Statin treatment considerations for cardiovascular disease prevention

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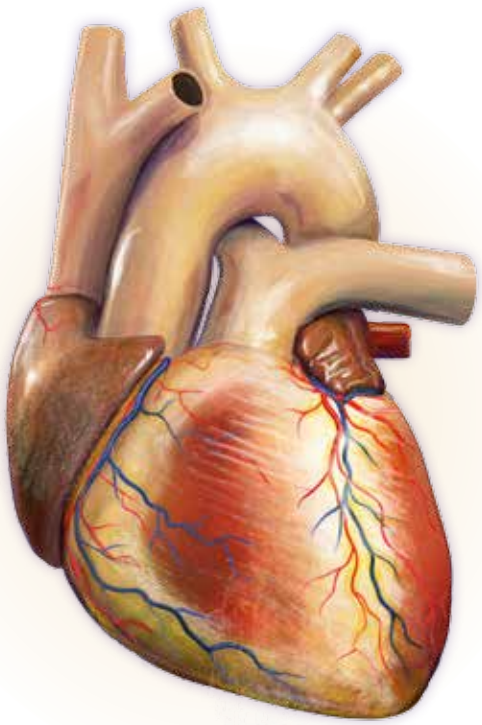
Current evidence-based guidelines support the use of statin drugs for primary prevention of cardiovascular (CV) events based on individual CV risk profiles rather than on target cholesterol levels. The purpose of this article is to increase awareness of the impact of CV disease in women and to discuss evidence-based guidelines for the use of statin drugs to decrease CV events in this population.



Heart illustration, provided by Michael F. Higgins

Heart disease is the No. 1 killer of women in the United States, accounting for nearly 400,000 deaths in 2013 and about one-third of deaths among women.[1] Although cardiovascular (CV)-related mortality has declined in the past 30 years, recent data show that this decline has leveled off, especially among women younger than 55 years.[1] Women who are at risk for developing cardiovascular disease (CVD)—a large percentage of the female population—are less likely than their male counterparts to receive preventive treatment.[2] If at-risk women are prescribed preventive treatment, it is generally less aggressive than that prescribed for men, and less likely to achieve optimal results.[2]

Women have many of the same risk factors for CVD as do men, including non-modifiable risk factors such as age and family history and modifiable ones such as smoking, overweight/obesity, physical inactivity, hypertension, dyslipidemia, and diabetes mellitus (DM).[1] Additional risk factors specific to women include history of preterm delivery, hypertensive pregnancy disorders, gestational diabetes, persistence of weight gain after pregnancy, and menopause. Autoimmune diseases, more common in women than in men, as well as radiation and chemotherapy for breast cancer, also increase CVD risk in women. Depression, especially in younger women, increases the lifelong risk of developing CVD.

In an October 2018 opinion, the American College of Obstetricians and Gynecologists (ACOG) stated that women's healthcare providers (HCPs) have an opportunity to influence the health of women across the lifespan.[3] ACOG recommends including preventive health screening and counseling in routine wellness checkups for women of all ages.[3] Women's healthcare visits should include a comprehensive personal and family health history and assessment of personal risk factors, including those for CVD.

Statin overview

One of the major treatable causes of CVD and stroke is dyslipidemia. Recent reports support the efficacy of prescribing statins to treat dyslipidemia and prevent CVD events.[4] Based on a hallmark 2013 guideline for managing blood cholesterol levels, the American College of Cardiology (ACC) reported that 56 million adults aged 40-75 years in the United States were eligible for statin therapy.[5,6] With the growing and aging population in the U.S., this number is no doubt even higher in 2019.

The changing focus of statin treatment

Over the years, treatment with statins has focused on reaching a person's target low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels, which are based on a personal CVD risk profile (more on this later).[5] Recent reports have

supported a change in dyslipidemia treatment focus, with an emphasis on primary and secondary prevention of CV events in persons at risk for them and prescribing statins to certain populations.[7] In 2017, guidelines for treatment of elevated cholesterol levels from the ACC and the American Heart Association (AHA) suggested a fundamental shift in hyperlipidemia treatment from focusing mainly on LDL-C values to using appropriate statin dosages in target benefit groups.[7] Based on this hallmark publication by the ACC/AHA, many more women now qualify for treatment with statins based on risk determinations. In addition, the new guidelines support less use of the older non-statin drugs (e.g., fibrates, nicotinic acid, bile-acid sequestrants).[7]

The new 2018 ACC/AHA guideline update suggests that no ideal target blood level for LDL-C exists.[2] The principle is that *lower is better* for LDL-C, and that an optimal total cholesterol (TC) level is about 150 mg/dL, with LDL-C at or below 100 mg/dL.[2] Adults with lower LDL-C levels have lower rates of heart disease and stroke.[2]

Cardiovascular benefits of statin therapy

Significant reduction of CV morbidity/mortality with statin drug use has been reported in multiple randomized controlled trials. Statins improve dyslipidemia, reduce the risk of myocardial events, lower stroke risk, reduce LDL-C and triglyceride levels, and raise HDL-C levels.[8]

High- or moderate-dosage statins, with the choice of dosage depending on a person's 10-year CVD risk, are used for primary CVD prevention (i.e., prevention of CVD and CVD-related events in persons who have never had CVD). Use of statins as secondary CVD prevention (i.e., to reduce the impact of CVD in individuals who already have the disease) is supported by findings of a reduced risk of major CV events with statin treatment and achievement of low levels of LDL-C, non-HDL-C, and apolipoprotein B, an atherogenic lipoprotein.[8]

Risk assessment

The **2018 Prevention Guidelines Tool CV Risk Calculator**[A], developed by the ACC/AHA, is used to estimate a person's 10-year atherosclerotic cardiovascular disease (ASCVD) risk.[2] The ASCVD risk calculator considers age, cholesterol level, and blood pressure. The ACC/AHA guideline suggests prescribing statins such as atorvastatin or rosuvastatin to any person aged 40-75 years whose 10-year risk for developing CVD is >7.5%.[7] A **patient self-administered risk calculator**[B] is also available.[2]

Box 1. ACC/AHA recommendations regarding CV history, risk status, and statin use[9]

- In patients with clinical ASCVD, reduce LDL–C with high–intensity statins or maximally tolerated statins to decrease ASCVD risk.
- In patients with very high–risk ASCVD, use an LDL–C threshold of 70 mg/dL to consider addition of non–statins to statins.
- In patients with severe primary hypercholesterolemia (LDL–C level ≥190 mg/dL without calculating 10–year ASCVD risk), begin high–intensity statin therapy.
- In patients aged 40–75 years with DM and an LDL–C ≥70 mg/dL, start moderate–intensity statins without calculating 10–year ASCVD risk. In patients with DM at higher risk, especially those with multiple risk factors or those aged 50–75 years, it is reasonable to use a high–intensity statin to reduce the LDL–C level by ≥50%.
- In adults aged 40–75 years without DM and with LDL–C levels ≥70 mg/dL and a 10–year ASCVD risk ≥7.5%, start a moderate–intensity statin if a discussion of treatment options favors statin therapy.
- In adults aged 40–75 years without DM and 10–year ASCVD risk 5%–19.9%, risk–enhancing factors favor initiation of statin therapy.
- In adults aged 40–75 years without DM and an LDL–C 70 mg/dL–89 mg/dL and a 10–year ASCVD risk 7.5%–19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CV, cardiovascular; DM, diabetes mellitus; LDL–C, low–density lipoprotein.

Prescribing statins: General recommendations

The 2018 ACC/AHA guidelines focus more on *intensity of statin therapy* and less on LDL-C goals and use of non-statin lipid-lowering agents. More specific recommendations regarding statin dosing depend on a person's history and CVD risk status (*Box 1*).[9]

The ACC/AHA recommendations for statins for most individuals involve *starting with the appropriate dosage*; no evidence supports the previous recommendation to start low and titrate the dosage upward. In the U.S., seven statins are available to treat high cholesterol or prevent cardiovascular events. *Box 2* lists these statins and the dosing for each category (high, moderate, low) if applicable.[7]

Additional considerations

Along with prescribing statins when indicated, HCPs should recommend lifestyle changes such as following a heart-healthy diet, getting regular exercise, and maintaining an appropriate weight. Despite the lifestyle interventions and a course of statin therapy, some women may find that they do not tolerate statins or

Box 2. Statin dosing[7]

High-dose (mean LDL-C reduction ≥50%)	Moderate-dose (mean LDL-C reduction 30% to <50%)	Low-dose (mean LDL-C reduction <30%
Atorvastatin 40-80 mg/day	Atorvastatin 10–20 mg/day	Fluvastatin 20–40 mg/day
Rosuvastatin 20-40 mg/day	Fluvastatin 40 mg twice daily or 80 mg XL once daily	Lovastatin 20 mg/day
	Lovastatin 40 mg/day	Pitavastatin 1 mg/day
	Pitavastatin 2-4 mg/day	Pravastatin 10-20 mg/day
	Pravastatin 40-80 mg/day Rosuvastatin 5-10 mg/day Simvastatin 20-40 mg/day	Simvastatin 10 mg/day

Note: Recommended doses are for individuals with normal renal function and no interacting medications.

that they fall into one of the following groups: patients who fail to meet LDL-C goals despite maximally tolerated statin therapy, those with recurrent CV events despite maximally tolerated statin therapy, those with significant co-morbidities or high 10-year risk, or those with familial hypercholesterolemia (FH).[7]

In these cases, patients should be referred to a cardiologist for consideration for additional therapies—in particular, one of the newer second-line cholesterol-lowering therapies.[7] These second-line options include ezetimibe, which works in the small intestine to block absorption of cholesterol from the diet,[10] and the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, which increase elimination of LDL from the circulation by blocking the PCSK9 enzyme reduction of LDL-C receptors on liver cells.[11] The FDA has approved two PCSK9 inhibitors, alirocumab and evolocumab, as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous FH or ASCVD who require additional lowering of LDL-C.[7]

Laboratory workup

Before starting a woman on a statin, HCPs should evaluate her use of other medications that might interact adversely with a statin.[7] In addition, HCPs should check her baseline liver function (aminotransferase levels) and kidney function and assess for and document any pre-existing muscle symptoms. Checking a baseline creatine kinase in women at increased risk for myopathy is suggested.[7] Women eligible to start a statin regimen should undergo a fasting lipid panel (TC, HDL-C, calculated LDL-C, triglycerides) at baseline, repeated in 4-12 weeks after initiation or dose adjustment and every 3-12 months as indicated.[7]

In addition to developing lab test abnormalities, some women may experience other adverse effects of statin treatment. Muscle-related symptoms are the most commonly reported event.[7] A thorough evaluation of possible statin-related effects is needed. Myalgias are consistent with statin use. Once the adverse effects and their severity, as well as other factors related to intolerance, are established, women can try a lower dose of the same statin or switch to a different statin.[7] In a woman who experiences severe muscle symptoms after a statin has been started, HCPs should consider the possibility of rhabdomyolysis, ask her to (perhaps temporarily) discontinue the statin, and check her creatinine level and perform a urinalysis to rule out rhabdomyolysis.

Conclusion

Cardiovascular disease is a serious health concern for women. Current guidelines indicate that all adults should be evaluated for CV risk and, if eligible, should receive statin therapy as primary prevention against CVD. Recent reports of statins' benefits in primary and secondary prevention of CVD support their use. The statin should be dosed based on a woman's CV risk, rather than titrating it to specific cholesterol targets. Statins lower levels of atherogenic lipoproteins and reduce CV event-related morbidity and mortality. In most individuals, the benefits of statins outweigh the risks.

Janis R. Guilbeau and Cynthia S. Watson are nursing faculty at the University of Louisiana at Lafayette. The authors state that they do not have a financial interest in or other relationship with any commercial product named in this article.

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Web resources

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B. ccccalculator.ccctracker.com/