9th Annual Women's Heart & Vascular Symposium

The Way to a Woman's Heart:

Assessing, Personalizing, and Reclassifying Atherosclerotic Cardiovascular Disease Risk in Female Patients

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in women in the United States. Here, we explore and summarize for this population the general principles and sex-specific nuances of ASCVD risk assessment, risk enhancers specific to women, the value of evaluating coronary artery calcium (CAC), the benefit of statin therapy, and the perception of ASCVD risk in women (Table I).

Pooled Cohort Equations for Risk Assessment

The pooled cohort equations (PCEs), originally recommended in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guideline, have been developed to predict the 10-year risk of "hard" ASCVD outcomes (coronary heart disease death, nonfatal myocardial infarction, and fatal or nonfatal stroke) in men and women 40 to 79 years of age.[1] The PCEs incorporate traditional risk factors such as age, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking, diabetes mellitus, and hypertension, but also include stroke as an outcome because in the United States more women than men have strokes. Separate PCEs have been developed for white men, black men, white women, and black women to enable sex- and race-specific estimation of ASCVD risk. However, even though the PCEs are derived from large community-based studies encompassing a wide spectrum of the U.S. population and have been validated in various natural history studies,[2] they may under- or overestimate true ASCVD risk when applied to individual patients.[1] This limitation can be overcome in part by accounting for each individual's baseline or acquired characteristics (called "risk enhancers" in the 2018 AHA/ACC/multisociety cholesterol guideline). These risk enhancers include a family history of premature ASCVD, ethnicity, and concurrent medical comorbidities and may significantly alter an individual's ASCVD risk.[1]

Risk Enhancers Specific to Women

Several conditions specific to women have been identified as risk enhancers that should be considered when estimating 10-year ASCVD risk. Premature ovarian failure and early-onset menopause are associated with an increased risk of ASCVD,[3] as is gestational diabetes.[4] Other female-specific risk enhancers are preeclampsia, gestational hypertension, preterm delivery, and delivery of infants small for their gestational age.[1]

Coronary Artery Calcium

For intermediate-risk patients in whom the decision to start statin therapy remains unclear, CAC can be used to guide management.[1] A CAC score can predict risk of ASCVD events in both men and women; however, recent studies have shown that the relationship between patterns of CAC distribution and risk may differ by sex. In a recent study from the multicenter CAC Consortium, across age deciles, detectable CAC

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TABLE I. Summary of Atherosclerotic Cardiovascular Disease Risk Assessment and Perception in Women

Topic	Main Points
Pooled cohort equations	10-year ASCVD risk estimators
	Separate equations for black and white women
	Coronary events and stroke included as outcomes
Risk enhancers specific to women	Premature ovarian failure
	Early-onset menopause
	Gestational diabetes
	Gestational hypertension
	Preeclampsia
	Preterm delivery
	Delivery of infants small for gestational age
CAC patterns in women vs men	Lower prevalence of detectable CAC across age deciles
	Older age when CAC detectable (~10 yr later in women than in men)
	Fewer calcified lesions
	Fewer calcified vessels
	Lower CAC volume
	Larger lesions and higher mean plaque density in women than in men with detectable CAC
CAC as predictor of CV death	Similar long-term CV mortality rates for men and women ***without*** detectable CAC
	A 1.3-fold higher hazard rate for CV death in women than in men ***with*** detectable CAC
ASCVD risk perception	Women ***less*** likely to:
	Receive statins
	Receive statins at guideline-specified dosages
	Believe statin therapy is safe and effective
	Women ***more*** likely to:
	Worry about heart attack or stroke
	Discontinue statin therapy because of side effects

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CV = cardiovascular

was less prevalent in women than in men.[5] The proportion of females with detectable CAC notably increased at around 46 years of age, approximately 10 years later than in males. Across subgroups stratified by CAC score in Hounsfield units (1–100, 101–399, >400), females had fewer calcified lesions, fewer calcified vessels, and lower CAC volume. In a subgroup of patients with detectable CAC, however, females had larger lesions and denser plaques. Moreover, the hazard rate for long-term CV death was similar (P=0.67) for males and females *without* detectable CAC, but 1.3-fold higher for females than for males *with* detectable CAC (P <0.001).[5] These data suggest that men and women with detectable CAC differ in their coronary artery atherosclerotic plaque patterns and their long-term CVD risk.

Statin Therapy

Statin therapy appears to be equally beneficial to men and women in preventing ASCVD. In a meta-analysis of 27 statin therapy trials, the proportional reduction in major vascular events per 1.0 mmol/L (~39 mg/dL) reduction in low-density-lipoprotein (LDL) cholesterol was similar for men and women and showed no sex-related heterogeneity.[6] The proportional reductions in coronary events, coronary revascularization, and stroke were also similar for both sexes.[6]

ASCVD Risk Perception in Women

Women receive less aggressive lipid management than men, even in the modern age of cardiovascular care. In the Patient and Provider Assessment of Lipid Management (PALM) Registry, 5,618 participants—43% of them female—were eligible for statin therapy according to the 2013 ACC/AHA cholesterol guideline for primary and secondary prevention.[7] However, females were significantly less likely than males to be treated with a statin (67% vs 78%, P <0.001) or to receive one at a guideline-recommended intensity (35% vs 44%, P <0.001). Women were also more likely to say that they occasionally or often worry about heart attack or stroke

(45.7% vs 34.4%, P <0.001), but were less likely to believe that people with high cholesterol are at higher risk of a heart attack. Furthermore, women were less likely than men to believe that statins are safe (47.9% vs 55.2%, P <0.001) or effective (67.9% vs 73.1%, P <0.001) and more likely to discontinue a statin because of side effects.[7]

Conclusion

Pooled cohort equations, by providing separate risk equations for women, enable female patients to be evaluated more specifically for ASCVD risk. This risk assessment can be further personalized by considering risk enhancers specific to women. Coronary artery calcium is predictive of ASCVD events in both sexes, although it is usually detected in women years later than in men. Better education and communication by clinicians are needed to address women's concerns about statin safety and effectiveness and to lessen the disparity in lipid management between the sexes.

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