

Detecting and Managing ASCVD in Women: A Focus on Statins

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LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Summarize important findings and trends involving women and atherosclerotic cardiovascular disease (ASCVD).
- Characterize the multiple cardiometabolic changes that occur during menopause and the associated ASCVD risk.
- Discuss the challenges of assessing ASCVD risk and dyslipidemia management in women.
- Identify women with elevated ASCVD risk and implement guideline-recommended statin therapy.

KEY TAKEAWAYS

- ASCVD remains the leading cause of death among women, with a stagnation

in downward ASCVD trends noted over the past decade.¹

- ASCVD has traditionally been viewed as a “male disease,” with research gaps in our knowledge of ASCVD in women resulting in underdiagnosis and undertreatment.¹
- Risk stratification in primary prevention in women is more challenging than in men because of unique risk factors and underestimation of ASCVD risk with 10-year risk scoring.¹⁻⁴
- No clinically relevant differences appear between sexes regarding safety, efficacy, and outcomes with statin therapy.^{1,3}
- Guideline-recommended therapy to manage low-density lipoprotein cholesterol (LDL-C) in women is similar to that for men, but consideration of sex-specific risk factors and common risk-enhancing factors, to better inform risk, is imperative.³⁻⁵

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CASE SCENARIO

A 52-year-old white female with a history of gestational diabetes mellitus (GDM), fibromyalgia, post-traumatic stress disorder, and major depression presents to the clinic. Her lipid panel has previously been unremarkable with low-density lipoprotein cholesterol (LDL-C) levels of <100 mg/dL, but since menopause she has gained 30 pounds and “lacks the energy to exercise.” To better risk stratify and due to premature cardiovascular (CV) events in both parents, a coronary artery calcium (CAC) scan is performed.

Key information

- **Cholesterol (mg/dL):** total cholesterol 215, LDL-C 135, high-density lipoprotein cholesterol (HDL-C) 57, triglycerides 115, non-HDL-C 158
- Blood pressure 116/72 mm Hg, glycated hemoglobin (HbA1c) 6.2%, C-reactive protein (CRP) 4.5 mg/L (<3 mg/L)
- Body mass index 26.8 kg/m², negative for tobacco or alcohol use
- **Current medications:** gabapentin, tramadol, estradiol patch, fluoxetine
- American College of Cardiology (ACC)/American Heart Association (AHA) 10-year atherosclerotic cardiovascular disease (ASCVD) risk=1.3%
- CAC score=73 (>90th percentile for age)

INTRODUCTION

Despite manifesting approximately 10 years later in women than in men, ASCVD remains the leading cause of mortality among women.^{1,6} As a relative comparison, ASCVD accounts for 35% of all deaths, compared to 2.6% for breast cancer,⁷ with ischemic heart disease and stroke being the most common subtypes of ASCVD.¹ Although ASCVD usually manifests later in women, one-third of CV events occur among those <65 years of age.⁶

Currently, ASCVD in women is understudied, underdiagnosed, and undertreated. The traditional view of ASCVD as primarily a “disease of men” has led to decades of poor representation of women in ASCVD research, including clinical trials.¹ As a result, there is now a limited understanding of sex differences (eg, in mechanisms and pathophysiology), ultimately resulting in higher rates of hospitalizations and mortality among women compared to men.^{1,2,8} Overall, ASCVD mortality has dropped markedly since the 1970s in both sexes.⁶ However, among women, ASCVD mortality has stagnated over the past decade and is even increasing in certain populations, including younger women.^{9,10} A major

concern is whether these disturbing trends will continue to uptick due to the rise in obesity and diabetes mellitus (DM) and the frequent utilization of e-cigarettes (ie, vaping) among young females.¹ These statistics prompted the formation of multiple initiatives to better understand and prevent ASCVD in women. Such programs include a state-of-the-art review on women and ASCVD from the ACC's CVD in Women Committee,¹¹ the "Follow YOUR Heart" campaign to empower older women with human immunodeficiency virus (HIV) to participate in ASCVD research,¹² and formation of the *Lancet* women and cardiovascular disease Commission.¹ Collectively, these initiatives focus on the unmet need to reduce the global burden of ASCVD among women.¹ The existing knowledge gaps, sex-specific differences, and trends present concerns and unique challenges for practitioners.

The goal of this article is to provide a guide for primary care clinicians to identify women at elevated ASCVD risk, with an end goal of reducing CV events and mortality with appropriate statin therapy.

DYSLIPIDEMIA ACROSS THE FEMALE LIFESPAN

Premenopausal women typically have favorable lipid profiles compared to men. Overall values of major lipoproteins including total cholesterol and LDL-C are usually lower, while HDL-C levels are ~10 mg/dL higher.¹³ However, menopause is a transitional period that often results in multiple negative metabolic changes that increase ASCVD risk. For example, a sharp increase in LDL-C levels coupled with a shift to the more atherogenic small, dense LDL-C results in an increase in LDL particle number.^{14,15} Other ASCVD risk factors often worsen or manifest during menopause, including weight gain, usually involving a pattern of central obesity, hypertension, and metabolic syndrome.² The utilization of estrogen replacement therapy reverses some of the lipoprotein changes and is unique in that it is one of only a few treatments effective at lowering lipoprotein(a).³ Nonetheless, randomized controlled trials involving hormone replacement therapy (HRT) have not confirmed CV benefit,¹ and a major study demonstrated a small but significant increase in ASCVD.¹⁶ Accordingly, HRT is not indicated for primary or secondary prevention of ASCVD and should be discontinued among women with existing ASCVD.^{1,5}

OUTCOME DATA—AVAILABLE EVIDENCE IN WOMEN

Early cardiovascular outcome trials (CVOTs) failed to enroll a substantial proportion of women, resulting in underrepresentation¹ and the inability to demonstrate sex-specific benefits. This fueled the idea that statins do not reduce CV events

when used in primary prevention among women. Presently, a host of outcome data are available that are specific to women.^{3,5,15} Numerous analyses indicate that women experience similar LDL-C reductions with statin therapy to those of men.^{2,17} More importantly, a 2013 Cochrane analysis reported that statins reduce ASCVD, total mortality, and the need for revascularization in primary prevention among women, similar to their male counterparts.¹⁸ These findings are further supported by the more comprehensive 2015 Cholesterol Treatment Trialists' Collaboration, which involved nearly 50,000 women.¹⁷ This meta-analysis evaluated statin vs placebo and more intensive compared to less intensive statin therapy among primary and secondary prevention patients. Overall, the investigators concluded that for every 1-mmol/L (39-mg/dL) reduction in LDL-C, proportional reductions in major adverse cardiovascular events and total mortality, and occurrence of adverse events (AEs), did not differ by sex.

In summary, despite early CVOT shortcomings, current data indicate that no clinically relevant differences exist between sexes regarding safety, efficacy, and outcomes with statin therapy.

CLINICAL ASSESSMENT AND CHALLENGES

In the clinical world, statins are underutilized and underdosed in women, creating disparities in the quality of CV care.¹ This is supported by findings indicating that women are less often treated with guideline-recommended therapies, including statins.^{19,20} These differences may be explained by challenges with ASCVD risk estimation, including assessment models that underestimate ASCVD risk in women.^{21,22} For example, risk stratification is arguably more complicated in females because of unique and sex-specific risk factors. These factors are not incorporated in common risk assessment models such as the Framingham Risk Score, resulting in ASCVD underestimation by the assessment tool, and possibly the clinician.

Major CV risk factors are critical for risk stratification in women (**TABLE 1**).^{1,2,23-26} Importantly, hypertension, dyslipidemia, DM, and smoking are all associated with higher CV event rates in women compared to men.^{1,2} Similarly, obesity and insufficient physical activity are more prevalent among women,¹ making them more likely to develop metabolic syndrome. A history of sex-specific factors associated with elevated ASCVD risk, including premature menopause or pregnancy-related complications, further confounds risk assessment. In addition, underrecognized CV risk factors or risk-enhancing factors may disproportionately affect women. Inflammatory-driven autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythemato-

TABLE 1. ASCVD risk factors in women^{1-3,23-26}

Category	Risk factor	Comments
Traditional	<ul style="list-style-type: none"> • Hypertension • Dyslipidemia • DM • Smoking 	<ul style="list-style-type: none"> • Major risk factors all associated with increased CV event rates compared to men; DM also associated with higher mortality • The prevalence of smoking, including e-cigs, is high among young women
Risk-enhancing ^a	<ul style="list-style-type: none"> • Autoimmune disorders (RA, SLE) • Increased systemic inflammation • Race/ethnicity (eg, South Asian) • Elevated lipoprotein(a) • Chronic kidney disease • Family history of premature ASCVD • Metabolic syndrome • Human immunodeficiency virus 	<ul style="list-style-type: none"> • Females account for nearly 80% of all autoimmune disorders • Chronic inflammation = increased ASCVD
Sex-specific	<ul style="list-style-type: none"> • Premature menopause (<40 years old) • Preeclampsia or preterm labor • Gestational DM • Low-birthweight infant 	<ul style="list-style-type: none"> • Premature menopause and preeclampsia are also classified as “risk-enhancing” factors
Underrecognized	<ul style="list-style-type: none"> • Psychosocial <ul style="list-style-type: none"> - Mood disorders, stress • Environmental/social factors 	<ul style="list-style-type: none"> • Women have increased rates of depression, anxiety, and perceived stress and are more likely to be victims of abuse and intimate partner violence • ASCVD risk and mortality are inversely related to socioeconomic status

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DM, diabetes mellitus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

^aDefined as a clinical condition or factor that is associated with ASCVD used to inform therapy decisions.

sus, have demonstrated accelerated atherosclerosis and increased ASCVD risk,^{3,5,27} while several psychosocial and environmental factors linked to ASCVD are more common among women.¹ A key message to emphasize among primary care clinicians is to utilize other tools when ASCVD risk is uncertain. Imaging modalities such as measuring carotid intima media thickness or, more commonly, CAC can provide substantial insight (eg, visualization of atherosclerosis) for risk stratification to further guide treatment.^{3,5}

Sex differences also exist regarding medication adherence and AEs. Women are more likely to be non-adherent with statin therapy while experiencing higher rates of medication-related side effects.^{2,28} Statin-associated myalgia (SAM) is the most commonly reported

AE,^{3,5} and the agents have also demonstrated a negative impact on energy and fatigue.²⁹ Factors that may influence predisposition to SAMs or other side effects compared to men include females having more concern regarding drug-related AEs,²⁸ potentially higher susceptibility to statin-associated fatigue and reduced energy,² and also a higher prevalence of hypothyroidism, in which the associated muscle symptoms may be misinterpreted as SAMs.³⁰ Another important factor to consider when prescribing drug therapy to women for managing dyslipidemia is childbearing potential. Recently, the Food and Drug Administration has softened the language surrounding statins and pregnancy.³¹ In essence, statins should generally be avoided during pregnancy, unless the patient is

TABLE 2. 2018 ACC/AHA Guideline on the Management of Cholesterol (women)³

Risk category	Recommendations
Clinical ASCVD or FH (LDL-C of ≥190 mg/dL)	<ul style="list-style-type: none"> • High-intensity statin ± ezetimibe to achieve LDL-C reduction of ≥50% • LDL-C goals (<i>ideal</i>) <ul style="list-style-type: none"> - (+) ASCVD: <70 mg/dL - (+) FH: <100 mg/dL
DM (40-75 years old)	<ul style="list-style-type: none"> • Moderate-intensity statin <i>regardless</i> of 10-year ASCVD risk • If DM + multiple risk factors: high-intensity statin to achieve LDL-C reduction of ≥50%
Primary prevention (40-75 years old)	<p><i>Most challenging group for risk estimation/stratification</i></p> <ul style="list-style-type: none"> • Use 10-year ASCVD risk calculator (<i>often underestimated in women</i>) <ul style="list-style-type: none"> - 5% to 7.5%: <i>consider</i> moderate-intensity statin - 7.5% to <20%: <i>favors</i> moderate-intensity statin - ≥20%: <i>initiate</i> statin to reduce LDL-C ≥50% • Factor in ASCVD risk enhancers* (<i>to better inform risk</i>) <ul style="list-style-type: none"> - Specific to women: preeclampsia, premature menopause - Family history of premature ASCVD, inflammatory diseases, CKD, HIV, metabolic syndrome, certain race/ethnicity (eg, South Asian) • If risk decision is uncertain: consider CAC in certain adults <ul style="list-style-type: none"> - CAC 0: statin <i>not indicated</i> unless: (+) tobacco, (+) DM, or strong family history of premature ASCVD - CAC 1 to 99: <i>favors</i> statin - CAC ≥100 and/or 75th percentile: <i>initiate</i> statin

TLCs including smoking cessation, moderate-intensity physical activity, and achieving and maintaining desired body weight are considered initial treatment for all women with dyslipidemia.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; TLC, therapeutic lifestyle change.

*Defined as a clinical condition or factor that is associated with ASCVD used to inform therapy decisions.

at very high risk for ASCVD (eg, previous CV event). The agency also communicated that statins are safe in women who are not pregnant but could become pregnant, noting that unintended exposure to statins during early pregnancy is unlikely to harm the fetus. Breastfeeding is not recommended while on statin therapy.

GUIDELINE-RECOMMENDED THERAPY

Early detection and management of dyslipidemia and other common cardiometabolic comorbidities is critical for preventing premature CV events and mortality in women.¹ An initial emphasis on therapeutic lifestyle changes (TLCs) is

recommended for all women with dyslipidemia, regardless of ASCVD risk category.^{3,5} Women are more prone to physical inactivity compared to men,¹ and TLCs can address many of the common cardiometabolic conditions strongly associated with menopause. Implementing components of the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets along with 150 minutes of physical activity per week can provide moderate improvements in numerous CV markers and reduce overall ASCVD risk.^{3,5}

Major cholesterol guidelines recommend similar approaches to managing dyslipidemia regardless of sex.^{3,5} **TABLE 2** provides treatment recommendations from the 2018

ACC/AHA Guideline on the Management of Blood Cholesterol, with recommendations specific to women incorporated.³ Major risk categories include those with clinical ASCVD or familial hypercholesterolemia (FH), adults with DM, and—the most challenging to risk stratify—primary prevention. The importance of treating women with a history of ASCVD with high-intensity statin therapy is widely recognized.^{3,5} The inherent ASCVD risk associated with FH and DM and the benefit of statin treatment are also established.^{3,5} Particularly challenging is identifying female patients who fall outside these categories and have unremarkable 10-year ASCVD risk scores. Tools available to improve risk stratification and guide therapy include utilizing risk-enhancing factors to better inform ASCVD risk and measuring CAC to visualize atherosclerosis in this population.³

CASE SCENARIO (CONT'D)

This case illustrates the numerous cardiometabolic changes (eg, weight gain, elevation in LDL-C, prediabetes) that can occur with menopause. It shows how sex-specific and underrecognized risk factors and risk-enhancing factors (eg, GDM, psychosocial stressors, family history of premature ASCVD) can contribute to atherosclerosis and ASCVD risk. The 10-year ASCVD risk score fails to capture her actual CV risk, as the elevated CAC indicates significant subclinical atherosclerosis and elevated risk for a CV event.^{3,5} Guideline recommendations would include aggressive TLCs to improve lipoproteins and limit additional weight gain and the development of type 2 DM. Moderate- to high-intensity statin therapy should be strongly considered given her risk factors and evidence of subclinical disease.

SUMMARY

ASCVD remains the primary cause of death among women. Additional concern stems from disturbing trends displaying a plateau in mortality and even an increase in CV events among younger women. These factors prompted the formation of multiple initiatives aimed at reducing ASCVD in women. Statins are the drugs of choice for managing LDL-C in women because data indicate that the agents are safe, effective, and reduce vascular events and mortality, similar to the agents' effect in men. Clinicians must be cognizant of the unique and sex-specific risk factors in women and the numerous negative cardiometabolic effects that manifest or worsen with menopause. Such awareness will identify women with elevated ASCVD risk, resulting in enhanced lipid management and, ultimately, reductions in premature CV morbidity and mortality. ●

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