

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 mortality in the United States, accounting for 1 of every 3 deaths among adults.

OBJECTIVE To update the 2008 US Preventive Services Task Force (USPSTF) recommendation on screening for lipid disorders in adults.

EVIDENCE REVIEW The USPSTF reviewed the evidence on the benefits and harms of screening for and treatment of dyslipidemia in adults 21 years and older; the benefits and harms of statin use in reducing CVD events and mortality in adults without a history of CVD events; whether the benefits of statin use vary by subgroup, clinical characteristics, or dosage; and the benefits of various treatment strategies in adults 40 years and older without a history of CVD events.

CONCLUSIONS AND RECOMMENDATIONS The USPSTF recommends initiating use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10% or greater (B recommendation). The USPSTF recommends that clinicians selectively offer low- to moderate-dose statins to adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors and a calculated 10-year CVD event risk of 7.5% to 10% (C recommendation). The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use in adults 76 years and older (I statement).

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The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

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. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendations and Evidence

The USPSTF recommends that adults without a history of cardiovascular disease (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 (B recommendation). See the Animated Summary Video.

Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40 to 75 years. See the "Clinical Considerations" section for more information on lipids screening and the assessment of cardiovascular risk.

Although statin use may be beneficial for the primary prevention of CVD events in some adults with a 10-year CVD event risk of less than 10%, the likelihood of benefit is smaller, because of a lower probability of disease and uncertainty in individual risk prediction. Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD 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 7.5% to 10% (C recommendation).

The USPSTF concludes that the current evidence is 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 and older without a history of heart attack or stroke (I statement) (Figure 1).

Considerations for Implementation

To determine whether a patient is a candidate for statin therapy, clinicians must first determine the patient's risk of having a future CVD event. However, clinicians' ability to accurately identify a patient's true risk is imperfect, because the best currently available risk

estimation tool, which uses the Pooled Cohort Equations from the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the assessment of cardiovascular risk,¹ has been shown to overestimate actual risk in multiple external validation cohorts.²⁻⁴

The reasons for this possible overestimation are still unclear. The Pooled Cohort Equations were derived from prospective cohorts of volunteers from studies conducted in the 1990s and may not be generalizable to a more contemporary and diverse patient

population seen in current clinical practice. Furthermore, no statin clinical trials enrolled patients based on a specific risk threshold calculated using a CVD risk prediction tool; rather, patients had 1 or more CVD risk factors other than age and sex as a requirement for trial enrollment.

Because the Pooled Cohort Equations lack precision, the risk estimation tool should be used as a starting point to discuss with patients their desire for lifelong statin therapy. The likelihood that a patient will benefit from statin use depends on his or her absolute baseline risk of having a future CVD event, a risk estimation that is imprecise based on the currently available risk estimation tool. Thus, clinicians should discuss with patients the potential risk of having a CVD event and the expected benefits and harms of statin use. Patients who place a higher value on the potential benefits than on the potential harms and the inconvenience of taking a daily medication may choose to initiate statin use for reduction of CVD risk. The USPSTF has made several other recommendations relevant to the prevention of CVD in adults (see the "Other Approaches to Prevention" section).

Patient Population Under Consideration

These recommendations apply to adults 40 years and older without a history of CVD who do not have current signs and symptoms of CVD (ie, symptomatic coronary artery disease or ischemic stroke) (Figure 2). Some individuals in this group may have undetected, asymptomatic atherosclerotic changes; for the purposes of this recommendation statement, the USPSTF considers these persons to be candidates for primary prevention interventions. These recommendations do not apply to adults with a low-density lipoprotein cholesterol (LDL-C) level greater than 190 mg/dL (to convert LDL-C values to mmol/L, multiply by 0.0259) or known familial hypercholesterolemia; these persons are considered to have very high cholesterol levels and may require statin use.

Rationale

Importance

Cardiovascular disease is a broad term that encompasses a number of atherosclerotic conditions that affect the heart and blood vessels, including coronary heart disease, as ultimately manifested by myocardial infarction (MI), and cerebrovascular disease, as ultimately manifested by stroke. Cardiovascular disease is the leading cause of morbidity and mortality in the United States, accounting for 1 of every 3 deaths among adults.⁵

Statins are a class of lipid-lowering medications that function by inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, which is involved in the rate-limiting step in the production of cholesterol. Statins reduce levels of total cholesterol and LDL-C and, to a lesser extent, triglycerides, and probably have anti-inflammatory and plaque stabilization effects as well.⁶

Potential Benefits of Statin Use

The USPSTF found adequate evidence that use of low- to moderate-dose statins reduces the probability of CVD events (MI or ischemic stroke) and mortality by at least a moderate amount in adults aged 40 to 75 years who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10% or greater.

The USPSTF found adequate evidence that use of low- to moderate-dose statins reduces the probability of CVD events and mortality by at least a small amount in adults aged 40 to 75 years who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 7.5% to 10%.

The USPSTF found inadequate evidence to conclude whether initiating statin use in adults 76 years and older who are not already taking a statin is beneficial in reducing the incidence of CVD events and mortality.

Potential Harms of Statin Use

The USPSTF found adequate evidence that the harms of low- to moderate-dose statin use in adults aged 40 to 75 years are small. Randomized clinical trials (RCTs) of statin use for the primary prevention of CVD events have largely used low and moderate doses; under these conditions, statin use was not associated with serious adverse events such as cancer, severely elevated liver enzyme levels, or severe muscle-related harms. However, evidence concerning the association between statin use and diabetes mellitus is mixed, with 1 prevention trial suggesting that there may be a small increased risk of developing diabetes with use of high-dose statins. Myalgia is a commonly reported adverse effect of statins, but placebo-controlled trial data do not support the conclusion that statin use has a major causative role in its occurrence. Evidence for cognitive harms is relatively sparse; further research would be needed to more definitively establish the relationship between statin use and cognitive function. The USPSTF found no clear evidence of decreased cognitive function associated with statin use. These findings are consistent with those from a recent systematic review of RCTs and observational studies assessing the effect of statins on cognition that found no effect on incidence of Alzheimer disease or dementia.⁷ The recently published HOPE-3 (Heart Outcomes Prevention Evaluation 3) trial found that statin use increased risk of cataract surgery,



Figure 1. US Preventive Services Task Force Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice		
Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

which was unanticipated and not a predetermined outcome of the trial.⁸ None of the other primary prevention trials reported this outcome.⁹

The USPSTF found inadequate evidence on the harms of statin use for the prevention of CVD events in adults 76 years and older without a history of heart attack or stroke.

USPSTF Assessment

The USPSTF concludes with moderate certainty that initiating use of low- to moderate-dose statins for the prevention of CVD events and mortality in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hyper-

tension, or smoking) and a calculated 10-year CVD event risk of 10% or greater has at least a moderate net benefit.

The USPSTF concludes with moderate certainty that initiating use of low- to moderate-dose statins for the prevention of CVD events and mortality in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 7.5% to 10% has a small net benefit. The decision to initiate therapy in this population should reflect an assessment of patients' specific circumstances and their preference for a potential small benefit relative to the potential harms and inconvenience of taking a lifelong daily medication.

Figure 2. Statin Use for the Primary Prevention of CVD in Adults: Clinical Summary

Population	Adults aged 40–75 y with no history of CVD, ≥ 1 CVD risk factors, and calculated 10-y CVD event risk $\geq 10\%$	Adults aged 40–75 y with no history of CVD, ≥ 1 CVD risk factors, and calculated 10-y CVD event risk of 7.5%–10%	Adults 76 y and older with no history of CVD
Recommendation	Initiate use of low- to moderate-dose statins. Grade: B	Discuss with patient and selectively offer use of low- to moderate-dose statins. Grade: C	No recommendation. Grade: I (insufficient evidence)
Risk Assessment	Risk factors for CVD include dyslipidemia (LDL-C >130 mg/dL or HDL-C <40 mg/dL), diabetes, hypertension, and smoking. The USPSTF recommends using the ACC/AHA Pooled Cohort Equations to calculate 10-year risk of CVD events. The calculator derived from these equations takes into account age, sex, race, cholesterol levels, systolic blood pressure level, antihypertension treatment, presence of diabetes, and smoking status as risk factors.		
Preventive Medication	Statins are a class of lipid-lowering medications that function by inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A reductase. Statins reduce levels of total cholesterol and LDL-C and, to a lesser extent, triglycerides. The most directly applicable body of evidence for patients without a history of CVD demonstrates benefits with use of low- to moderate-dose statins.		
Considerations for Implementation	The likelihood that a patient will benefit from statin use depends on his or her absolute baseline risk of having a future CVD event, a risk estimation that is imprecise based on the currently available risk estimation tools. Thus, clinicians should discuss with patients the potential risk of having a CVD event and the expected benefits and harms of statin use.		
Balance of Benefits and Harms	The USPSTF concludes with moderate certainty that initiating use of low- to moderate-dose statins in this population has at least a moderate net benefit.	The USPSTF concludes with moderate certainty that initiating use of low- to moderate-dose statins in this population has a small net benefit.	The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of initiating statin use in this population.
Other Relevant USPSTF Recommendations	The USPSTF has made other recommendations relevant to the prevention of CVD in adults, including aspirin use for the prevention of CVD, screening for coronary heart disease using electrocardiography, use of nontraditional risk factors in CVD risk assessment, screening for high blood pressure, screening for abnormal blood glucose levels and type 2 diabetes mellitus, interventions for tobacco smoking cessation, behavioral counseling to promote a healthful diet and physical activity for CVD prevention in adults, and screening for and management of obesity in adults. These recommendations are available on the USPSTF website (https://www.uspreventiveservicestaskforce.org).		

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to <https://www.uspreventiveservicestaskforce.org>.



ACC indicates American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; USPSTF, US Preventive Services Task Force.

The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults 76 years and older without a history of CVD.

Clinical Considerations

Risk Factors for CVD

For the purposes of this recommendation, dyslipidemia is defined as an LDL-C level greater than 130 mg/dL or a high-density lipoprotein cholesterol (HDL-C) level less than 40 mg/dL (to convert HDL-C values to mmol/L, multiply by 0.0259). Most participants enrolled in trials of statin use for the prevention of CVD had an LDL-C level of 130 to 190 mg/dL or a diabetes diagnosis; hypertension and smoking were also common among trial participants.⁶ Persons with an LDL-C level greater than 190 mg/dL were usually excluded from trial participation, as it was not considered appropriate to randomly assign them to placebo. Thus, these recommendations do not pertain to persons with very high cholesterol levels

(ie, LDL-C >190 mg/dL) or familial hypercholesterolemia, as they were excluded from most prevention trials.

One trial, JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), which excluded persons with dyslipidemia or diabetes, evaluated the effect of high-dose rosuvastatin vs placebo in participants with elevated C-reactive protein (CRP) levels.¹⁰ The USPSTF previously reviewed the evidence on the utility of CRP as a risk predictor of coronary heart disease and found that although there is an association between elevated CRP levels and coronary heart disease events, there is insufficient evidence that a reduction in CRP levels results in fewer CVD events.¹¹ Additionally, CRP is not currently included in any of the major risk prediction calculators, and the effects of using CRP in addition to traditional CVD risk factors to guide the prescription of statins for reducing CVD risk are uncertain. As such, the USPSTF does not recommend for or against the use of CRP alone as a risk factor in screening to prevent CVD events in asymptomatic adults without a history of CVD.¹² In JUPITER, most of the trial participants either also had hypertension (57%) or were smokers (15%)¹⁰—risk factors the USPSTF

prioritized for determining potential suitability for statin therapy. In the recent HOPE-3 trial, there was no difference in the effects of statins among participants with or without elevated CRP levels.⁸

10-Year Risk of CVD Events

The USPSTF recommends using the ACC/AHA Pooled Cohort Equations to calculate 10-year risk of CVD events.¹³ In 2013, the ACC/AHA released the Pooled Cohort Equations with the publication of new statin therapy guidelines.¹ The calculator derived from these equations takes into account age, sex, race, cholesterol levels, systolic blood pressure level, antihypertension treatment, presence of diabetes, and smoking status as risk factors in the prediction model and focuses on hard clinical outcomes (heart attack and death from coronary heart disease; ischemic stroke and stroke-related death) as the outcomes of interest.

This risk calculator has been the source of some controversy, as several investigators not involved with its development have found that it overestimates risk when applied to more contemporary US cohorts, especially those at the lower end of the risk spectrum.¹⁴ Although other risk prediction tools are available, they address varying populations, risk factors, and outcomes and have their own limitations. The ACC/AHA risk calculator is, to date, the only US-based CVD risk prediction tool that has published external validation studies in other US-based populations. Other advantages are that it can generate sex- and race-specific risk predictions and that it includes ischemic stroke as an outcome.

Nonmodifiable risk factors for CVD include older age, male sex, and race/ethnicity; however, statin trials have not included persons with only these risk factors. Other risk factors, such as family history of premature coronary artery disease, have not been demonstrated to improve risk prediction in a clinically meaningful way.¹⁵

It is important to note that the calculated 10-year CVD event risk derived from the ACC/AHA risk calculator is heavily influenced by age. For example, 41% of men and 27% of women aged 60 to 69 years without a history of CVD will be found to have a calculated 10-year CVD event risk of 10% or greater.¹⁶ Many older adults, particularly those aged 65 to 75 years, may meet the recommended risk threshold for treatment with statins in spite of the absence of dyslipidemia, diabetes, hypertension, or smoking. No trial data evaluated statin use among persons in this age group without CVD risk factors; thus, the evidence is insufficient to know whether statin use provides them the same or less benefit than in similarly aged adults with CVD risk factors. Decisions about initiating statin use in this age group should be based on shared decision making between patients and clinicians about the potential benefits and harms. Specific recommendations from other organizations for such individuals are discussed in the "Recommendations of Others" section.

Periodic assessment of cardiovascular risk factors from ages 40 to 75 years, including measurement of total cholesterol, LDL-C, and HDL-C levels, is required to implement this recommendation. The optimal intervals for cardiovascular risk assessment are uncertain. Based on other guidelines and expert opinion, reasonable options include annual assessment of blood pressure¹⁷ and smoking status¹⁸ and measurement of lipid levels every 5 years.¹ Shorter intervals may be useful for persons whose risk levels are close to those warranting therapy, and longer intervals are appropriate for persons who are not at increased risk and have repeatedly normal levels.

Screening and Statin Use in Adults Aged 21 to 39 Years

The USPSTF systematically searched for evidence on the effect of screening for dyslipidemia in adults aged 21 to 39 years. It found insufficient evidence that screening for dyslipidemia before age 40 years has an effect on either short- or longer-term cardiovascular outcomes.^{19,20} The USPSTF found no studies that evaluated the effects of screening vs no screening, treatment vs no treatment, or delayed vs earlier treatment in adults in this age group. Thus, the USPSTF recommends neither for nor against screening for dyslipidemia in this age group. A separate recommendation statement also found insufficient evidence to assess the balance of benefits and harms of screening for dyslipidemia in children and adolescents.²¹

The USPSTF recognizes the rationale for screening for dyslipidemia in adults aged 20 to 39 years to identify those at risk for the development of early atherosclerosis, including those with familial hypercholesterolemia. Unfortunately, the evidence is lacking in this age group. The USPSTF found 4 trials of statin use for primary prevention that enrolled patients younger than 40 years. However, results were not reported separately for this age group, and it comprised a small part of the overall population.^{19,20} One cohort study compared the effects of statins vs no statins for the treatment of familial hypercholesterolemia.²² However, the mean age of patients in this study was 44 years. Given the lack of data on the efficacy of screening for or treatment of dyslipidemia in adults aged 20 to 39 years, the USPSTF encourages clinicians to use their clinical judgment for patients in this age group.

Statin Use in Adults Aged 40 to 75 Years

Nineteen RCTs evaluated the effects of statins vs placebo or no statins in adults aged 40 to 75 years without known CVD. Most of the trials, including the recently published HOPE-3 trial,⁸ enrolled participants based on an elevated LDL-C level, a diabetes diagnosis, or at least 1 CVD risk factor. Use of low- or moderate-dose statins was associated with a reduced risk of all-cause mortality (pooled risk ratio [RR], 0.86 [95% CI, 0.80-0.93]), cardiovascular mortality (RR, 0.69 [95% CI, 0.54-0.88]), ischemic stroke (RR, 0.71 [95% CI, 0.62-0.82]), heart attack (RR, 0.64 [95% CI, 0.57-0.71]), and a composite cardiovascular outcome (RR, 0.70 [95% CI, 0.63-0.78]).⁶

Among the study populations, the proportion of CVD events prevented (ie, the relative risk reduction) was similar across age, sex, race/ethnicity, lipid level, and other risk factor categories.⁶ Among trials that stratified participants according to a baseline global cardiovascular risk score, similar relative risk estimates were observed among those classified at a higher vs lower CVD event risk.^{10,23}

Given similar relative risk reductions, the absolute magnitude of benefit that an intervention with demonstrated efficacy can have in a specific population directly depends on the incidence of disease over time in that population. In other words, the more likely it is that persons in a certain population will have a heart attack or ischemic stroke, the greater the potential reduction in the number of CVD events with statin use will be in that population. This is one of the fundamental reasons for the distinction between a grade B and C recommendation for the population that presents with dyslipidemia, diabetes, hypertension, or smoking and a 10% or greater vs 7.5% to 10% 10-year CVD event risk.

In the absence of other risk factors, adults with an LDL-C level greater than 190 mg/dL may still fall below the risk threshold for statin use for CVD prevention. As noted previously, these persons

Table. Statin Regimens Used in Available Trials

Statin	Dose, mg ^a		
	Low	Moderate	High
Atorvastatin		10-20	40-80
Fluvastatin	20-40	40 twice daily	
Fluvastatin extended release		80	
Lovastatin	20	40	
Pitavastatin	1	2-4	
Pravastatin	10-20	40-80	
Rosuvastatin		5-10	20-40
Simvastatin	10	20-40	

^a Dose categories are from the American College of Cardiology/American Heart Association 2013 guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults.²⁴

were generally excluded from the prevention trials evaluating the effects of statin use on health outcomes, because expert opinion strongly favors intervention for these individuals. It is possible that the relative risk reduction in this group is higher than in adults with a lower LDL-C level and that the absolute benefit is greater than would be predicted from a risk calculator.²⁴

Dosage

As previously noted, available RCTs evaluating statins for the prevention of CVD events largely used low and moderate doses. There were no clear differences in estimates of effect when the trials were stratified according to statin dose (see the Table for the drug regimens used in the available trials). The Cholesterol Treatment Trialists meta-analysis showed that greater degree of LDL-C reductions achieved were associated with proportional reductions in major cardiovascular events.²⁵ However, these analyses were based not on randomized comparisons but on the degree of LDL-C reduction achieved. The degree of cholesterol reduction may be attributable, in part, to interindividual variability in response to statins, not just statin dosage.

Limited information is available about use of high-dose statins in a primary prevention population. As such, the harms of statin use for the prevention of CVD events in adults aged 40 to 75 years can only be bounded as small for low- or moderate-dose statins. There may be individual clinical circumstances that warrant consideration of use of high-dose statins; decisions about dose should be based on shared decision making between patients and clinicians. However, the most directly applicable body of evidence for patients without a history of CVD demonstrates benefits with use of low- to moderate-dose statins.

Available information about use of high-dose statins in a prevention population comes from the JUPITER trial. The trial found an increased risk of physician-reported incident diabetes with statin use compared with placebo after 2 years of follow-up (3.2% vs 2.4%; RR, 1.25 [95% CI, 1.05-1.49]), which was not reported in trials evaluating use of moderate- or low-dose statins.¹⁰ Post hoc analysis subsequently suggested that many of the diabetes cases in JUPITER may have occurred in participants who had other risk factors for diabetes at baseline (eg, impaired fasting blood glucose or obesity).²⁶

Summary

The incidence of CVD events in a population increases linearly with CVD risk level; there is no threshold at which event rates abruptly escalate. As such, any cut point for assessing where the net benefit

of statin use shifts from small to moderate for a population requires judgment. Evidence indicates that currently available risk calculators tend to overestimate CVD risk, suggesting that actual benefits may be lower than estimated. Issues to consider include the uncertainty of current risk prediction methods, the overall probability of CVD events occurring in the population, the known and unknown associated harms of statin use, and patient preferences.

The USPSTF concludes that adults who smoke or have dyslipidemia, diabetes, or hypertension and a 10% or greater 10-year CVD event risk should be offered a low- to moderate-dose statin. Adults with diabetes or dyslipidemia and a 20% or greater 10-year CVD event risk are most likely to benefit from statin use.

Clinicians may selectively offer adults who smoke or have dyslipidemia, diabetes, or hypertension and a 7.5% to 10% 10-year CVD event risk a low- to moderate-dose statin. Fewer persons in this population will benefit from the intervention, so the decision to initiate use of low- to moderate-dose statins should reflect shared decision making that weighs the potential benefits and harms, the uncertainty about risk prediction, and individual patient preferences, including the acceptability of long-term use of daily medication.

Suggestions for Practice Regarding the I Statement for Initiating Statin Therapy for Primary Prevention in Adults 76 Years and Older

Potential Preventable Burden

Adults 76 years and older were not included in any of the randomized trials of statin use for the primary prevention of CVD.⁶ Thus, understanding of the potential benefits of initiating statin use for primary prevention in this age group is limited.

Potential Harms

Evidence on the potential harms of statin use for the primary prevention of CVD events in adults 76 years and older is very limited. Observational evidence suggests there may be an association between very low cholesterol levels and an increased risk of mortality with advanced age, after adjusting for other risk factors.^{27,28}

Current Practice

The most current data from the National Health and Nutrition Examination Survey indicate that nearly half (47.6%) of adults 75 years and older in the United States use prescription cholesterol-lowering medications. The majority (>80%) use a statin alone.²⁹ The

survey did not distinguish between the use of cholesterol-lowering medications for the purposes of primary vs secondary prevention, so it is not possible to determine how many of these persons have had a previous heart attack or ischemic stroke. Another study using data from the Medical Expenditure Panel Survey, which did allow for the differentiation of individuals with and without vascular disease (defined as coronary heart disease, stroke, or peripheral vascular disease), found that the rate of statin use among adults 80 years and older for the purposes of primary prevention increased from about 9% in 1999-2000 to 34% in 2011-2012.³⁰

The Society for Post-Acute and Long-Term Care Medicine, as part of the Choosing Wisely campaign, highlighted the use of cholesterol-lowering medications in adults with limited life expectancy (ie, 70 years and, most particularly, 85 years and older) among its "10 Things Physicians and Patients Should Question" because of the increased likelihood of an overall unfavorable risk-to-benefit ratio.³¹

Other Approaches to Prevention

The USPSTF has made other recommendations relevant to the prevention of CVD in adults, including aspirin use for the prevention of CVD,³² screening for coronary heart disease using electrocardiography,³³ use of nontraditional risk factors in CVD risk assessment,¹² screening for high blood pressure,¹⁷ screening for abnormal blood glucose levels and type 2 diabetes mellitus,³⁴ interventions for tobacco smoking cessation,¹⁸ behavioral counseling to promote a healthful diet and physical activity for CVD prevention in adults,³⁵ and screening for and management of obesity in adults.³⁶

Other Considerations

Research Needs and Gaps

Given the lack of studies on screening for and treatment of dyslipidemia in adults aged 20 to 39 years, more research is needed to examine the efficacy of screening and treatment in this age group. More research is needed to address the efficacy and safety of long-term statin use in this population and to determine effects of earlier vs delayed initiation of statin use, particularly in persons with highly elevated lipid levels (eg, persons with familial hypercholesterolemia). Additional research is needed to further clarify the true predictive accuracy of the Pooled Cohort Equations to predict cardiovascular risk in more contemporary and diverse populations to optimally guide clinical risk assessment. Research is needed to evaluate the optimal frequency of cardiovascular risk assessment, including serum lipid screening. There are limited data on different statin dosing strategies; trials that directly compare titrated statin therapy to attain target lipid levels vs fixed-dose therapy would be of great value, as would studies that directly compare higher- vs lower-dose statin regimens. Such trials should use hard clinical outcomes as end points rather than intermediate markers.

Additional research is also warranted on the potential long-term harms of statin therapy, particularly regarding the possible association with increased incidence of diabetes and cataract surgery. Last, research is needed to assess the balance of benefits and harms of initiating statin use for the primary prevention of cardiovascular events in adults 76 years and older. Currently, there is no trial evidence to evaluate the net benefit of initiating statin therapy in this population.

Discussion

Burden of Disease

In 2011, an estimated 375 000 adults died of coronary heart disease and 130 000 died of cerebrovascular disease.³⁷ Coronary heart disease is responsible for approximately one-fifth of deaths among adults aged 45 to 64 years and one-fourth of deaths among those 65 years and older.³⁸ The prevalence of coronary heart disease increases with age, ranging from about 7% in adults aged 45 to 64 years to 20% in those 65 years and older, and is somewhat higher in men (8%) than in women (5%).³⁹

Scope of Review

The USPSTF commissioned 2 systematic evidence reviews to update its 2008 recommendation on screening for lipid disorders in adults. The reviews addressed the benefits and harms of screening for and treatment of dyslipidemia in asymptomatic adults 21 years and older on CVD-related morbidity and mortality; the benefits and harms of statin use in reducing the incidence of CVD-related morbidity and mortality or all-cause mortality in asymptomatic adults without a history of CVD events; whether the benefits of statin use vary by subgroup, clinical characteristics, or dosage; and the benefits of treatment-to-target vs other treatment strategies in asymptomatic adults 40 years and older without a history of CVD events.

Benefits of Statin Use

Nineteen randomized trials (n = 71 344 participants) evaluated the effects of statins in adults at increased cardiovascular risk but without a history of CVD events. The median duration of follow-up was 3 years, and 3 trials were stopped early because of observed benefits in the intervention group. The majority of participants were men and white.⁶

Most of the available trials relied on a composite outcome of CVD events as the primary outcome of interest; the exact composition of this combined end point varied across trials. In general, statin therapy was statistically significantly associated with a reduced incidence of composite CVD outcomes compared with placebo; pooled analysis of 13 trials found an RR of 0.70 (95% CI, 0.63-0.78) after 1 to 6 years. Fifteen trials reported on all-cause mortality after 1 to 6 years, and pooled analysis estimated an RR of 0.86 (95% CI, 0.80-0.93). Although this estimate was heavily influenced by the JUPITER, HOPE-3, and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm) trials^{10,40} because of their large sample sizes, the estimate was robust in multiple sensitivity analyses.⁶

Ten trials reported on cardiovascular mortality. Pooled analysis found an RR of 0.69 (95% CI, 0.54-0.88) after 2 to 6 years, although statistical heterogeneity was present and there was some inconsistency in the individual trials.⁶ Twelve trials provided information about fatal and nonfatal MI. Results were mixed, but most large trials found that statin use led to a statistically significant reduction in the incidence of any MI; the pooled RR after 2 to 6 years of follow-up was 0.64 (95% CI, 0.57-0.71).⁶ Thirteen trials reported on the incidence of fatal and nonfatal stroke. After 6 months to 6 years of follow-up, statin use was associated with a decreased risk of any stroke (RR, 0.71 [95% CI, 0.62-0.82]).⁶

Across these outcomes, benefits appeared consistent across different demographic and clinical subgroups, including patients

without severe dyslipidemia at baseline.⁶ Given similar relative risk estimates across a population, the absolute degree of benefit will be greatest in persons with higher baseline risk of experiencing a CVD event.

Fifteen trials used fixed-dose statin therapy, of which the majority evaluated moderate doses; there were no clear differences in estimates when trials were stratified according to dose. Two trials directly compared different statin doses but were underpowered to draw reliable conclusions about clinical outcomes. No studies were identified that directly compared treatment with statins titrated to attain target cholesterol levels vs fixed-dose or other strategies. Although 3 trials used high-dose statin therapy, only 1 (JUPITER) investigated hard clinical outcomes (eg, fatal or nonfatal MI or CVD mortality).^{6,10} Thus, direct evidence on whether different doses of statin therapy or treatment-to-target strategies affect clinical outcomes is extremely limited.

Harms of Statin Use

In randomized trials of statin use for the primary prevention of CVD, statin therapy was not associated with an increased risk of withdrawal because of adverse events compared with placebo, and there were no statistically significant differences in the risk of experiencing any serious adverse event. The trials also found no evidence of an increase in cancer or elevated aminotransferase levels with statin use.⁶

Evidence on the association between statin use and adverse cognitive effects is very limited, but no clear increase in risk was observed.⁶ A systematic review of RCTs and observational studies on the effects of statin use for any indication on cognition found no statistically significant differences in performance scores on tests of attention, visual perception, motor and processing speed, memory, cognitive performance, or executive function, and no effect on the incidence of Alzheimer disease or dementia.⁷

Although muscle pain, soreness, or weakness are commonly reported with statin use, there were no statistically significant differences between the intervention and control groups for myalgia (7 trials; pooled RR, 0.96 [95% CI, 0.79-1.16]), myopathy (3 trials; pooled RR, 1.09 [95% CI, 0.48-2.47]), or rhabdomyolysis (4 trials; pooled RR, 1.57 [95% CI, 0.41-5.99]), although the confidence intervals for the latter 2 conditions were very wide because of a low number of reported events.⁶

Data from 5 RCTs and 2 observational studies provided evidence on the potential association between statin use and diabetes incidence. Pooled analysis of the RCTs demonstrated no association between statin use and increased risk of diabetes compared with placebo (RR, 1.05 [95% CI, 0.91-1.20])⁶; however, the only trial that evaluated a high-dose statin (JUPITER) reported a statistically significant increased risk of diabetes with statin use.¹⁰ In post hoc stratified analysis, participants with 1 or more risk factors for diabetes (eg, obesity or the metabolic syndrome) were at higher risk of developing diabetes than those without such factors (hazard ratio, 1.28 [95% CI, 1.07-1.54] vs 0.99 [95% CI, 0.45-2.21]).²⁶ Observational studies also reported mixed findings; a UK case-control study found no association with statin use,⁴¹ but an analysis from the Women's Health Initiative noted an increased diabetes risk (adjusted hazard ratio, 1.48 [95% CI, 1.38-1.59]).⁴²

The HOPE-3 trial found that statin use 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, 1.03-1.49]). No other trials noted this outcome.

Estimate of Magnitude of Net Benefit

No direct evidence from RCTs is available to guide the choice of a specific CVD risk threshold for statin use. However, in the available trials of statin use among adults at increased risk of CVD but without a history of CVD events, benefits have been generally consistent across different clinical and demographic subgroups (even among adults without marked dyslipidemia). As such, the likelihood that patients will benefit from statin use is directly associated with their absolute baseline risk of experiencing a CVD event.

The USPSTF concludes that adults who smoke or have dyslipidemia, diabetes, or hypertension and have a 10% or greater 10-year CVD event risk should be offered a low- to moderate-dose statin. In this population, the higher the underlying 10-year CVD event risk, the greater the likelihood of benefit from statin use. Because the absolute underlying risk is lower, fewer adults who smoke or have dyslipidemia, diabetes, or hypertension and a 7.5% to 10% 10-year CVD event risk will benefit from statin use. As such, any decision to initiate use of a low- to moderate-dose statin in this population should involve shared decision making that weighs the potential benefits and harms and the uncertainty surrounding individual CVD risk prediction. It should also take into consideration the personal preferences of each patient, including the acceptability of long-term use of daily medication.

The USPSTF concludes that the balance of benefits and harms of initiating statin use for the primary prevention of CVD events in adults 76 years and older without a history of CVD cannot be determined.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from December 22, 2015, to January 25, 2016. Some comments asked why the USPSTF recommended evaluation of CVD risk factors in addition to the use of a risk calculator or why it used different cut points compared with the ACC/AHA guidelines. In response, the USPSTF clarified its rationale, noting that trial participants generally had 1 or more CVD risk factors and were not recruited based on any particular calculated risk score or cut point. Reliance on a risk calculator such as the Pooled Cohort Equations alone as a basis for prevention may be problematic, given its possible overestimation of risk in some populations. As such, the USPSTF clarified that the benefits of statin use may be linear according to a patient's absolute risk level, and any cut points used are only population estimates of benefits. Clinicians should encourage individualized decision making regarding statin use in their patients, given the known potential benefits and harms.

A few comments requested clarification on the I statement regarding statin use among adults 76 years and older. The USPSTF clarified that the I statement pertains to initiating statin use for primary prevention in adults 76 years and older who are not already taking a statin. Some comments requested clarification regarding the optimal dose of statins. The USPSTF clarified that its recommendation for use of low- to moderate-dose statins is based on the fact that most of the trials were primarily of low to moderate doses, and there were no clear differences in estimates of benefit when trials were stratified according to dose.

In addition, the USPSTF clarified that these recommendations do not pertain to adults with very high CVD risk, such as those with familial hypercholesterolemia or an LDL-C level greater than 190 mg/dL, since they were excluded from primary prevention trials. These persons should be screened and treated in accordance to clinical judgment for the treatment of dyslipidemia. Last, some comments inquired about the use of other factors for CVD risk assessment. The USPSTF clarified that CRP level, coronary artery calcium score, ankle-brachial index, and other factors for CVD risk assessment are addressed in other USPSTF recommendations (available at <https://www.uspreventiveservicestaskforce.org/>).

Update of Previous USPSTF Recommendation

This recommendation replaces the USPSTF 2008 recommendation on screening for lipid disorders in adults. When making a recommendation on a preventive medication, the USPSTF uses the systematic evidence review to determine how to identify persons in the general population for whom the USPSTF can be moderately certain about the balance of benefits and harms of a preventive medication on health outcomes.

Accumulating evidence on the role of statins in preventing CVD events across different populations led the USPSTF to reframe its main clinical question from "which population should be screened for dyslipidemia?" to "which population should be prescribed statin therapy?" Screening for elevated lipid levels is a necessary (but not sufficient) step in the overall assessment of CVD risk to help identify persons who may benefit from statin therapy. In the age range in which statins have been studied for primary prevention, universal screening for elevated lipid levels is required to make this determination. Therefore, the screening framework used in the previous USPSTF recommendation statement is no longer relevant and has been replaced by a preventive medication framework. This recommendation statement focuses on the assessment of overall CVD risk to identify adults aged 40 to 75 years without a history of CVD who will benefit most from statin use to reduce their risk of experiencing a CVD event. The USPSTF found no studies that evaluated the effects of statin use on health outcomes in disease-free adults younger than 40 years. The research plan that guided the evidence review, which served as the foundation of this recommendation statement, did not

consider reduction in LDL-C level to be a sufficient surrogate for health outcomes.

Recommendations of Others

The ACC and AHA recommend statin use in asymptomatic adults aged 40 to 75 years without a history of CVD who have an LDL-C level of 70 to 189 mg/dL if they also have diabetes (use of moderate- to high-dose statins is recommended, depending on the patient's 10-year CVD event risk) or an estimated 10-year CVD event risk of 7.5% or greater, as calculated with the Pooled Cohort Equations risk calculator (shared decision making is recommended before initiating use of moderate- to high-dose statins). Instead of treating to a specific LDL-C target, the ACC and AHA recommend fixed-dose statin therapy using either a high-intensity regimen (daily dose reduces LDL-C level by approximately $\geq 50\%$) or a moderate-intensity regimen (daily dose reduces LDL-C level by approximately 30% to $<50\%$).²⁴ In response, the Mayo Clinic established a task force, which generally provides consistent recommendations, although it emphasizes lifestyle modifications rather than statin therapy in adults 40 years and older who have an LDL-C level less than 100 mg/dL or are sufficiently motivated to reduce their CVD event risk to less than 7.5%.⁴³

The Canadian Cardiovascular Society recommends statin therapy combined with health behavior modification in men 40 years and older and women 50 years and older without CVD risk factors and in adults of any age with CVD risk factors who also have a 20% or greater 10-year CVD event risk or an LDL-C level of 135 to 190 mg/dL and a 10% to 20% CVD event risk (based on the Framingham risk score). Statin therapy in adults with a Framingham risk score of less than 10% is reserved for those with genetic hypercholesterolemia or an LDL-C level of 193 mg/dL or greater. The treatment strategy is treatment-to-target rather than by therapy dose (eg, $\geq 50\%$ reduction in LDL-C level).⁴⁴

The UK National Institute for Health and Care Excellence recommends that statin therapy (specifically, atorvastatin [20 mg]) for the primary prevention of CVD events be offered to adults 40 years and older with a 10% or greater 10-year CVD event risk, as estimated by the QRISK2 assessment tool. Before offering statin therapy, clinicians should discuss the benefits of lifestyle modification and optimize the management of all other modifiable CVD risk factors.⁴⁵

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REFERENCES

- Goff DC Jr, Lloyd-Jones DM, Bennett G, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S49-S73.
- Rana JS, Tabada GH, Solomon MD, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. *J Am Coll Cardiol*. 2016;67(18):2118-2130.
- Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. *JAMA Intern Med*. 2014;174(12):1964-1971.
- DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015;162(4):266-275.
- Mensah GA, Brown DW. An overview of cardiovascular disease burden in the United States. *Health Aff (Millwood)*. 2007;26(1):38-48.
- Chou R, Dana T, Blazina I, et al. *Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the US Preventive Services Task Force: Evidence Synthesis No. 139*. Rockville, MD: Agency for Healthcare Research and Quality; 2016. AHRQ publication 14-05206-EF-2.
- Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med*. 2013;159(10):688-697.
- Yusuf S, Bosch J, Dagenais G, et al; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374(21):2021-2031.
- Chou R, Dana T, Blazina I, Daeges M, Jeanne T. Statins for prevention of cardiovascular disease in adults: a systematic review and meta-analysis for the US Preventive Services Task Force. *JAMA*. doi:10.1001/jama.2015.15629
- Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.
- Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(7):483-495.
- U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009;151(7):474-482.
- American Heart Association, American College of Cardiology. Pooled Cohort Equations Cardiovascular Risk Calculator. 2014. <http://tools.acc.org/ASCVD-Risk-Estimator/>. Accessed September 16, 2016.
- Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet*. 2013;382(9907):1762-1765.
- Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(7):496-507.
- Dehmer SP, Maciosek MV, Flottemesch TJ. *Aspirin Use to Prevent Cardiovascular Disease and Cancer: A Decision Analysis*. Rockville, MD: Agency for Healthcare Research and Quality; 2015. AHRQ publication 15-05229-EF-1.
- Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163(10):778-786.
- Siu AL; US Preventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163(8):622-634.
- Chou R, Dana T, Blazina I, Daeges M, Bougatsos C, Jeanne T. *Screening for Dyslipidemia in Younger Adults: A Systematic Review to Update the 2008 US Preventive Services Task Force Recommendation: Evidence Synthesis No. 138*. Rockville, MD: Agency for Healthcare Research and Quality; 2016. AHRQ publication 14-05206-EF-1.
- Chou R, Dana T, Blazina I, Daeges M, Bougatsos C, Jeanne TL. Screening for dyslipidemia in younger adults: a systematic review for the US Preventive Services Task Force. *Ann Intern Med*. 2016;165(8):560-564.
- Bibbins-Domingo K, Grossman DC, Curry SJ, et al; US Preventive Services Task Force. Screening for lipid disorders in children and adolescents: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316(6):625-633.
- Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ*. 2008;337:a2423.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279(20):1615-1622.
- Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S1-S45.
- Mihaylova B, Emberson J, Blackwell L, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-590.
- Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet*. 2012;380(9841):565-571.
- Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet*. 2001;358(9279):351-355.
- Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. *Lancet*. 1997;350(9085):1119-1123.
- Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. *NCHS Data Brief*. 2014;(177):1-8.
- Johansen ME, Green LA. Statin use in very elderly individuals, 1999-2012. *JAMA Intern Med*. 2015;175(10):1715-1716.
- AMDA—The Society for Post-Acute and Long-Term Care Medicine. Ten things physicians and patients should question. <http://www.choosingwisely.org/societies/amda-the-society-for-post-acute-and-long-term-care-medicine/>. 2015. Accessed September 16, 2016.
- Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164(12):836-845.
- Moyer VA; U.S. Preventive Services Task Force. Screening for coronary heart disease with electrocardiography: U.S. Preventive Services Task

Force recommendation statement. *Ann Intern Med.* 2012;157(7):512-518.

34. Siu AL; U S Preventive Services Task Force. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2015;163(11):861-868.

35. Moyer VA; U.S. Preventive Services Task Force. Behavioral counseling interventions to promote a healthful diet and physical activity for cardiovascular disease prevention in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157(5):367-371.

36. Moyer VA; U.S. Preventive Services Task Force. Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157(5):373-378.

37. Hoyert DL, Xu J. Deaths: preliminary data for 2011. *Natl Vital Stat Rep.* 2012;61(6):1-51.

38. Miniño AM. Death in the United States, 2011. *NCHS Data Brief.* 2013;(115):1-8.

39. Centers for Disease Control and Prevention (CDC). Prevalence of coronary heart disease—United States, 2006-2010. *MMWR Morb Mortal Wkly Rep.* 2011;60(40):1377-1381.

40. Sever PS, Dahlöf B, Poulter NR, et al; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;361(9364):1149-1158.

41. Jick SS, Bradbury BD. Statins and newly diagnosed diabetes. *Br J Clin Pharmacol.* 2004;58(3):303-309.

42. Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in

postmenopausal women in the Women's Health Initiative. *Arch Intern Med.* 2012;172(2):144-152.

43. Lopez-Jimenez F, Simha V, Thomas RJ, et al. A summary and critical assessment of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: filling the gaps. *Mayo Clin Proc.* 2014;89(9):1257-1278.

44. Anderson TJ, Grégoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol.* 2013;29(2):151-167.

45. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. <https://www.nice.org.uk/Guidance/CG181>. 2016. Accessed September 16, 2016.