Cardiovascular Risk Factors and Disease in Women

Sharon K. Gill, MD

KEYWORDS
- ASCVD • Heart disease • Stroke • Risk factors • Women • Prevention

KEY POINTS
- Use American Heart Association (AHA) and American College of Cardiology (ACC) guidelines and calculator to assess atherosclerotic cardiovascular disease (ASCVD) risk.
- Use evidence-based recommendations to counsel women on risk reduction strategies.
- Statin medications reduce risk for women at elevated risk but have important adverse effects to discuss with patients.
- Women have unique cardiovascular disease (CVD) risk factors, including hypertensive disorders of pregnancy, polycystic ovarian syndrome (PCOS), and migraine.

DEFINITIONS

Cardiovascular Disease

CVD means damage to or narrowing of arteries due to atherosclerosis. Therefore, it is a systemic disease that can lead to a variety of end-organ manifestations:

- Coronary artery disease (CAD) with or without acute coronary syndrome
- Heart failure (ischemic)
- Arrhythmia (atrial fibrillation)
- Stroke (especially related to carotid artery stenosis and cerebrovascular disease)
- Peripheral vascular disease (PVD)
- Aortic aneurysm
- Chronic kidney disease (CKD)

For purposes of discussing risk factors and primary prevention, CVD does not include valvular disease, pericarditis, endocarditis, nonischemic cardiomyopathy, or other arrhythmia (eg, supraventricular tachycardia).
**Statin**

Statin is a medication class that inhibits HMG CoA reductase, thus blocking a key step in cholesterol synthesis. Originally used primarily to lower cholesterol, especially low-density lipoprotein (LDL), recently it has been found to lower overall ASCVD risk via incompletely understood beneficial effects on endothelial function, inflammation, and plaque stabilization.¹

**Primary Prevention**

Primary prevention refers to preventing development of a disease state that a person does not already have. In cases of ASCVD, it refers to preventing a first coronary event or stroke in a person not known to have ASCVD.

**Secondary Prevention**

Secondary prevention refers to preventing subsequent events or symptoms in a person known to have a disease.

**Polycystic Ovary Syndrome**

PCOS is a heterogeneous disorder of unknown etiology characterized by hyperandrogenism and anovulation, which present as insulin resistance, menstrual irregularity, infertility, obesity, hirsutism, and/or acne.

**Number Needed to Treat**

Number needed to treat (NNT) is a statistical representation of the likelihood of beneficial effect of a treatment, or “How many patients do I need to treat before I can expect to prevent 1 adverse outcome?” It is calculated from the absolute risk reduction: 1/(adverse outcome rate with placebo – adverse outcome rate with treatment). For example, in a randomized controlled trial, if that study’s adverse outcome occurred in 5% of patients in the medication-treated group and 10% of patients in the placebo group, then NNT = 20.

**Number Needed to Harm**

Number needed to harm (NNH) is a statistical representation of the likelihood of a patient experiencing an adverse effect of an intervention, calculated from absolute harm reduction: 1/(adverse event rate with treatment – adverse event rate with placebo).

**INTRODUCTION**

CVD and stroke are the most frequent causes of death in women. Knowledge among women themselves has improved (from 30% to 56% from 1997 to 2012), but this still leaves approximately half of women unaware that they are at highest risk of dying from heart disease or stroke as opposed to other causes, such as cancer (Table 1).²

Reducing cardiovascular risk in women may initially evoke questions, such as “When should we start aspirin in a diabetic woman?” and, “In whom should we start a statin?” These are important questions, but addressing CVD prevention completely must start much earlier, with questions for young women, such as, “Are your periods regular?” and “Did you have high blood pressure during pregnancy?” Obesity, smoking, PCOS, migraine history, and pregnancy complications should all be considered when assessing current and future cardiovascular risk and advising young women about choices that lead to lower versus higher risk later in life. For all women, the usual culprits must be addressed: obesity, smoking, hypertension (HTN), and
diabetes. This article reviews current evidence on ASCVD risk factors as they pertain to women and presents information that is most useful for educating and counseling women on what they can do to reduce their risk of an ASCVD event.

RISK FACTOR ASSESSMENT

In November 2013, the AHA and ACC released new guidelines for assessing risk of ASCVD and treating based on multiple risk factors.3,4 The approach to risk factor assessment and modification shifted focus from treat to target (LDL cholesterol) to overall risk factor assessment (Box 1).5

Using albeit a controversial calculation, 10-year and lifetime risk of an ASCVD event can be calculated based on well-established and readily available risk factors. An ASCVD event comprises nonfatal myocardial infarction (MI), coronary heart disease (CHD)-related death, or stroke (fatal or nonfatal). A person who meets high-risk criteria or whose 10-year ASCVD event risk exceeds 7.5% should receive a recommendation for statin medication. Statin therapy is estimated to reduce 10-year ASCVD risk by 30% for moderate-intensity and 45% for high-intensity statin. For example, if 10-year ASCVD event risk for a nondiabetic is 12%, taking a statin reduces 10-year risk to approximately 8%. Additionally, the calculator can be used as part of a clinic visit to demonstrate the effect of risk factor modification on an individual’s ASCVD 10-year and lifetime risk level (eg, quitting smoking or exercising to control blood

<table>
<thead>
<tr>
<th>Table 1 Causes of death in women</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Heart disease + stroke</td>
</tr>
<tr>
<td>Heart disease</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Stroke</td>
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<tr>
<td>Chronic lower respiratory diseases</td>
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<tr>
<td>Unintentional injuries</td>
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<tr>
<td>Suicide</td>
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<tr>
<td>Influenza and pneumonia</td>
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<tr>
<td>Kidney disease</td>
</tr>
<tr>
<td>Septicemia</td>
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</tbody>
</table>

pressure [BP]). The calculator is available via the AHA Web site in multiple formats (http://my.americanheart.org/cvriskcalculator) (Box 2, Table 2, Box 3).

Diabetes is a stronger predictor of CVD in women than in men.6,7 Women who smoke even a small amount (1–4 cigarettes per day) double their CAD risk.8 In women, low high-density lipoprotein (HDL) seems a stronger predictor of CVD than high LDL.9,10 Because there is no current evidence that raising HDL via medication has a meaningful effect on lowering ASCVD risk, and recent evidence is mounting for excess harm with niacin, the ability to focus interventions for women based on this information is limited.11–13 Exercise and heart-healthy diet may have some beneficial effect on HDL, and these lifestyle interventions are globally recommended for general ASCVD risk reduction.

Lifetime risk calculation is not linked to specific medication or other treatment recommendations; rather, it can be useful in young adults to highlight the importance of risk factor modification. For example, a 35-year-old woman who is overweight, has newly diagnosed diabetes, and smokes but has normal BP and cholesterol values can be counseled that her lifetime ASCVD risk would drop from 50% to 27% if she quit smoking and lost enough weight to reverse the early diabetes. A sedentary 35-year-old woman who smokes and has a systolic BP 130 (untreated) could reduce her lifetime ASCVD risk from 39% to 8% if she quit smoking and lowered her BP to under 120 via regular exercise and weight loss; this profile represents “optimal risk factors.”14–21 Box 4 illustrates risk reduction counseling in terms of added disease-free years of life with optimized risk factors.22

**Special Considerations for Older Women**

- There are not enough women (or men) ages 75 years or older in studies to make strong conclusions about statin use.
- For secondary prevention, use a moderate-intensity instead of a high-intensity statin.
- Consider starting statin for primary prevention, depending on comorbidities.
- Continue statin if already taking and tolerating.

**Box 2**
**Data needed for statin recommendation assessment with the American Heart Association calculator**

| History of preexisting ASCVD (CAD, PVD, or stroke) |
| Age |
| Gender |
| Race |
| Total cholesterol |
| HDL cholesterol |
| Systolic BP |
| Use of hypertensive medications |
| Diabetes |
| Smoking (current) |

Notes on the risk factors: women overall have a lower risk of an ASCVD event. Race is represented only by black or white. Hispanic Americans and Asian Americans generally have lower risk than whites, so using “white” is the best estimate but may overestimate risk.
Do not calculate ASCVD risk score for women over 75; even with optimal risk factors, their 10-year ASCVD risk is 12% or more.

Atrial fibrillation substantially increases stroke risk; use the CHADS2 or CHA2DS2-VASc calculator to quantify this risk and make an anticoagulation recommendation. Female gender is a risk factor for stroke, particularly in women over 65, and is included as a risk factor in the newer CHA2DS2-VASc calculation. The 2014 American Stroke Association (ASA)/AHA stroke prevention guidelines for women recommend screening for atrial fibrillation in women 65 and older to prevent stroke. Initial screen is pulse check, followed by ECG if abnormal.

Additional Risk Factors

Even though these additional tests are not used to calculate a risk number nor should they be done routinely for risk assessment, the AHA/ACC guidelines recommend considering these other factors/tests if the risk calculation is borderline or unclear:

- Primary LDL cholesterol ≥160 mg/dL or other evidence of genetic hyperlipidemias
- Family history of premature ASCVD with onset less than 55 years of age in a first-degree male relative or less than 65 years of age in a first-degree female relative

### Table 2
Race/ethnicity and cardiovascular disease–related causes of death in women

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Heart Disease (%)</th>
<th>Stroke (%)</th>
<th>Diabetes (%)</th>
<th>Kidney Disease (%)</th>
<th>Hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>24.1</td>
<td>6.4</td>
<td>4.6</td>
<td>3.4</td>
<td>2.1</td>
</tr>
<tr>
<td>White</td>
<td>23.5</td>
<td>6.2</td>
<td>2.4</td>
<td>1.9</td>
<td>—</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>21.3</td>
<td>8.5</td>
<td>3.7</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20.9</td>
<td>6.0</td>
<td>4.9</td>
<td>2.4</td>
<td>—</td>
</tr>
<tr>
<td>American Indian/Alaska</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All races</td>
<td>23.5</td>
<td>6.2</td>
<td>2.7</td>
<td>2.1</td>
<td>—</td>
</tr>
</tbody>
</table>


### Box 3
Algorithm for determining statin recommendation

Patient already has ASCVD → Recommend high-intensity statin

LDL ≥190 → Recommend high-intensity statin

Calculate 10-year ASCVD event risk for patients ages 40–75 years and not in one of the high-risk groups listed previously:

Patients without diabetes

- Less than 7.5% risk → Do not recommend statin
- ≥7.5% Risk → Recommend moderate- or high-intensity statin

Patients with diabetes

- Less than 7.5% risk → Recommend moderate-intensity statin
- ≥7.5% Risk → Recommend high-intensity statin
High-sensitivity C-reactive protein (hs-CRP) \( \geq 2 \) mg/L

Coronary artery calcium (CAC) score \( \geq 300 \) Agatston units or \( \geq 75\)th percentile for age, gender, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx)

Ankle-brachial index (ABI) less than 0.9

High lifetime risk of ASCVD

Other Disorders That Increase Atherosclerotic Cardiovascular Disease Risk

These chronic diseases increase ASCVD risk, but are not specifically addressed in the AHA/ACC guideline/calculation.

- Obesity (body mass index [BMI] \( \geq 30 \)) is more prevalent in women than in men (37\% vs 34\%). More women than men are obese in all age groups and across all races/ethnicities. Non-Hispanic black women have the highest rates at 57\% versus the lowest rates in Asian women at 11\%. \(^{26}\) Although obesity is not considered in calculations of risk factors, it is the major underlying disorder for future development of HTN, diabetes, and unfavorable lipid profile. Diet and exercise for weight loss are critical interventions addressed in 2 additional AHA/ACC guidelines. \(^ {27,28} \)

- Rheumatologic diseases (eg, rheumatoid arthritis and lupus) are more prevalent in women than men and are independently associated with 59\% higher risk of CAD than in the unaffected population. \(^ {29} \) Chronic inflammatory disorders are also associated with increased risk of other CVDs, including heart failure, atrial fibrillation, and stroke.

- Chronic kidney disease: a glomerular filtration rate reduction of 10 mL/min/1.73 m\(^2\) correlates with a 5\% increased risk of CVD. This study included 55\% women, with no difference between men and women in effect of renal disease on ASCVD risk. \(^ {30} \)

- Sleep apnea is well established as increasing risk of HTN and other cardiovascular outcomes. Prevalence of sleep apnea is 9\% in women compared with 24\% in men. Sleep apnea is, however, estimated as undiagnosed in 90\% of women with moderate to severe sleep apnea, suggesting that women frequently do not have classic symptoms of obstructive sleep apnea. Women often present with atypical symptoms, such as insomnia, fatigue (not sleepiness), depression/anxiety, decreased libido, palpitations, ankle edema, and/or nocturia. \(^ {31-34} \)

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**Box 4**

**Patient counseling example**

A 45-year-old woman has a 55.6\% risk of any CVD event in her lifetime. This woman would live up to 14 years longer free of CVD events if she had an optimal risk factor profile instead of 2 or more major risk factors:

- BP greater than 160 \( \rightarrow \) less than 120
- Total cholesterol greater than 240 \( \rightarrow \) less than 180
- Diabetes YES \( \rightarrow \) NO
- Smoking YES \( \rightarrow \) NO

If this 45-year-old woman were a smoker with a new diagnosis of diabetes, then quitting smoking and losing approximately 10\% of her body weight would likely add 14 CVD-free years to her life.
RISK FACTORS UNIQUE TO WOMEN

Polycystic Ovarian Syndrome

Women with PCOS are at increased risk for obesity, diabetes, HTN, and ultimately CVD. Polycystic Ovarian Syndrome confers double the risk of diabetes and elevated cholesterol levels 18 to 20 years from baseline, independent of obesity. After making a diagnosis of PCOS, women should have more aggressive CVD risk factor management:

- BP and BMI measured regularly, per usual guidelines
- Lipids measured at diagnosis (this is likely earlier than otherwise indicated)
- Oral glucose tolerance test, if possible, or fasting glucose and hemoglobin A1C measured at diagnosis. If a woman has impaired glucose tolerance, then screen for diabetes every year. If she has normal glucose tolerance, then screen for diabetes at least every 2 years and more often if other risk factors are present.

Menopause

Postmenopausal women are at higher risk of ASCVD events than premenopausal women; however, menopause itself does not seem to be the culprit. Rather, other CVD risk factors increase with age. Menopause can have a negative impact on cardiovascular risk factors; early menopause seems to be associated with increased risk of CHD events. Within a year of menopause, total cholesterol, LDL, and apolipoprotein B have been shown to increase substantially in women, a change noted across ethnicities and geography. Although other risk factors for CVD, such as diabetes and HTN, increase in older women, it is not clear if menopause itself increases the prevalence of these risk factors versus aging alone. Alternatively, estrogen seems to play a protective role in premenopausal women, such that premenopausal women have a lower risk of CVD compared with men of a similar age.

In premenopausal women, estrogen is thought to alter the lipid profile favorably by increasing HDL and reducing vascular injury and atherosclerosis. The effect of postmenopausal hormone therapy on cardiovascular risk is complex and understanding its impact on CVD has evolved over the past decade. Analyses of the Women’s Health Initiative (WHI) cohort have found that hormone therapy initiated within 10 years of menopause significantly reduces CAC, a marker of atherosclerosis and a risk factor for future cardiovascular events. In addition, an unrelated secondary analysis of the WHI found a nonsignificant trend toward reduced CHD events and mortality in younger women receiving hormone therapy compared with older women. More recent follow-up analysis shows a persistent increase in thrombotic stroke risk (approximately 15%, barely statistically significant) and neutral CHD risk in most groups. In women ages 50 to 59, estrogen alone (for women without a uterus) may be protective, whereas combination therapy trends toward increased CHD risk. At this time, there is not enough evidence to support the use of hormone therapy to reduce CVD risk, particularly when other interventions that reduce CVD risk are underutilized by women. I continue to advise women to use hormone therapy sparingly, at the lowest dose, for the shortest period of time and for intolerable vasomotor symptoms and to inform women that there may be some increased risk of ASCVD.

Pregnancy Complications

ASCVD risk assessment and management include pregnancy planning. Planned pregnancies along with risk factor reduction prior to pregnancy can reduce women’s CVD risk long term. The following list describes the magnitude of effect of these risk factors and risk factor reduction on pregnancy outcomes and long-term ASCVD risk.
- Preeclampsia confers a 4-fold increased risk of HTN later in a woman’s life, triples the risk of a CVD event in her lifetime, and doubles her future stroke risk. Evidence supports this association but does not explain if the association is due to a common underlying condition or actual endothelial damage done by preeclampsia. Consider screening for high BP, obesity, smoking, and high cholesterol starting 1 year after delivery (limited evidence).46

- Obesity prior to pregnancy greatly increases risk of multiple complications, including gestational diabetes (adjusted odds ratio [OR] 6.5), HTN of pregnancy (adjusted OR 7.9), and preeclampsia (adjusted OR 3.7). In turn, these pregnancy complications increase risk of diabetes and HTN later in life and ultimately raise ASCVD risk.47 Weight loss prior to pregnancy makes a difference. Among women whose weight changed from one pregnancy to the next, those who lost 10 or more pounds reduced their risk of gestational diabetes by 40%. Those who gained 10 or more pounds increased their risk by 50%.48

- Gestational diabetes increases risk of developing type 2 diabetes later in life. Within 5 to 15 years after pregnancy, 15% to 60% of these women develop diabetes.49

- Preterm delivery is independently associated with future hospitalization related to CVD (adjusted hazard ratio [HR] 1.4).50

- Multiple miscarriages are an independent risk factor for future MI (adjusted HR 5.1), as is stillbirth (adjusted HR 3.4) (Fig. 1).51

**Stroke Risk Factors**

Stroke risk factors generally are the same as for CHD, but young women have several unique stroke risk factors. Their strokes generally are thrombotic, and the elevated risk ceases to be a factor if condition/therapy is discontinued (eg, pregnancy or oral contraceptive pills [OCPs]). Migraine with aura, however, confers a lifelong 2.5-fold elevated risk of stroke.52 Frequency of migraine directly correlates with higher stroke risk, but only minimal evidence supports reducing migraine frequency with medications to reduce stroke risk. Women with migraine with aura who smoke have a 9-fold increased risk of stroke; these women should be strongly encouraged to stop smoking (AHA/ASA guideline).25

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**Fig. 1.** Cascade of complications from prepregnancy obesity.
**Oral Contraceptives**

Combination estrogen/progestin OCP use contributes to thrombotic stroke and MI risk in young women, but is NOT an independent risk factor for ASCVD risk long-term.\(^53\)\(^-\)\(^{55}\) Stroke risk for young women increases greatly when OCPs are combined with other risk factors. Women taking OCPs should be advised to manage their modifiable stroke risk factors (OR = OR for stroke compared with women with each risk factor NOT taking OCPs)\(^56\):

- OCPs + migraine/aura = OR 7.02
- OCPs + HTN = OR 7.6
- OCPs + smoking (at any age) = OR 4.4
- OCPs + hyperlipidemia = OR 10.8
- OCPs + diabetes = OR 5.3
- OCPs + obesity = OR 4.6
- OCPs + thrombophilia = OR for stroke 11–200 (lupus anticoagulant worst)
  - Do not screen for thrombophilia, prevalence is too low.
  - Do obtain personal and family VTE history; check serum markers only if significant positive history.

**RISK FACTOR MODIFICATION—PHARMACOLOGIC**

Statins have a large body of evidence supporting their role in reducing ASCVD risk. They lower LDL cholesterol and to a lesser degree triglycerides, but recent studies have shown reduced CVD outcomes independent of lipid profile changes (Table 3).\(^4\)

**Statin Adverse Effects**

Many randomized controlled trials have demonstrated statin effectiveness with reducing cardiovascular events, but they suffer from a fundamental challenge to compliance: statin benefit cannot be felt by the patient taking the medication, but the adverse effects often can. Liver toxicity is feared but exceedingly rare and occurs only in patients with underlying liver disease. Hepatic transaminases should be checked prior to starting a statin, but monitoring transaminases in asymptomatic patients is not indicated.\(^57\) Mild muscle aches are common and not harmful in themselves, but any patient experiencing new pain or discomfort should be evaluated with history, physical examination, and laboratory measurements to rule out more serious myopathy or rhabdomyolysis and the statin stopped. Alternative diagnoses must also be considered, such as vitamin D or B\(_{12}\) deficiency, thyroid disease, radicular pain, alcohol-related

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**Table 3**

<table>
<thead>
<tr>
<th>Relative potency of statins</th>
<th>Low-Density Lipoprotein (%)</th>
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<tbody>
<tr>
<td><strong>Atorvastatin</strong></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>40 mg</td>
<td>80 mg</td>
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<tr>
<td><strong>Fluvastatin</strong></td>
<td></td>
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<tr>
<td>80 mg</td>
<td>40 mg</td>
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<tr>
<td><strong>Lovastatin</strong></td>
<td></td>
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<tr>
<td>20 mg</td>
<td>20 mg</td>
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<tr>
<td><strong>Pravastatin</strong></td>
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<tr>
<td>10 mg</td>
<td>10 mg</td>
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<tr>
<td><strong>Rosuvastatin</strong></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>10 mg</td>
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<tr>
<td><strong>Simvastatin</strong></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

Bold, moderate-intensity statin.

Italics, high-intensity statin.
myopathy, myositis, or PVD. Whether a statin can be restarted depends on diagnostic evaluation, clinical response to stopping the medication, patient preference, and thoughtful counseling about alternative statin and/or dosing schedules.

**Myalgia**
Myalgia is muscle ache, heaviness, cramp, weakness, or fatigue without creatine kinase (CK) elevation. Statin-induced myalgia usually is symmetric, is diffuse, and affects lower more than upper extremities. It may resolve after the first few weeks of therapy; in those who discontinue the statin, myalgia should resolve within 2 weeks of stopping the medication. Studied incidence of myalgia ranges from 1% to 25%, with many studies having the same rate of myalgia in the placebo arm as the statin arm. Actual rates in the general population (many of whom are excluded from trials) are likely higher. Higher prevalence in women is suggested in some studies, one of which showed that 60% of myalgia patients were women. No treatment for statin myalgia is supported by strong evidence, but the following may relieve statin myalgia for some patients:

- Coenzyme Q10 may be helpful; this is supported only by weak evidence. Because statins block the common pathway for cholesterol and coenzyme Q10 production, it makes physiologic sense that adding back the enzyme could mitigate adverse effects. Clinical trials have not reported adverse effects significant enough for stopping therapy. The usual dose is 100 mg per day; cost ranges from $20 to $60/month.

- Alternative dosing regimens may help patients tolerate statins without myalgia. Such regimens are possible with a long-acting statin (atorvastatin, rosuvastatin, or fluvastatin). Dosing with double dose every other day may reduce myalgia as well as cost and yields similar LDL reduction. Weekly rosuvastatin has been studied in patients with prior statin intolerance; 70% of patients tolerated this regimen, with an LDL reduction of 23%. Whether these dosing regimens result in reduction of ASCVD events has not yet been studied.

**Myopathy**
Myopathy refers to muscle symptoms with CK elevation. This occurs in 0.1% to 0.5% of patients on a statin during randomized controlled trials and may also be under-representative of incidence in general population.

**Rhabdomyolysis**
Rhabdomyolysis is a rare and serious disorder, usually defined as muscle symptoms with CK elevation greater than 10 times the upper limit of normal and creatinine elevation. Women represented approximately 54% of cases in 1 retrospective cohort study, which is not a significant difference. This same study showed an NNH greater than 20,000 per year on statin monotherapy but an NNH of 484 in older diabetic patients on statin and fibrate, emphasizing the risks of combination therapy and underlying comorbidities. Monitoring CK in asymptomatic patients is not recommended.

**Cognitive decline**
Cognitive decline is experienced by some patients who take a statin, but this effect resolves after discontinuation of the medication. Clinical trial evidence is conflicting on the incidence.

**Hyperglycemia/diabetes**
Hyperglycemia/diabetes occurs in a small percentage of patients on statins. The incidence and magnitude of the effect, however, are both small, and the beneficial effect far outweighs the harm. Because this is a particularly distressing and ironic
complication for many patients, it may be helpful to present this in terms of NNT versus NNH. These statistics should be interpreted with caution, because they come from 2 different studies but do illustrate the approximate difference in magnitude of benefit versus harm:

NNH = 225 patients treated for 4 years to cause 1 new case of diabetes
NNT = 30 patients for 5 years to prevent 1 CVD event or death

**Other Pharmaceutical Agents**

**Triglycerides**
Elevated triglyceride levels correlate with higher ASCVD risk, with this association stronger in women than in men. Convincing evidence is still lacking, however, for a causal link between reducing triglyceride levels with targeted medications (eg, fibrates) and clinical outcomes.66–68

**Niacin**
There is no benefit on cardiovascular outcomes when niacin is added to statin therapy in patients on statin, and there is a higher incidence of adverse events when niacin is added to statin.11,12

**Aspirin**
US Preventive Services Task Force (USPSTF) recommendations (2009) for aspirin for primary prevention of CVD are currently being reviewed. Daily aspirin reduces stroke risk in women at high risk of stroke but does not reduce CHD risk. Daily aspirin (81 mg) should be recommended for women ages 55 to 79 when the benefit of reducing ischemic stroke risk outweighs potential harm of increasing gastrointestinal (GI) bleeding risk. Precise calculations of stroke risk and bleeding risk are not a realistic part of a typical clinic visit, so an overall assessment of ASCVD and bleeding risk factors should guide this decision. The American Diabetes Association and the AHA have similar recommendations based on CVD versus bleeding risk factors.59 Because the guidelines are not exactly the same, I recommend daily aspirin for women ages 55 to 79 based on the overall risk profile and preferences of the patient. I recommend aspirin for a woman with known ASCVD equivalent (diabetes, PVD, atrial fibrillation, or left ventricular hypertrophy) or 2 other risk factors (high BP, smoking, dyslipidemia, family history of premature CVD, and kidney disease). I tend not to recommend daily aspirin in patients who frequently use nonsteroidal antiinflammatory medications (NSAIDs), have a history of GI bleeding or peptic ulcer disease, or have advanced cirrhosis. For example, I recommend aspirin for smokers with high BP and strong family history, even if they sometimes use NSAIDs, but do not recommend aspirin for cirrhotic patients with known varices who smoke and have HTN.

**Antihypertensive medications**
Therapy recommendations for antihypertensive medications were revised by the Eighth Joint National Committee; there are no different recommendations for women versus men.70

- Treatment goal for adults 60 years or older is more permissive than for adults under 60 years old: ≤150/90. If the patient’s blood pressure is <140/90 (previously recommended treatment goal), and is tolerating her current medication without adverse effect, then, there is no need to change therapy.
- There is no change to general population treatment goal; this is still ≤140/90.
- Diabetics and patients with CKD now have the same goal as general population: ≤140/90.
Initial medication choices have a few significant differences compared to prior guidelines. The following recommendations apply to both diabetics and patients without diabetes:

- For nonblack patients, first line therapy: thiazide, calcium channel blocker, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin II receptor blocker (ARB)
- For black patients, first line therapy: thiazide or calcium channel blocker (note ACEI and ARB are NOT on this list)
- For CKD patients, treatment regimen should include ACEI or ARB, regardless of race (Table 4).

**RISK FACTOR MODIFICATION—NONPHARMACOLOGIC STRATEGIES**

- Diet: With minor variations, the USPSTF and AHA/ACC both recommend a diet rich in fruits, vegetables, whole grains/legumes, low-fat dairy products, nuts, and seafood. Please see recent review of lifestyle interventions for diabetes treatment.
- Physical activity: ACC/AHA lifestyle guidelines recommend at least 150 minutes per week of moderate-intensity exercise, in episodes of at least 10 minutes.
- Vitamins and supplements: patients should save their money and eat more vegetables.
  - Vitamin E: according to the USPSTF D recommendation, the harms of vitamin E supplements outweigh benefits.
  - Multivitamins: according to the USPSTF I recommendation, there is no evidence to recommend for or against multivitamins (Table 5).

**FUTURE CONSIDERATIONS**

- New potential risk factors: the USPSTF cites insufficient evidence to assess benefit/harm balance for the following nontraditional risk factors (2009):
  - Hs-CRP: higher levels of CRP are associated with higher ASCVD risk. Statins reduce CRP levels. Therefore, there may be a future role for incorporating CRP measurements into risk factor calculations and statin recommendations, but currently the evidence does not support this.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Choosing an antihypertensive medication based on patient preference and comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
<td><strong>May Also Benefit</strong></td>
</tr>
<tr>
<td>Thiazides</td>
<td>Venous insufficiency, some kidney stones</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Diabetic renal protection</td>
</tr>
<tr>
<td>Losartan</td>
<td>Gout (lowers uric acid), renal protection</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Anxiety, migraine prevention</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Raynaud phenomenon, stable angina</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Raynaud phenomenon</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Cluster headache</td>
</tr>
<tr>
<td>Spiironolactone</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Anxiety, vasomotor symptoms</td>
</tr>
<tr>
<td>Screening Test</td>
<td>Recommendation Grade</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>I: insufficient evidence to assess benefit/harm balance for asymptomatic adults at intermediate–high risk</td>
</tr>
<tr>
<td>Peripheral artery disease with ABI</td>
<td>I: insufficient evidence to assess benefit/harm balance</td>
</tr>
<tr>
<td>Carotid artery stenosis with duplex</td>
<td>D: harms outweigh benefits. Low prevalence, high false-positive rate of duplex, harms from intervention.</td>
</tr>
<tr>
<td>ECG</td>
<td>D: harms outweigh benefits in asymptomatic patients at low ASCVD risk I: insufficient evidence to assess benefit/harm balance for asymptomatic adults at intermediate–high risk.</td>
</tr>
<tr>
<td>BP</td>
<td>A: strong evidence supports annual BP screening.</td>
</tr>
<tr>
<td>Dyslipidemia (nonfasting blood draw IS acceptable); this recommendation is currently under review.</td>
<td>A: strongly recommends screening women 45 or older if they have CVD risk factors B: recommends screening women 20–40 years old if they have CVD risk factors</td>
</tr>
<tr>
<td>Tobacco cessation counseling</td>
<td>A: strongly recommends asking all adults about tobacco use and counseling on cessation; offering pharmacotherapy.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>B: recommends screening all adults if BP &gt;135/80. Fasting glucose or hemoglobin A1C acceptable.</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>B: recommends screening all adults for obesity and offering/referreeing for intervention.</td>
</tr>
<tr>
<td>Healthful diet and physical activity</td>
<td>B: recommends offering or referring overweight/obese adults with CVD risk factors for intensive behavioral counseling interventions.</td>
</tr>
</tbody>
</table>
- ABI
- Leukocyte count
- Fasting blood glucose level
- Periodontal disease
- Carotid intima-media thickness
- CAC score on electron-beam CT
- Homocysteine level
- Lipoprotein(a) level

- A multitude of lipid subclasses, apolipoproteins, and other novel biomarkers have been and are being studied as independent risk factors for ASCVD. This line of research is promising, but none has yet shown reliable predictable effect and an effect of intervention on lowering risk.\textsuperscript{77}

**SUMMARY**

CAD and stroke predominantly affect older women as opposed to younger women, but the risk factors that contribute to ASCVD risk often start in very young women. Additionally, young women with PCOS, with migraine, and who use OCPs have short-term increases in thrombotic complications that can result in coronary events or stroke. Attention should be focused on risk reduction in women of all ages. Screening for and discussing diabetes, HTN, obesity, smoking, migraine, PCOS, and pregnancy complication history and carefully discussing the pros and cons of hormone and statin medications are all part of reducing cardiovascular risk for women.

**REFERENCES**


