

# Statin Use for the Primary Prevention of Cardiovascular Disease in Adults

## US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** Cardiovascular disease (CVD) is the leading cause of morbidity and death in the US and is the cause of more than 1 of every 4 deaths. Coronary heart disease is the single leading cause of death and accounts for 43% of deaths attributable to CVD in the US. In 2019, an estimated 558 000 deaths were caused by coronary heart disease and 109 000 deaths were caused by ischemic stroke.

**OBJECTIVE** To update its 2016 recommendation, the US Preventive Services Task Force (USPSTF) commissioned a review of the evidence on the benefits and harms of statins for reducing CVD-related morbidity or mortality or all-cause mortality.

**POPULATION** Adults 40 years or older without a history of known CVD and who do not have signs and symptoms of CVD.

**EVIDENCE ASSESSMENT** The USPSTF concludes with moderate certainty that statin use for the prevention of CVD events and all-cause mortality in adults aged 40 to 75 years with no history of CVD and who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 10% or greater has at least a moderate net benefit. The USPSTF concludes with moderate certainty that statin use for the prevention of CVD events and all-cause mortality in adults aged 40 to 75 years with no history of CVD and who have 1 or more of these CVD risk factors and an estimated 10-year CVD event risk of 7.5% to less than 10% has at least a small net benefit. The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of statin use for the primary prevention of CVD events and mortality in adults 76 years or older with no history of CVD.

**RECOMMENDATION** The USPSTF recommends that clinicians prescribe a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD risk of 10% or greater. (B recommendation) The USPSTF recommends that clinicians selectively offer a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more of these CVD risk factors and an estimated 10-year CVD risk of 7.5% to less than 10%. The likelihood of benefit is smaller in this group than in persons with a 10-year risk of 10% or greater. (C recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD events and mortality in adults 76 years or older. (I statement)

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**Group Information:** A complete list of the members of the US Preventive Services Task Force appears at the end of this article.

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## Summary of Recommendations

See the Summary of Recommendation Figure.

## Importance

Cardiovascular disease (CVD) is the leading cause of morbidity and death in the US, resulting in more than 1 of every 4 deaths.<sup>1</sup> Coronary heart disease is the single leading cause of death and accounts for 43% of deaths attributable to CVD in the US.<sup>2,3</sup> In 2019, an estimated

558 000 deaths were caused by coronary heart disease and 109 000 deaths were caused by ischemic stroke. Men have a higher overall prevalence of and mortality from CVD, although women experience higher mortality from certain cardiovascular events, such as stroke. On average, men experience CVD events earlier in life compared with women. The prevalence of CVD also differs by race and ethnicity. Among both sexes, Black adults have the highest prevalence of CVD.<sup>4</sup>

Population	Recommendation	Grade
Adults aged 40 to 75 years who have 1 or more cardiovascular risk factors and an estimated 10-year cardiovascular disease (CVD) risk of 10% or greater	The USPSTF recommends that clinicians prescribe a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year risk of a cardiovascular event of 10% or greater.	B
Adults aged 40 to 75 years who have 1 or more cardiovascular risk factors and an estimated 10-year CVD risk of 7.5% to less than 10%	The USPSTF recommends that clinicians selectively offer a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year risk of a cardiovascular event of 7.5% to less than 10%. The likelihood of benefit is smaller in this group than in persons with a 10-year risk of 10% or greater.	C
Adults 76 years or older	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD events and mortality in adults 76 years or older.	I

USPSTF indicates US Preventive Services Task Force.

## USPSTF Assessment of Magnitude of Net Benefit

The US Preventive Services Task Force (USPSTF) concludes with moderate certainty that statin use for the prevention of CVD events and all-cause mortality in adults aged 40 to 75 years with no history of CVD and who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 10% or greater has at least a **moderate net benefit**.

The USPSTF concludes with moderate certainty that statin use for the prevention of CVD events and all-cause mortality in adults aged 40 to 75 years with no history of CVD and who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 7.5% to less than 10% has at least a **small net benefit**. The decision to initiate therapy should depend on individual patient preference for a potential small benefit relative to the potential harms and inconvenience of taking a daily medication.

The USPSTF concludes that the **evidence is insufficient** to determine the balance of benefits and harms of statin use for the primary prevention of CVD events and mortality in adults 76 years or older with no history of CVD.

See the [Table](#) for more information on the USPSTF recommendation rationale and assessment and the eFigure in the [Supplement](#) for information on the recommendation grade. See the [Figure](#) for a summary of the recommendation for clinicians. For more details on the methods the USPSTF uses to determine the net benefit, see the USPSTF Procedure Manual.<sup>5</sup>

## Practice Considerations

### Patient Population Under Consideration

These recommendations apply to adults 40 years or older without a history of known CVD and who do not have signs and symptoms of CVD. These recommendations do not apply to adults with a low-density lipoprotein cholesterol (LDL-C) level greater than 190 mg/dL (4.92 mmol/L) or known familial hypercholesterolemia. These populations are at very high risk for CVD, and considerations on the

use of statins in these populations can be found in other organizations' guidelines.

### Assessment of Risk

The American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations may be used to estimate 10-year risk of CVD. The ACC/AHA risk estimator is, to date, the only US-based CVD risk prediction tool that has published external validation studies in other US-based populations.<sup>6</sup> The estimator has separate equations based on sex and for Black persons and non-Black persons, which include the risk factors of age, cholesterol levels, systolic blood pressure level, antihypertension treatment, presence of diabetes, and smoking status, and focuses on hard clinical outcomes (myocardial infarction and death from coronary heart disease; ischemic stroke and stroke-related death) as the outcomes of interest. Age is one of the strongest risk factors for CVD, and the 10-year CVD event risk estimated by the ACC/AHA risk estimator is heavily influenced by increasing age. The risk prediction equations generally show higher risk for Black persons than White persons.<sup>6</sup> The USPSTF recognizes that race is a social construct, and it is an imperfect proxy for social determinants of health and the effects of structural racism. Concerns about calibration of the Pooled Cohort Equations exist, with many external validation studies showing overprediction in broad populations (men and women across racial and ethnic groups).<sup>7-9</sup> Limited evidence also suggests underprediction in disadvantaged communities<sup>10,11</sup> that could lead to underutilization of preventive therapies. Clinicians should recognize that predictions of 10-year CVD events using the Pooled Cohort Equations are estimates.

The likelihood that a patient will benefit from statin use depends on their absolute risk of having a future CVD event, a risk estimation that, as noted above, is imprecise based on the currently available risk estimation tools. The higher a person's 10-year risk of a CVD event, the greater the chance of benefit from statin use. Thus, the expected benefit of statin therapy for persons with a 10-year CVD risk of 10% or greater exceeds the expected benefit for persons with a 10-year CVD risk of 7.5% to less than 10%. Clinicians should discuss with patients the potential risk of having a CVD event and the expected benefits and harms of statin use. For patients with an estimated 10-year CVD risk of 10% or greater and who smoke or have

Table. Summary of USPSTF Rationale

Rationale	Assessment
Benefits of statin use	<ul style="list-style-type: none"> <li>• Convincing evidence that statin use reduces the probability of CVD events (myocardial infarction or ischemic stroke) and all-cause mortality by at least a moderate amount in adults aged 40 to 75 years with no history of CVD and who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 10% or greater.</li> <li>• Convincing evidence that statin use reduces the probability of CVD events (myocardial infarction or ischemic stroke) and all-cause mortality by at least a small amount in adults aged 40 to 75 years with no history of CVD and who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 7.5% to less than 10%.</li> <li>• Inadequate evidence to conclude whether initiating statin use in adults 76 years or older with no history of CVD and who are not already taking a statin is beneficial in reducing the incidence of CVD events and mortality.</li> </ul>
Harms of statin use	<ul style="list-style-type: none"> <li>• Convincing evidence that the harms of statin use in adults aged 40 to 75 years are at most small.</li> <li>• Inadequate evidence on the harms of statin use for the primary prevention of CVD events in adults 76 years or older.</li> </ul>
USPSTF assessment	<ul style="list-style-type: none"> <li>• The USPSTF concludes with moderate certainty that statin use for the prevention of CVD events and all-cause mortality in adults aged 40 to 75 years with no history of CVD and who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 10% or greater has at least a moderate net benefit.</li> <li>• The USPSTF concludes with moderate certainty that statin use for the prevention of CVD events and mortality in adults aged 40 to 75 years with no history of CVD and who have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 7.5% to less than 10% has at least a small net benefit. The decision to initiate therapy should depend on individual patient preference for a potential small benefit relative to the potential harms and inconvenience of taking a daily medication.</li> <li>• The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of statin use for the primary prevention of CVD events and mortality in adults 76 years or older with no history of CVD.</li> </ul>

Abbreviations: CVD, cardiovascular disease; USPSTF, US Preventive Services Task Force.

dyslipidemia, diabetes, or hypertension, the USPSTF recommends that clinicians prescribe a statin once the rationale has been explained and the patient agrees to take a statin.<sup>12</sup> For patients with an estimated 10-year CVD risk of 7.5% to less than 10% (and who have  $\geq 1$  of the risk factors noted above), clinicians may selectively offer a statin, taking patient values and preferences into account. Patients in this estimated risk range who place a higher value on the potential benefits than on the potential harms and inconvenience of taking a daily medication may choose to initiate a statin.

Given that participants in clinical trials of statin therapy were enrolled based on the presence of 1 or more CVD risk factors, and that the magnitude of benefit of statin use is proportional to a person's estimated 10-year CVD risk, the USPSTF recommends that clinicians evaluate both the presence of CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) as well as estimated 10-year risk of CVD in determining which persons should initiate use of statins.

### Treatment and Statin Intensity

There are limited data directly comparing the effects of different statin intensities on health outcomes. A majority of the trials reviewed by the USPSTF used moderate-intensity statin therapy.<sup>13</sup> Based on available evidence, use of moderate-intensity statin therapy seems reasonable for the primary prevention of CVD in most persons.

### Implementation

Several studies have reported inequities in statin use based on demographic and socioeconomic factors such as race and ethnicity, sex, area poverty level, and income level. Some studies found that Black adults have a decreased likelihood of being prescribed a statin<sup>14</sup> and statin use<sup>15</sup> compared with White adults. Having no health insurance was also associated with decreased likelihood of statin use, as was having multiple vulnerabilities (defined as age 65 years or older, being a woman, being Black, area poverty level of 10% or greater, or no health insurance).<sup>15</sup> Older age, having health insurance, and higher income were associated with an increased likelihood of statin use.<sup>16,17</sup> Data from the 2013-2014 National Health and Nutrition Examination Survey found that among persons eligible for statin use,

statin use was higher among non-Hispanic White (58.3%) persons compared with non-Hispanic Asian (49.2%), non-Hispanic Black (44.3%), or Hispanic (33.7%) persons.<sup>18</sup> It is essential to equitably improve statin use in both women and men of all races and ethnicities, regardless of socioeconomic level or health insurance status, to achieve the full benefits of statin use, and especially among Black adults and Hispanic adults, who have the highest prevalence of CVD<sup>4</sup> and the lowest use of statins, respectively.

### Additional Tools and Resources

The Centers for Disease Control and Prevention provides information about cholesterol-lowering medications, including statins ([https://www.cdc.gov/cholesterol/treating\\_cholesterol.htm](https://www.cdc.gov/cholesterol/treating_cholesterol.htm)), and resources for clinicians ([https://www.cdc.gov/cholesterol/educational\\_materials.htm](https://www.cdc.gov/cholesterol/educational_materials.htm)).

Million Hearts, a national initiative from the US Department of Health and Human Services to prevent myocardial infarctions and strokes, provides information on statins (<https://millionhearts.hhs.gov/learn-prevent/scoop-on-statins.html>).

### Suggestions for Practice Regarding the I Statement

#### Potential Preventable Burden

According to the National Center for Health Statistics, heart disease and cerebrovascular disease were respectively the first and fourth leading causes of death in adults 65 years or older in 2018, although data were not reported separately for adults older than 75 years.<sup>19</sup> However, trial data on the benefits of statin use in persons older than 75 years are limited,<sup>13</sup> and the available evidence is insufficient to recommend for or against initiating statin use for the primary prevention of CVD in this age group.

#### Potential Harms

Evidence on the potential harms of statin use for the primary prevention of CVD events specifically in adults 76 years or older is limited. Evidence from trials in the general adult population shows that statins are not associated with an increased risk of myalgia, elevated alanine aminotransferase level, or cognitive harms

Figure. Clinician Summary: Statin Use for the Primary Prevention of Cardiovascular Disease in Adults

What does the USPSTF recommend?	<p>For adults aged 40 to 75 years who have 1 or more cardiovascular risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year cardiovascular disease (CVD) risk of 10% or greater: Initiate a statin. <b>Grade: B</b></p> <p>For adults aged 40 to 75 years who have 1 or more cardiovascular risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD risk of 7.5% to less than 10%: Selectively offer a statin. <b>Grade: C</b></p> <p>For adults 76 years or older: The evidence is insufficient to recommend for or against starting a statin. <b>I statement</b></p>
To whom does this recommendation apply?	These recommendations apply to adults 40 years or older who do not already have CVD or signs or symptoms of CVD. They do not apply to adults with a low-density lipoprotein cholesterol level greater than 190 mg/dL (4.92 mmol/L) or known familial hypercholesterolemia. These populations are at very high risk for CVD and considerations on the use of statins in these populations can be found in other organizations' guidelines on management of hypercholesterolemia.
What's new?	This recommendation is consistent with the 2016 USPSTF recommendation.
How to implement this recommendation?	<p>Consider the patient's age.</p> <ul style="list-style-type: none"> <li>• <b>For adults aged 40 to 75 years:</b> <ul style="list-style-type: none"> <li>◦ Determine whether the patient has a cardiovascular risk factor (ie, dyslipidemia, diabetes, hypertension, or smoking).</li> <li>◦ Estimate CVD risk using a CVD risk estimator.</li> <li>◦ In patients who have a cardiovascular risk factor and an estimated 10-year CVD risk of 10% or greater, initiate a moderate-intensity statin after discussing the rationale and provided the patient agrees.</li> <li>◦ In patients who have a cardiovascular risk factor and an estimated 10-year CVD risk of 7.5% to less than 10%, the benefit of starting a statin is smaller, so clinicians should selectively offer a statin, taking patient values and preferences into account.</li> </ul> </li> <li>• <b>For adults 76 years or older:</b> The evidence is insufficient to recommend for or against starting a statin.</li> </ul>
What additional information should clinicians know about this recommendation?	<ul style="list-style-type: none"> <li>• Age is one of the strongest risk factors for CVD.</li> <li>• Men have a higher prevalence of CVD than females, although women experience higher mortality from certain cardiovascular events. On average, men experience CVD events earlier in life compared with women.</li> <li>• Among both sexes, Black persons have the highest prevalence of CVD.</li> <li>• To achieve the full benefits of statin use, it is essential to equitably improve statin use in both women and men of all races and ethnicities, and especially among Black and Hispanic adults, who have the highest prevalence of CVD and the lowest utilization of statins, respectively.</li> </ul>
Why is this recommendation and topic important?	CVD is the leading cause of mortality in the US, accounting for more than 1 in 4 deaths. In 2019, there were an estimated 558 000 deaths caused by coronary heart disease and 109 000 deaths caused by ischemic stroke.
What are additional tools and resources?	<ul style="list-style-type: none"> <li>• The Million Hearts initiative provides information on statins at <a href="https://millionhearts.hhs.gov/learn-prevent/scoop-on-statins.html">https://millionhearts.hhs.gov/learn-prevent/scoop-on-statins.html</a></li> <li>• The Centers for Disease Control and Prevention has information about cholesterol-lowering medications, including statins, at <a href="https://www.cdc.gov/cholesterol/treating_cholesterol.htm">https://www.cdc.gov/cholesterol/treating_cholesterol.htm</a>, and resources for clinicians at <a href="https://www.cdc.gov/cholesterol/educational_materials.htm">https://www.cdc.gov/cholesterol/educational_materials.htm</a></li> </ul>
Where to read the full recommendation statement?	Visit the USPSTF website ( <a href="https://www.uspreventiveservicestaskforce.org/uspstf/">https://www.uspreventiveservicestaskforce.org/uspstf/</a> ) or the JAMA website ( <a href="https://jamanetwork.com/collections/44068/united-states-preventive-services-task-force">https://jamanetwork.com/collections/44068/united-states-preventive-services-task-force</a> ) to read the full recommendation statement. This includes more details on the rationale of the recommendation, including benefits and harms; supporting evidence; and recommendations of others.

*The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision-making to the specific patient or situation.*

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compared with placebo.<sup>13</sup> Almost all trials did not find an association between statin use and incidence of diabetes; 1 trial, JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), found that high-intensity statin therapy was associated with increased risk of diabetes,<sup>20</sup> although a subsequent analysis found that this increased risk was limited to participants with diabetes risk factors at baseline (metabolic syndrome, impaired fasting glucose, body mass index  $\geq 30$  [calculated as weight in kilograms divided by square of height in meters], or hemoglobin A<sub>1c</sub> level  $>6\%$ ).<sup>21</sup>

#### Current Practice

Data on statin use for the primary prevention of CVD in persons 76 years or older are limited. One study estimated that 10.7 million adults 75 years or older were taking a statin in 2013 to 2014, although it did not distinguish between statin use for primary vs secondary prevention.<sup>18</sup> A second study reported that among adults 75 years or older without a history of CVD, those with diabetes had rates of statin use more than 2 times higher than among those without diabetes (76.1 and 34.5 initiators per 1000 person-years, respectively). This study did not report the prevalence of statin use.<sup>22</sup>

### Other Related USPSTF Recommendations

The USPSTF has made several recommendations related to the prevention of CVD in adults, including aspirin use to prevent CVD,<sup>23</sup> screening for high blood pressure,<sup>24</sup> screening for prediabetes and type 2 diabetes,<sup>25</sup> interventions for tobacco smoking cessation,<sup>26</sup> behavioral counseling to promote a healthy diet and physical activity for CVD prevention in adults (with and without cardiovascular risk factors),<sup>27,28</sup> and behavioral interventions to prevent obesity-related morbidity and mortality in adults.<sup>29</sup>

### Update of Previous USPSTF Recommendation

This recommendation replaces the 2016 USPSTF recommendation on statin use for the primary prevention of CVD and is generally consistent with that recommendation.<sup>30</sup> In 2016, the USPSTF recommended that adults without a history of CVD (ie, symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: (1) they are aged 40 to 75 years; (2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and (3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. The USPSTF also recommended that clinicians may choose to offer a low- to moderate-dose statin to adults without a history of CVD who meet criteria 1 and 2 above and have a calculated 10-year risk of a cardiovascular event of 7.5% to less than 10%. The USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults 76 years or older.<sup>30</sup>

### Supporting Evidence

#### Scope of Review

To update its 2016 recommendation statement, the USPSTF commissioned a systematic review<sup>13,31</sup> of the evidence on the benefits and harms of statins in reducing CVD-related morbidity or mortality or all-cause mortality. The evidence review also investigated whether the benefits or harms of statin treatment vary in populations of interest defined by demographic, clinical, or socioeconomic characteristics, by statin intensity, or by titration of statin therapy to a target LDL-C level vs use of a fixed statin dose.

#### Benefits of Preventive Medication

The USPSTF reviewed 22 trials that reported on the benefits of statin use for primary prevention. Mean duration of follow-up was 3.3 years. Mean age of study participants ranged from 52 to 66 years in all trials except for 1, PROSPER (Prospective Study of Pravastatin in the Elderly at Risk), which enrolled persons aged 70 to 82 years (mean age, 75 years).<sup>32</sup> Among the trials that used a fixed statin dose, most (12/16) used a moderate-intensity statin, as defined by ACC/AHA criteria. Fifteen trials reported race and ethnicity; White persons were the most common group in 14 of those trials, representing 41% to 99% of the study population. The proportion of Black participants, reported in 5 trials, ranged from less than 1% to 37%. Data for other races and ethnicities were limited. All trials enrolled persons with at least 1 cardiovascular risk factor, and a few required the presence of

multiple cardiovascular risk factors at baseline. The most common risk factors were dyslipidemia (which was variably defined), diabetes, and hypertension.<sup>13,31</sup>

In pooled analyses, statin therapy was associated with decreased risk of all-cause mortality (18 trials;  $n = 85\,816$ ; relative risk [RR], 0.92 [95% CI, 0.87 to 0.98]; absolute risk difference [ARD],  $-0.35\%$ ), fatal or nonfatal stroke (15 trials;  $n = 76\,610$ ; RR, 0.78 [95% CI, 0.68 to 0.90]; ARD,  $-0.39\%$ ), and fatal or nonfatal myocardial infarction (12 trials;  $n = 76\,498$ ; RR, 0.67 [95% CI, 0.60 to 0.75]; ARD,  $-0.89\%$ ). In several trials, primary outcome was reported as a composite of CVD events, with the exact components of this end point varying across trials. In a pooled analysis of 15 trials, statin therapy was also associated with a decreased risk of composite cardiovascular outcomes ( $n = 74\,390$ ; RR, 0.72 [95% CI, 0.64 to 0.81]; ARD,  $-1.28\%$ ).<sup>13,31</sup>

Twelve trials ( $n = 75\,138$ ) reported on cardiovascular mortality. Only 1 trial, WOSCOPS (West of Scotland Coronary Prevention Study;  $n = 6595$ ), reported a statistically significant difference between statin and placebo in risk of cardiovascular mortality (RR, 0.68 at 6 years [95% CI, 0.48 to 0.98]; ARD,  $-0.70\%$  [95% CI,  $-1.36\%$  to  $-0.05\%$ ]).<sup>33</sup> In pooled analyses of all 12 trials, statin therapy was associated with a slight reduction in cardiovascular mortality risk at 2 to 6 years that was not statistically significant (RR, 0.91 [95% CI, 0.81 to 1.02]; ARD,  $-0.13\%$  [95% CI,  $-0.25\%$  to  $-0.02\%$ ]).<sup>13,31</sup>

Evidence on the benefits of statins in persons 75 years or older is limited. As noted, most trials had a mean participant age in the 50s and 60s; only 1 trial, PROSPER ( $n = 3239$  for primary prevention), had a study population with a mean age of 75 years.<sup>32</sup> One additional trial, ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial), reported stratified results for the age group 75 years or older (in addition to other age groups).<sup>34,35</sup> The primary prevention data from PROSPER found no decrease in all-cause mortality (RR, 1.07 [95% CI, 0.86 to 1.35]), risk of stroke (RR, 1.03 [95% CI, 0.73 to 1.45]), or in a composite cardiovascular outcome (RR, 0.94 [95% CI, 0.78 to 1.14]) among persons taking a statin compared with placebo.<sup>32</sup> In the ALLHAT-LLT primary prevention population, statin therapy was associated with higher risk of all-cause and cardiovascular mortality in persons 75 years or older than in those aged 65 to 74 years (hazard ratio, 1.36 [95% CI, 0.98 to 1.89] vs 1.05 [95% CI, 0.82 to 1.33], respectively, for all-cause mortality; RR, 1.39 [95% CI, 0.85 to 2.25] vs 0.99 [95% CI, 0.71 to 1.39], respectively, for cardiovascular mortality), but estimates for the age group 75 years or older were imprecise and the difference was not statistically significant.<sup>34,35</sup> However, ALLHAT-LLT had several limitations, including its open-label design, high loss to follow-up, and high crossover from the usual care treatment group. This trial reported a small differential in LDL-C-lowering effect between the statin therapy group and usual care group and showed no benefit of statin use overall.

In stratified analyses, the relative benefits of statin therapy did not appear to differ across a variety of demographic and clinical variables, including age (with the caveat that data are limited for persons older than 75 years), sex, and race and ethnicity, or the presence or absence of specific risk factors such as hypertension or diabetes. No trials reported how benefits of statin therapy vary according to socioeconomic characteristics.<sup>13,31</sup>

No study directly compared treatment with statins titrated to attain a target cholesterol level vs fixed-dose treatment strategies.



There were also limited data directly comparing the effects of different statin intensities on health outcomes. Across-study comparisons did not indicate differences in outcomes based on dose titration vs fixed-dose statin therapy or based on statin intensity. As noted, most trials used a moderate-intensity statin.<sup>13,31</sup>

### Harms of Preventive Medication

The USPSTF reviewed 19 trials (n = 75 005) and 3 observational studies (n = 417 523) that reported on the harms of statin therapy in adults without a history of a CVD event. In pooled analyses of trial data, statin therapy was not associated with increased risk of study withdrawal due to adverse events or serious adverse events.<sup>13,31</sup> Although observational studies have reported an association between statin use and muscle pain,<sup>36</sup> a pooled analysis of 9 trials (n = 46 388) found no increased risk of myalgia with statin therapy compared with placebo.<sup>13,31</sup> Trials also did not find an association between statin therapy and myopathy or rhabdomyolysis, although these events were uncommon, so the estimates of relative risk are imprecise.<sup>13,31</sup>

Twelve trials (n = 55 358) reported no difference between statin therapy and placebo in risk of elevation in aminotransferase levels, and pooled analyses of 13 trials (n = 71 733) found no difference between statin therapy and placebo or no statin in risk of any cancer.<sup>13,31</sup>

Six trials (n = 59 083) and 3 observational studies (n = 417 523) reported on risk of new-onset diabetes with statin therapy. Based on a pooled analysis of 6 trials, there was no difference between statins and placebo or no statin in risk of diabetes (RR, 1.04 [95% CI, 0.92 to 1.19];  $I^2 = 52\%$ ; ARD, 0.00% [95% CI, -0.00% to 0.01%]).<sup>12</sup> One trial of high-intensity statin therapy (JUPITER) reported an increased risk of diabetes with statin use (3.0% vs 2.4%; RR, 1.25 [95% CI, 1.05 to 1.49])<sup>20</sup> that was subsequently found to be limited to study participants with 1 or more diabetes risk factors (metabolic syndrome, impaired fasting glucose, body mass index  $\geq 30$ , or hemoglobin A<sub>1c</sub> level  $>6\%$ ) at baseline.<sup>21</sup> Cohort studies reported mixed findings. One case-control study found no association between statin use and risk of diabetes,<sup>37</sup> an analysis from the Women's Health Initiative found an increased risk (adjusted hazard ratio, 1.48 [95% CI, 1.38 to 1.59]),<sup>38</sup> and a third cohort reported mixed findings that varied by 10-year cardiovascular mortality risk (based on the SCORE instrument) and adherence to statin therapy.<sup>39</sup>

Evidence on the association between statins and renal or cognitive harms is very limited but does not indicate increased risk.<sup>13,31</sup> In 1 trial, statin therapy was associated with increased risk of cataract surgery, which was unanticipated and not a predetermined outcome of the trial (3.8% vs 3.1%; RR, 1.24 [95% CI, 1.03 to 1.49]; ARD, 0.73%).<sup>40</sup> Other trials did not note or report on this outcome.

### Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from February 22 to March 21, 2022. Some comments sought clarification on why the USPSTF is recommending that both presence of a CVD risk factor and estimated 10-year CVD risk be used when considering initiation of a statin. As noted in the Practice Considerations section, statin trial inclusion criteria required the presence of 1 or more CVD risk factors. Additionally, the magnitude of the benefits of statin use is proportional to a person's CVD risk level; thus, the USPSTF concluded

that a 10-year CVD risk of 7.5% to less than 10% provides at least a small net benefit and a 10-year CVD risk of 10% or greater provides at least a moderate net benefit. Some comments sought clarification on whether coronary artery calcium score could be used as a criterion for statin use. The USPSTF addressed the use of coronary artery calcium score for CVD risk assessment in a separate recommendation.<sup>41</sup> Some comments sought clarification on whether persons 76 years or older who are already taking a statin should continue its use. The USPSTF reiterates that this recommendation is about initiating a statin for the primary prevention of CVD events and mortality; in adults 76 years or older, the evidence is insufficient to assess the balance of benefits and harms of initiating statins. Some comments expressed concerns about the accuracy of the Pooled Cohort Equations across populations. The USPSTF understands these concerns and calls for more research on improving the accuracy of CVD risk prediction in all racial and ethnic and socioeconomic groups in the Research Needs and Gaps section. In addition, the USPSTF wants to clarify that these recommendations do not pertain to adults with familial hypercholesterolemia or an LDL-C level greater than 190 mg/dL (4.92 mmol/L). Considerations for statin use in these populations can be found in other organizations' guidelines and resources on management of these conditions.

### Research Needs and Gaps

More studies are needed that address the following.

- Improving the accuracy of CVD risk prediction in all racial and ethnic and socioeconomic groups.
- The balance of benefits and harms of initiating statin use for the primary prevention of cardiovascular events in adults 76 years or older.
- The efficacy and safety of long-term statin use in adults younger than 40 years, and to determine the effects of earlier vs delayed initiation of statin use, particularly in persons with an estimated high long-term (longer than 10 years [eg, lifetime]) risk of CVD.
- The causes of disparities in statin use and effective methods to reduce disparities.
- Trials that directly compare statin therapy titrated to target lipid levels vs fixed-dose therapy to inform optimal dosing strategies. Trials that directly compare higher- vs lower-intensity statin therapy and are powered to assess clinical outcomes are also needed.
- Definitively determining whether statin therapy is associated with increased risk of diabetes in primary prevention populations.
- The role of patient preferences in decisions to prescribe statins for persons across the spectrum of CVD risk.

### Recommendations of Others

The 2018 and 2019 ACC/AHA guidelines define cardiovascular risk categories as high (10-year risk of cardiovascular events  $\geq 20\%$ ), intermediate (10-year risk of cardiovascular events  $\geq 7.5\%$  to  $<20\%$ ), and borderline (10-year risk of cardiovascular events  $5\%$  to  $<7.5\%$ ).<sup>42,43</sup> The guidelines recommend initiation of statin therapy in persons at intermediate or high risk and a risk discussion for persons at borderline risk, and recommend consideration of risk enhancers to refine risk assessments based on the Pooled Cohort

Equations and inform decision-making for persons at intermediate and borderline risk.<sup>42,43</sup> These risk enhancers include family history of early coronary heart disease, presence of chronic kidney disease, metabolic syndrome, preeclampsia, premature menopause, inflammatory diseases, HIV, and South Asian ancestry.<sup>42,43</sup>

The 2014 US Department of Veterans Affairs/US Department of Defense Clinical Practice Guideline recommends initiation of a moderate-dose statin in persons with an estimated 10-year cardiovascular risk of 12% or greater and shared decision-making for persons with an estimated 10-year cardiovascular risk of 6% to 12%.<sup>44</sup>

## ARTICLE INFORMATION

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