART other than in vitro fertilization.

The association between diastolic blood pressure and live birth rate was significant among:

- Participants aged 30 to 35 years;
- Participants with a BMI less than 18.5 kg/m2;
- Participants without male factor infertility; and,
- Participants without uterine adhesions.

Study limitations include its single-center design, a lack of generalizability beyond Han Chinese patients, and the absence of data regarding family history of hypertension.

The researchers concluded that "our findings on blood pressure and [live birth rate] after infertility treatment align with general population data on cardiovascular outcomes."

23. Burden of cardiometabolic disorders and lifetime risk of new-onset atrial fibrillation among men and women: the Rotterdam Study

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide, with high-risk of complications and mortality.1,2 Advancing age is the most important risk factor for AF development. AF prevalence ranges from 0.2% in adults younger than 55 years to around 10% in those 85 years or older.2 Meanwhile, sex differences have been suggested in AF epidemiology, pathophysiology, and prognosis.3–5 The Framingham Heart Study has estimated an AF lifetime risk at the age of 55 years as 29.8% for men and 20.5% for women with the optimal CHARGE-AF risk score,6 implying a need to establish a sex-specific risk profile for AF prevention.

The pathophysiologic mechanisms underlying AF are complex.7 Cardiometabolic disorders, including obesity, hypertension, diabetes mellitus (DM), coronary heart disease (CHD), heart failure (HF), and stroke are intertwined with AF. Overweight/obesity and hypertension serve as the most well-documented AF risk factors.1 Besides, DM, CHD, stroke, and HF all contribute to the occurrence and persistence of AF by inducing systemic inflammation, haemodynamic changes, and/or nervous system dysregulations which are further responsible for abnormal atrial remodelling.7–10

The prevalence of cardiometabolic multimorbidity, defined as coexistence of two or more cardiometabolic diseases, has increased worldwide in both women and men.8,11–15 Investigating multimorbidity rather than focusing solely on single diseases holds immense importance. In the real-world scenario, individuals often present with multiple health conditions simultaneously. Studying multimorbidity acknowledges and addresses this complexity, providing a more accurate representation of the health challenges individuals face. Multiple health conditions can interact synergistically, influencing disease progression, treatment outcomes, and overall health status. The presence of one condition can exacerbate or modify the course of another, leading to different clinical manifestations and complexities that may not be evident when considering diseases in isolation. To date, considerable evidence has demonstrated that presence of either of these conditions alone leads to an increased AF risk.8,11–15 However, the combined impact of cardiometabolic disorders on AF onset remains largely unknown.

To date, stronger associations between obesity and CHD with AF among men have been observed,4,16–18 while stronger associations between hypertension, diabetes, stroke, and HF with AF have been found for women.17,19–21 Besides, a sex-specific association, more evident for men, between cardiometabolic multimorbidity and mortality has been documented as well.22 Herein, investigating the impact of the burden of cardiometabolic multimorbidity on AF among men and women is central for AF prevention and improvement of patient management and prognosis.

Identifying the association between cardiometabolic multimorbidity and incident AF would aid in proper risk stratification, early detection, and targeted interventions aimed at mitigating the development of AF in high-risk populations with comorbid cardiometabolic conditions. In addition, given the rising prevalence of cardiometabolic disorders globally, elucidating their (collective) impact on AF holds significant public health relevance. Insights gained from this research could inform preventive strategies and healthcare policies aimed at reducing the burden of AF and associated

cardiovascular complications. Therefore, this research aimed to comprehensively evaluate the sex-specific association between cardiometabolic multimorbidity and incident AF. Our primary objective was to assess the collective impact of cardiometabolic disorders on developing AF among men and women. The secondary objective was to estimate the lifetime risk for new-onset AF at index ages of 55, 65, and 75 years old.

Methods

Study population

The current study was performed within the framework of the Rotterdam Study.23 The Rotterdam Study is a prospective population-based cohort study that aims to investigate the occurrence and progression of risk factors for chronic diseases in middle-age and elderly individuals. Between 1990 and 1993, all inhabitants of Ommoord district in the city of Rotterdam in The Netherlands aged ≥ 55 years were invited for the study. A total of 7983 (78% of all invitees) agreed to participate (RS-I). In 2000, the cohort was extended to 3011 participants who had become ≥ 55 years or had migrated into the research area (RS-II). In 2006, the cohort was again extended with 3932 participants who were ≥45 years (RS-III). The overall response rate at baseline was 72%. Participants visited the study research centre every 3–5 years on average. (see Supplementary material online, *Figure S1*).

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, licence number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.onderzoekmetmensen.nl) and into the World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to

participate in the study and to have their information obtained from treating physicians.

For this study, we included participants from the third visit of the first cohort (RS-I-3) the first visit of the second (RS-II-1) and the third cohorts (RS-III-1). From 11587 individuals at baseline with informed consent for follow-up, participants with prevalent AF were excluded (*n* = 512). Further, participants with incomplete information about cardiometabolic disorders at baseline were excluded as well (*n* = 1553). Finally, 9522 participants were included in the final analyses (*Figure 1*).

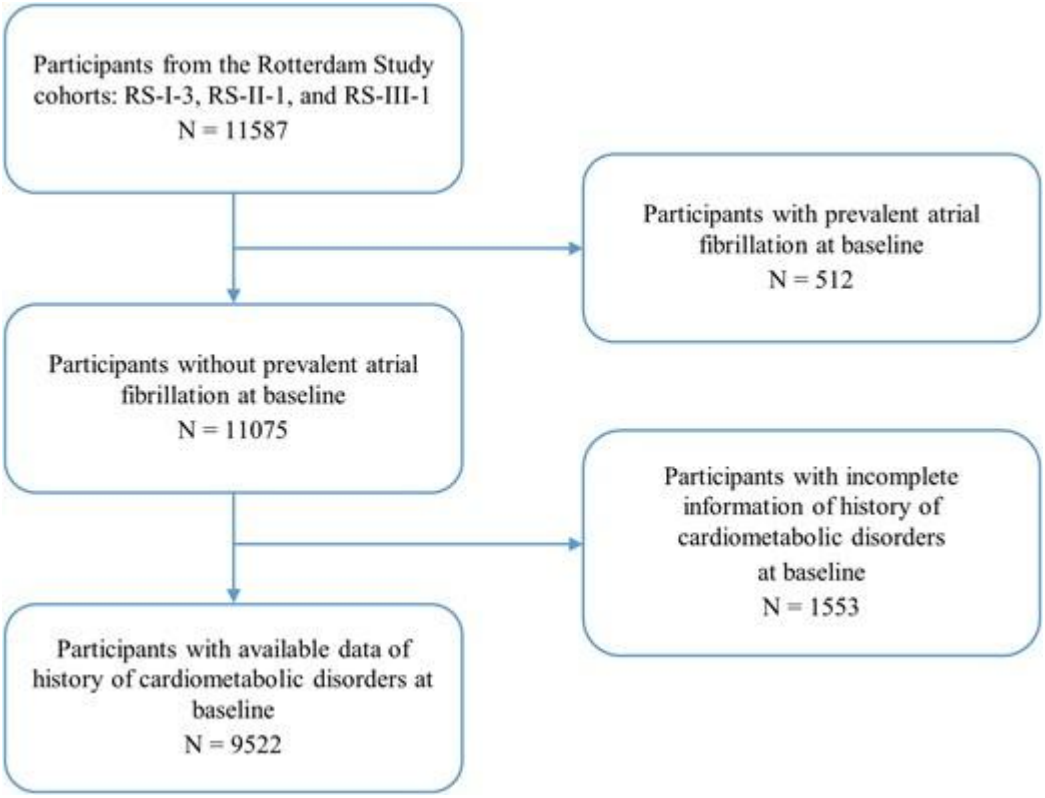


Figure 1

Flow chart of the study population.

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Assessment of cardiometabolic disorders

All participants responded to comprehensive questionnaires at the study baseline about their current health status, medical history, medication, and

lifestyle. They were interviewed at home by trained interviewers and underwent more extensive clinical examinations and laboratory assessments at the research centre.

In the present study, adiposity including both obesity and overweight was defined as a body mass index (BMI) ≥ 25 kg/m2. Systolic and diastolic blood pressures were calculated as the mean of the two consecutive measurements. Hypertension was defined as a systolic blood pressure (SBP) of ≥140 mmHg or a diastolic blood pressure (DBP) ≥ 90 mmHg or the use of blood pressure lowering drugs prescribed for hypertension (ATC-codes C02, C03, C07, C08, and C09).24,25 DM was defined as fasting serum glucose levels ≥126 mg/dL (7.0 mmol/L), non-fasting serum glucose levels ≥200 mg/dL (11.1 mmol/L), or the use of antidiabetic therapy [ATC-code A10]. The assessment and definition of prevalent CHD, stroke, and HF have been described in detail previously.26–28 In brief, CHD was defined as fatal or non-fatal myocardial infarction and surgical or percutaneous coronary revascularization procedures (as a proxy for unstable or incapacitating angina).27 Stroke was defined according to WHO criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, with no apparent cause other than of vascular origin.26 HF was defined as the combination of typical symptoms and signs, confirmed by objective evidence of cardiac dysfunction or a positive response to initiated treatment.27 The measurement standardization in the Rotterdam Study was meticulously established and reported previously.23,27 In short, for each outcome two cardiovascular research physicians independently classify information on occurrence, certainty, and date of onset of all data collected on potential events, cases on which the research physicians disagree are discussed in order to reach consensus in a separate session. Afterwards, a panel of medical specialists in cardiovascular disease (CVD) reviews potential events for each diagnosis separately. The medical specialist's judgment is considered decisive.

Assessment of atrial fibrillation

Methods on event adjudication for prevalent and incident AF have been described previously.27 The definition of AF was in accordance with the Guidelines of the European Society of Cardiology (ESC).1 Ascertainment of AF at baseline and follow-up examinations in our study has been based on clinical information from the medical records of all participants of the Rotterdam Study. Within the Rotterdam Study, data on medical history and medication use are continuously being collected through multiple sources including a baseline home interview, a physical examination at our research centre, the pharmacy prescription records, the Nationwide Medical Registry of all primary and secondary hospital discharge diagnosis and screening of general practitioner's records. In addition, a resting 10-s 12-lead electrocardiogram (ECG) used with an ACTA Gnosis IV ECG recorder (Esaote; Biomedical, Florence Italy) is obtained from all participants at every visit of the Rotterdam Study to verify AF. The ECG records are stored digitally and analyzed with the Modular ECG Analysis system (MEANS).29 Subsequently, the AF outcomes are adjudicated independently by two research physicians. In case of disagreement, a senior cardiologist is consulted. The date of incident AF was defined as the date of the first occurrence of symptoms suggestive of AF with subsequent ECG verification obtained from the medical records. Participants were followed until the date of onset of AF, date of death, loss to follow-up, or to 1 January 2014, whichever occurred first.

Assessment of covariates

Serum total and high-density lipoprotein (HDL) cholesterol were measured with an automated enzymatic method. Smoking information derived from baseline questionnaires was categorized into current, former, and never smokers. Information on lipid-lowering [anatomical therapeutic chemical (ATC)-code C10)] and cardiac medication use was derived from baseline questionnaires and pharmacy data. Cardiac medication was defined as use

of digoxin (ATC-code C01AA05), nitrates (ATC-code C01DA), or antiarrhythmic drugs (ATC-code C01B).

Statistical analyses

All analyses were performed among overall population and among men and women separately. We categorized participants into five groups corresponding to having experienced (i.e. baseline prevalence) 0, 1, 2, 3, and ≥4 of the following comorbid disorders at baseline: adiposity, hypertension, DM, CHD, stroke, and HF. Means (standard deviations) and numbers (percentages) were calculated to describe baseline characteristics of the study population among men and women. Differences were examined by Student's *t*-tests for continuous variables and Chi-square tests for categorical variables.

Cox proportional-hazards models, taking competing risk of death into account, were used to estimate the associations between the burden of cardiometabolic disorders and the risk of new-onset AF. Hazard ratios (HRs) and 95% CIs were calculated for various groups, with no comorbid cardiometabolic disorders as the reference. A sample size calculation was performed and described in section of the supplementary material online, *Methods*. Models were adjusted for baseline age, sex (if applicable), and Rotterdam Study cohorts (Model 1), and additionally for total and HDL-cholesterol, smoking, and use of serum lipid-reducing agents and cardiac medication (Model 2). Sex difference was assessed by adding an interaction term to the models and a *P*-value <0.05 was considered as significant. The proportional-hazards assumptions were tested initially by graphical examination of the cumulative incidence function and then by using Schoenfeld residuals. There was no evidence of violation of the proportionality assumption. In sensitivity analyses, we repeated all analyses among participants free of incident cardiometabolic disorders before AF onset to rule out the potential impact of long-term changes in health status. In addition, we removed each cardiometabolic disorder from the model, one at a time, to evaluate the importance of each disorder individually.

Then, the lifetime risk for AF onset was estimated by a modified version of survival analysis which takes the competing event of death into account, with age as the time scale.30 We calculated the remaining lifetime risks for incident AF from index ages 55, 65, and 75 years up to age 108. In this type of analysis, at each age category, the incidence of each CVD outcome is calculated during follow-up. Furthermore, we compared the overall difference of lifetime risk estimates across groups of cardiometabolic disorders by the Fine–Gray method based on sub-hazard distributions.31 Lifetime risks in groups with one or more comorbid cardiometabolic disorders were also compared with the lifetime risk estimates in the lowest group (no cardiometabolic disorder) by a *z*-ratio test.6

Missing values in covariates (each of all ≤ 3%) were imputed under the assumption of missing at random using multiple imputation with a fully conditional specification using package 'MICE'.32 For multiple imputation, all available data were used to generate ten imputed data sets. Statistical significance was considered at two-tailed *P*-value < 0.05. The analyses were done using R software (R 4.0.4; R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows the baseline characteristics among men and women. Of 9522 participants, 5421 (56.9%) were women. At baseline, the mean (standard deviation) age was 64.1 (9.2) years for men and 64.7 (9.8) years for women. During a median follow-up of 12.8 (inter-quartile range 10.1–18.1) years, 624 (15.2%) men and 634 (11.7%) women experienced new-onset AF. The incidence density was 12.3 per 1000 person-years for men and 8.6 per 1000 person-years for women. Baseline characteristics were reported among five groups of comorbid cardiometabolic disorders in detail in the Supplementary material online, *Table S1*. Overall, participants with a greater number of cardiometabolic disorders exhibited poorer health status, for example higher BMI, SBP, and total cholesterol (TC) levels and larger

proportion of using lipid-lowering and cardiac medications (all *P* values <0.001).

Baseline characteristics of the study population

	Overall	**Men**	**Women**	***P* values**
No. of participants	9522	4101	5421	
Age (years)	64.4 (9.5)	64.1 (9.2)	64.7 (9.8)	<0.001
BMI (kg/m2)	27.3 (4.3)	27.0 (3.6)	27.5 (4.7)	<0.01
SBP (mmHg)	140 (21)	141 (20)	138 (22)	<0.001
DBP (mmHg)	79 (11)	80 (11)	78 (11)	<0.001
TC (mmol/L)a	5.7 (1.0)	5.5 (1.0)	5.9 (1.0)	<0.001
HDL-C (mmol/L)a	1.4 (0.4)	1.2 (0.3)	1.5 (0.4)	<0.001
Smoking (*n*, %)				<0.001
Never	2914 (30.6)	642 (15.7)	2272 (41.9)	
Ex-smoker	4449 (46.7)	2363 (57.6)	2086 (38.5)	
Current	2159	1096	1063	

	Overall	**Men**	**Women**	***P* values**
smoker	(22.7)	(26.7)	(19.6)	
Medications (*n*, %)				
Lipid-lowering medication	531 (5.6)	259 (6.3)	272 (5.0)	<0.01
Cardiac medication	1555 (16.3)	740 (18.0)	815 (15.0)	<0.001
Cardiometabolic disorders (*n*, %)				<0.001
Adiposity	6519 (68.5)	2884 (70.3)	3635 (67.1)	<0.001
Hypertension	5835 (61.3)	2601 (63.4)	3234 (59.7)	<0.001
Diabetes mellitus	1138 (12.0)	588 (14.3)	550 (10.1)	<0.001
Coronary heart disease	630 (6.6)	469 (11.4)	161 (3.0)	<0.001
Heart failure	288 (3.0)	91 (2.2)	82 (1.5)	0.01
Stroke	173 (1.8)	166 (4.0)	122 (2.3)	<0.001
Groups of comorbid				<0.001

	Overall	Men	Women	*P* values
cardiometabolic disorders				
None	1444 (15.2)	512 (12.4)	934 (17.2)	
1	3135 (32.9)	1280 (31.2)	1855 (34.2)	
2	3642 (38.2)	1589 (38.7)	2053 (37.9)	
3	1075 (11.3)	569 (13.9)	506 (9.3)	
≥4	226 (2.4)	153 (3.7)	73 (1.3)	

Values are shown as mean (standard deviation) or median (inter-quartile range) for continuous variables and number (percentage) for categorical variables. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol.

aTo get from mmol/L to mg/dL multiply by 38.67.

Supplementary material online, *Table S2* shows the comparisons of the baseline variables between the included and excluded participants. It seems that participants included in the present study were healthier than those excluded participants.

Association between burden of cardiometabolic disorders and incident AF

Table 2 describes the association between the burden of cardiometabolic disorders and the risk of new-onset AF. In the crude models (Model 1), the increased burden of cardiometabolic disorders conferred a higher AF risk among the overall population (HR; 95% CI per one additional disorder: 1.35; 1.28–1.43), as well as men (1.24; 1.14–1.34) and women (1.45; 1.34–1.57). Such associations remained statistically significant, while slightly attenuated, after adjustments for traditional cardiovascular risk factors (Model 3) (HRs; 95% CIs per one additional disorder: 1.25; 1.17–1.33 for all, 1.18; 1.08–1.29 for men, and 1.33; 1.22–1.46 for women). In the fully adjusted models (Model 3), significant sex differences were observed with a stronger association between the burden of cardiometabolic disorders and AF among women, as compared to men. Compared to participants with no disorder, men in the upper group of ≥4 cardiometabolic disorders had a 1.8-fold higher risk of AF (1.76; 1.12–2.76), whereas women had a 3.6-fold substantially higher risk of AF (3.60; 1.93–6.72). In sensitivity analyses, consistent results were suggested among participants free of incidence of any cardiometabolic disorders before AF onset (see Supplementary material online, *Table S3*).

Table 2

Association between the burden of cardiometabolic disorders and risk of new-onset atrial fibrillation, after accounting for competing risk of death

	Per one additional disorder	**Number of cardiometabolic disorders**					***P* for trend**
		0	**1**	**2**	**3**	**≥4**	
Total (*n* = 9522)							
Mo	1.35	1.0	1.47	2.14	2.48	3.55	<0.00

	Per one additional disorder	Number of cardiometabolic disorders					*P* for trend
		0	1	2	3	≥4	
del 1	(1.28–1.43)	0 (Ref.)	(1.19–1.83)	(1.74–2.63)	(1.96–3.15)	(2.54–4.96)	01
Model 2*	1.26 (1.19–1.33)	1.00 (Ref.)	1.38 (1.11–1.72)	1.88 (1.53–2.31)	2.02 (1.59–2.58)	2.56 (1.81–3.62)	<0.0001
Model 3*	1.25 (1.17–1.33)	1.00 (Ref.)	1.40 (1.13–1.74)	1.89 (1.53–2.34)	1.98 (1.54–2.54)	2.40 (1.67–3.47)	<0.0001
Men (*n* = 4101)							
Model 1	1.24 (1.14–1.34)	1.00 (Ref.)	1.02 (0.76–1.36)	1.35 (1.02–1.77)	1.71 (1.26–2.33)	2.13 (1.41–3.20)	<0.0001
Model 2	1.20 (1.10–1.30)	1.00 (Ref.)	1.01 (0.75–1.35)	1.28 (0.97–1.69)	1.58 (1.15–2.16)	1.86 (1.22–2.83)	<0.0001
Mo	1.18	1.0	1.02	1.29	1.53	1.76	<0.00

	Per one additional disorder	Number of cardiometabolic disorders					*P* for trend
		0	1	2	3	≥4	
del 3	(1.08–1.29)	0 (Ref.)	(0.76–1.36)	(0.97–1.70)	(1.11–2.12)	(1.12–2.76)	1
Women (*n* = 5421)							
Model 1	1.45 (1.34–1.57)	1.00 (Ref.)	2.07 (1.49–2.87)	3.23 (2.36–4.42)	3.27 (2.26–4.73)	5.53 (3.10–9.89)	<0.0001
Model 2	1.34 (1.23–1.45)	1.00 (Ref.)	1.90 (1.37–2.63)	2.72 (1.98–3.75)	2.58 (1.77–3.76)	3.83 (2.11–6.96)	<0.0001
Model 3	1.33 (1.22–1.46)	1.00 (Ref.)	1.93 (1.39–2.69)	2.79 (2.02–3.86)	2.57 (1.75–3.80)	3.60 (1.93–6.72)	<0.0001

Values are shown as hazard ratio and 95% confidence intervals (95% CI). **P* for sex-interaction <0.05.

Model 1 was the unadjusted model.

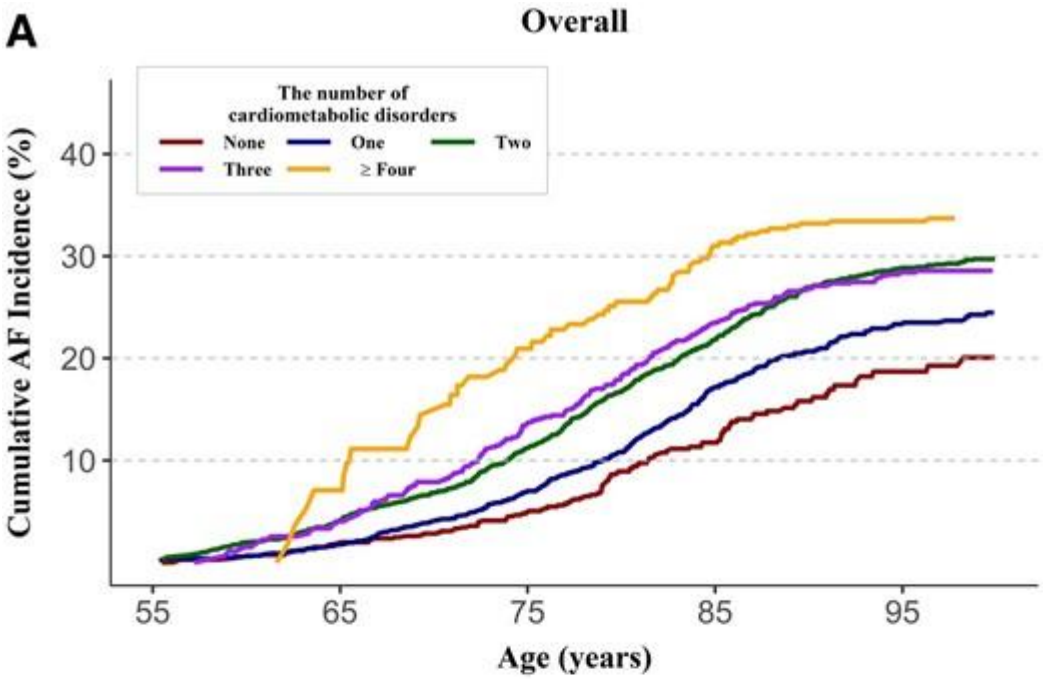
Model 2 was adjusted for age, sex (if applicable), and Rotterdam Study cohort.

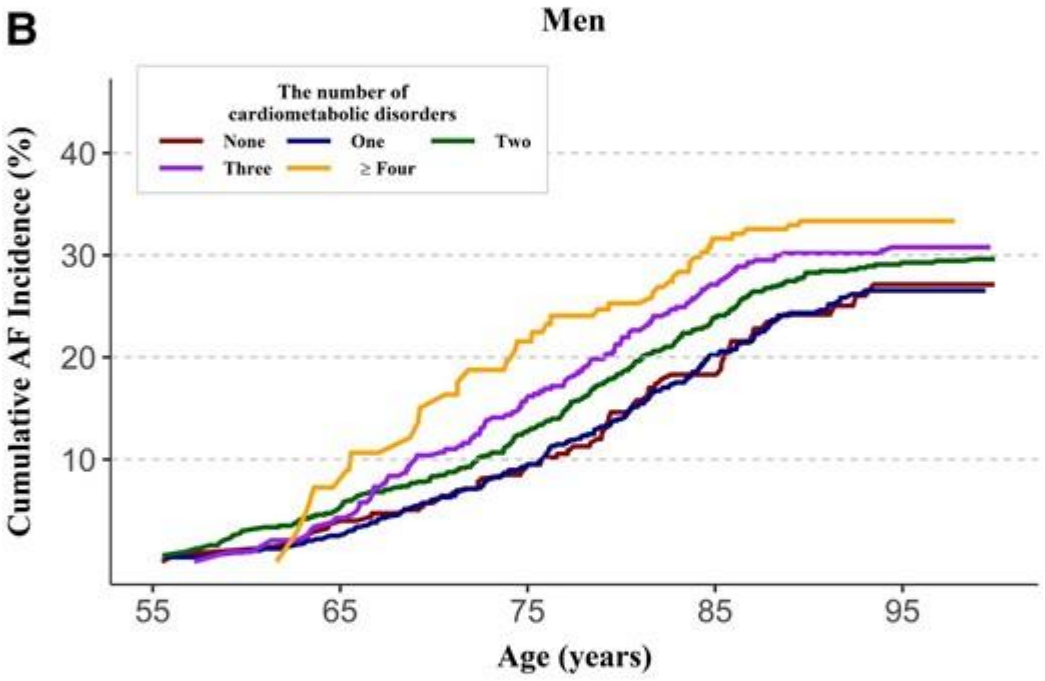
Model 3 was additionally adjusted for total cholesterol, high-density lipoprotein cholesterol, smoking status, use of lipid-lowing medication, and cardiac therapy.

Supplementary material online, *Table S4* demonstrates the results of sensitivity analysis that we removed each cardiometabolic disorder from the model, one at a time, to evaluate the importance of each disorder individually. In general, removing any one specific disorder did not change the significance of our results.

Lifetime risks for AF onset among groups of comorbid cardiometabolic disorders

The remaining lifetime risk for AF gradually increased with the higher burden of cardiometabolic disorders among the overall population and more evidently at a younger index age (*Figures 2A* and *3A*). For example, at an index age 55 years, the remaining lifetime risk (95% CI) for AF was 20.1% (16.1–24.0) in the no-disorders group, 24.5% (22.0–26.9) in the one disorder group, 30.0% (27.9–32.2) in the two disorders group, 28.7% (25.0–32.4) in the three disorders group, and 33.7% (25.0–42.4) in group with ≥4 disorders ($P < 0.0001$). A similar trend was observed among men (*Figures 2B* and *3B*) and women (*Figures 2C* and *3C*) at index ages of 55 years. Men with ≥4 disorders had the highest lifetime risk for AF onset, and the estimated AF incidence rate was 33.3% (23.1–43.6) at an index age of 55 years old. In women, the highest lifetime risk was also estimated among those with more than 4 disorders as 34.2% (17.3–51.1). However, at an index age of 75 years, lifetime AF risk was significantly associated with the burden of cardiometabolic disorders among women ($P < 0.01$), but not men ($P = 0.76$).


A
Overall
The number of cardiometabolic disorders
None
One
Two
Three
≥ Four
Cumulative AF Incidence (%)
40
30
20
10
55
65
75
85
95
Age (years)


B
Men
The number of cardiometabolic disorders
None
One
Two
Three
≥ Four
Cumulative AF Incidence (%)
40
30
20
10
55
65
75
85
95
Age (years)

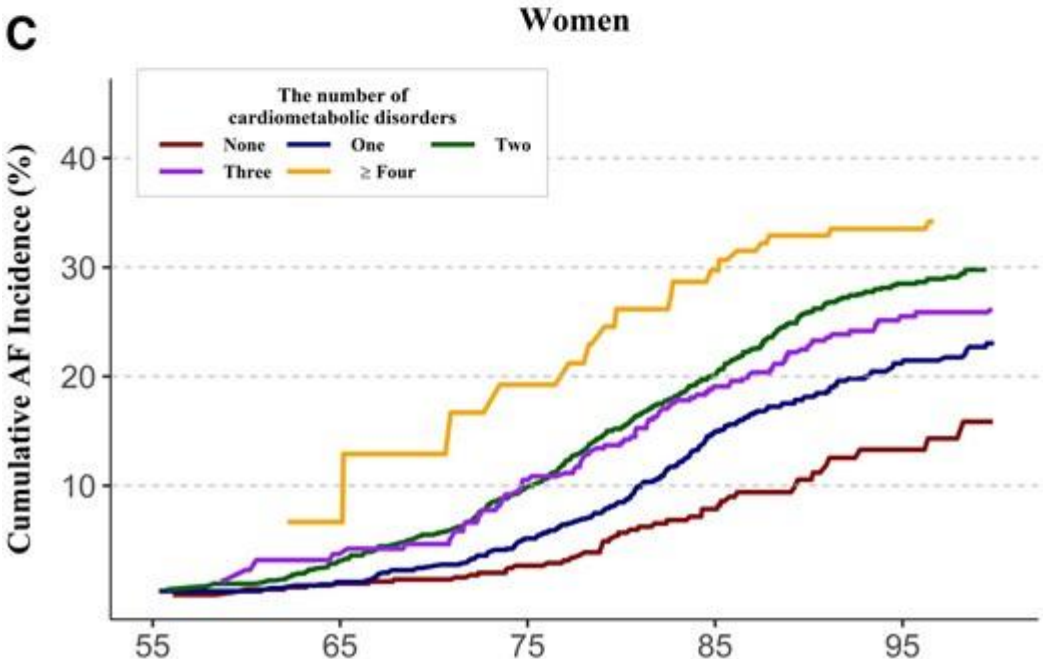

C
Women
The number of cardiometabolic disorders
None
One
Two
Three
≥ Four
Cumulative AF Incidence (%)
40
30
20
10
55
65
75
85
95

Figure 2

Cumulative incidence of atrial fibrillation among groups of cardiometabolic disorders at an index age of 55 years old among overall population (*A*), men (*B*), and women (*C*). AF, atrial fibrillation.

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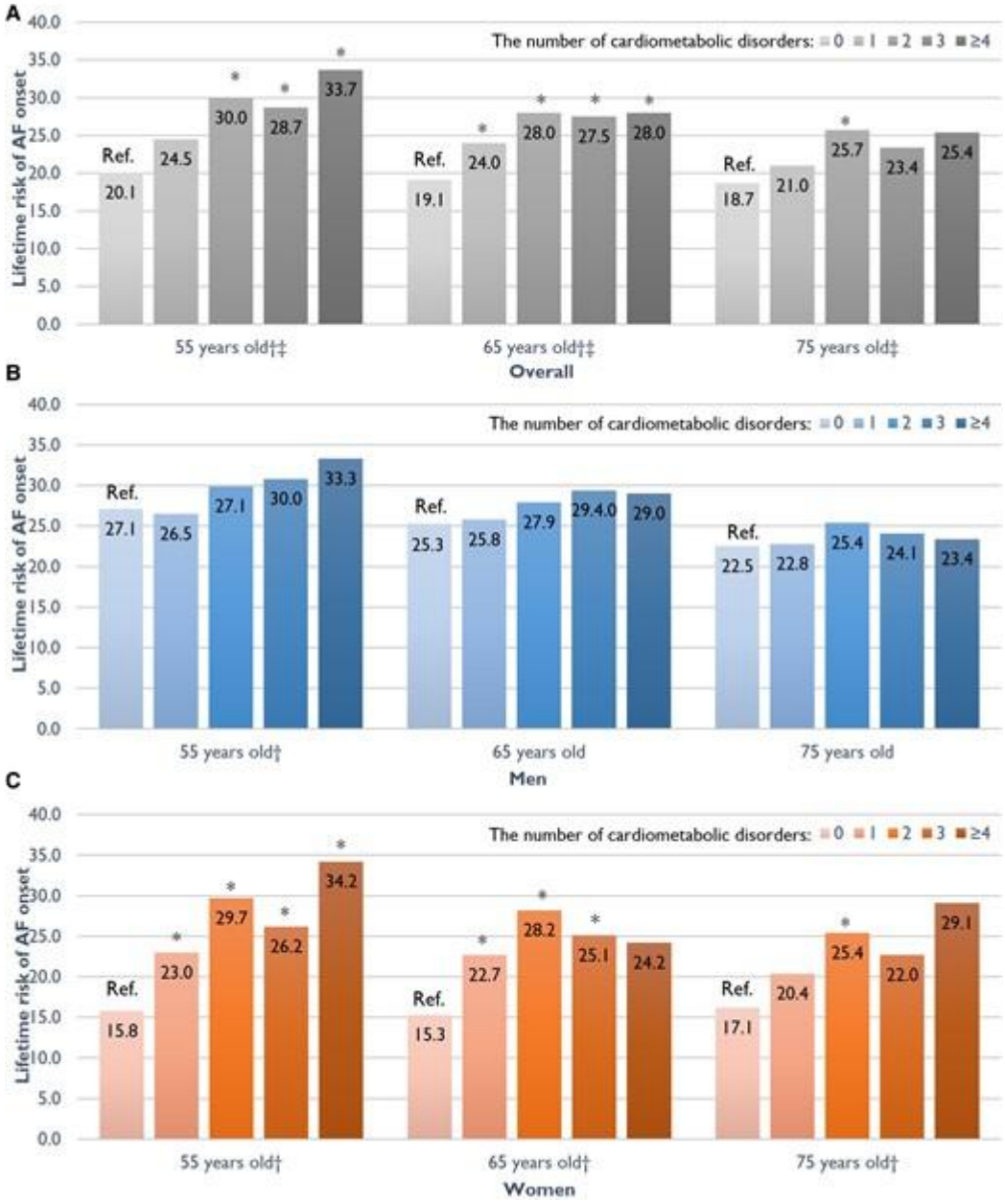

Figure 3

Remaining lifetime risk of incident atrial fibrillation onset at an index age of 55, 66, and 75 years across the groups of comorbid cardiometabolic disorders among overall population (*A*), men (*B*), and women (*C*). AF, atrial

fibrillation. †Overall test comparing sub-hazard distributions among groups of comorbid cardiometabolic disorders by Fine–Gray method. ‡Significant sex difference at index ages 55, 65, and 75 years (all $P < 0.05$). *Test comparing lifetime risk in groups of 1, 2, 3, or ≥4 cardiometabolic disorders with the group of no cardiometabolic disorder by two-sample *z*-test. The lifetime risk of AF incidence and 95% confidence interval are mentioned in detail in the Supplementary material online, *Tables S5* and *S6*.

Discussion

In this study, findings suggested a significant collective impact of multiple cardiometabolic disorders on new-onset AF. In particular, we found that a larger burden of comorbid cardiometabolic disorders was associated with increased AF risk, most distinct in women. Moreover, the sex-specific estimations of lifetime risks for AF onset among coexistent cardiometabolic disorders presented novel findings. Compared to women, the AF lifetime risks were generally higher among men, especially at a younger age. However, with the increasing burden of cardiometabolic disorders, the lifetime risks for AF onset increased more rapidly among women.

We investigated the impact of a range of cardiometabolic disorders including adiposity, hypertension, DM, CHD, stroke, and HF, on AF incidence. The presence of any singular disorder was demonstrated to be an independent risk factor for incident AF. However, studies addressing isolated management of a specific disorder have yielded inconsistent results for preventing AF. For example, in an open-labeled clinical trial, a blood pressure control did not reduce AF recurrence after catheter ablation for AF.33 Such evidence reflects a potential interaction between various cardiometabolic disorders and warrants an overview of the collective impact of various comorbid disorders on AF risk to improve AF prevention. To our knowledge, only two studies have investigated the associations between a combined impact of obesity and hypertension, and of obesity and diabetes on incident AF among Korean population.14,34 Both suggested that the

pairwise comorbidities significantly augmented the risk for incident AF. Our findings extend to the previous studies by assessing a collective impact of main cardiometabolic disorders on AF onset. Each additional disorder conferred a 31% higher AF risk among the overall population. Given the global increase in the prevalence of cardiometabolic multimorbidity and the complexity of cardiovascular system,35 it is important to target high-risk groups for AF prevention. Moreover, studies have suggested a higher mortality rate among patients with CHD, stroke, or HF with concomitant AF, as compared to those without concomitant AF.36–38 These findings, together with the results from the present study, highlight the importance of screening for AF among patients with cardiometabolic multimorbidity.

Our findings demonstrated a stronger impact of the burden of cardiometabolic disorders on AF onset among women. Women with a higher burden of cardiometabolic disorders showed twofold higher risks for incident AF, compared to men. Indeed, a body of evidence has suggested sex differences in epidemiology of single cardiometabolic disorders in relation to AF,3 with stronger associations between obesity and CHD with AF among men,4,16–18 but stronger associations between hypertension, diabetes, stroke, and HF with AF among women.17,19–21 However, sex-specific evidence of synergetic impact of cardiometabolic disorders on AF development is undocumented. Several underlying mechanisms might account for the observed stronger associations among women. First, the majority of women in the present study were post-menopausal. It is well-documented that the risk of cardiovascular disease increases among post-menopausal women due to the diminishing levels of oestrogen. Endogenous oestrogen also carries a beneficial impact on AF by extending action potential duration and the atrial effective refractory period.39 Second, women tend to have a longer life span than men. Since AF occurrence rapidly increases with aging, older women might be more likely to develop AF, compared to men. However, in our sensitivity analyses, results remained consistent after accounting for competing risk of death and changes in

health status during follow-up, implying that they did not fully explain the observed sex differences.

Our study demonstrated an increase in lifetime risk of AF across the groups of cardiometabolic disorders and parallel to the increase in comorbidities. Among participants aged 55 years or older, the lifetime risk of AF was 27.1% among healthy men and 15.8% among healthy women. The AF lifetime risk gradually increased among both men and women with the increasing burden of cardiometabolic disorders. Of those individuals who experienced ≥4 comorbid disorders at age 55 years or older, around one in three developed new-onset AF, and the pattern was similar among men and women. Our results are in line with a previous report from the Framingham Heart Study that estimated an AF lifetime risk at the age of 55 years as 29.8% for men and 20.5% for women with the optimal CHARGE-AF risk score.6 Our study adds to the previous evidence by underscoring the strikingly higher AF incidence among both men and women with the high burden of cardiometabolic disorders. Furthermore, the difference in AF lifetime risks across various groups of comorbid cardiometabolic disorders diminished with aging, especially among men. Given the studied cardiometabolic disorders are modifiable or semi-modifiable, our results highlight implementing interventions for reducing cardiometabolic risks as early as possible to have an optimal impact on AF prevention and to avoid a high residual risk for AF development at older ages.

Our findings can help in shaping clinical approaches to cardiovascular health, particularly regarding AF risks associated with cardiometabolic disorders. The observed heightened risk of new-onset AF among individuals with multiple cardiometabolic disorders, especially among women, underscores the critical need for sex-specific risk assessment and management strategies. Our study highlights that women with a larger burden of cardiometabolic disorders exhibit a disproportionately higher susceptibility to AF compared to men. Men have overall larger lifetime risk for AF. However, among women with larger number of cardiometabolic disorders, this sex gap in AF lifetime risk is further narrowed. Moreover, the

escalating lifetime risk of AF with an increasing burden of comorbidities at a younger age among both sexes, emphasizes the importance of proactive interventions targeting multimorbidity in early stages to mitigate AF incidence.

Major strengths of this study include its prospective design, large sample size, and the long follow-up to enable comparisons between groups of main cardiometabolic disorders, and between men and women, while some had a limited prevalence. In addition, new-onset AF were meticulously adjudicated, validated, and confirmed on electrocardiograms. Moreover, we reported the robust association between the burden of cardiometabolic disorders with new-onset AF by taking death as completing risk into account, as well as excluding participants with major changes in health status before AF onset. However, certain limitations should be acknowledged to better interpret our findings. First, most of our participants were of European ancestry and older adults, limiting the generalizability of our findings to younger populations and other ethnicities. However, considering the rapidly increasing prevalence of AF in the elderly, identifying AF risk factors and devising AF screening strategies targeting the older population is of clinical importance. Second, due to the observational study design, we cannot rule out residual confounding. Third, despite the relatively large sample size and long follow-up of this study, the number of women with four or more cardiometabolic disorders was significantly lower compared to men, due to the lower prevalence of these disorders among women in contrast to men. Thus, our study faced limitations in interpreting the results within this particular subgroup. Fourth, our sample size limits our further analysis in assessing the impact of differential combinations/patterns of cardiometabolic disorders on incident AF, which is one limitation of the current study. Fifth, given a significant ethnic difference in AF prevalence,40 examining the potential heterogeneity of associations across diverse ethnic backgrounds is an essential aspect that warrants attention. While our research delves into the relationship between cardiometabolic disorders and new-onset AF among a specific demographic, future studies with a broader spectrum of

ethnic backgrounds could provide an opportunity for a more nuanced exploration of these associations. Finally, since AF may be paroxysmal and asymptomatic, we might have underestimated the true number of AF cases in our study population, although this would have probably led to an underestimation of the real associations. Nonetheless, the prevalence of AF in the Rotterdam Study is ~ 4% which is in line with the global estimate of AF prevalence.1

Conclusions

Our study reveals a significant collective impact of cardiometabolic disorders on AF susceptibility, notably prominent among women. Among participants aged 55 years or older, the lifetime risk of AF was 25.2% among healthy men and 16.3% among healthy women. Individuals with cardiometabolic multimorbidity exhibited a markedly escalated lifetime risk of AF, particularly evident at a younger age. These results underscore the imperative for intensified focus within clinical practice on AF prevention among those with cardiometabolic multimorbidity.