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Treatment of Blood Cholesterol to Reduce Risk for Atherosclerotic Cardiovascular Disease

Grand Rounds Discussion From the Beth Israel Deaconess Medical Center

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In November 2013, the American College of Cardiology and the American Heart Association released a clinical practice guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk in adults. The recommendation identifies 4 patient groups with strong evidence that the benefits of reduction in ASCVD events from statin therapy exceed adverse events. For these patients, initiating statin therapy of an appropriate intensity to reduce ASCVD risk and minimize adverse effects is recommended. A new risk estimator based on a pooled cohort equation is presented for estimating 10-year ASCVD risk. There is also a recommendation to engage in a clinician–patient discussion before initiating a statin, especially for primary prevention of ASCVD. This paper summarizes a discussion between a cardiologist and an internist about how each clinician would balance these factors and what treatment they would suggest for an individual patient.

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Ms. T is a 67-year-old woman with a history of hypertension who was first noted to have elevated cholesterol in 2009; at that time, her total cholesterol was 286 mg/dL and her high-density lipoprotein cholesterol (HDL) was 62 mg/dL. According to the Framingham tables, her 10-year risk for coronary heart disease was 5% (1). Because she had 2+ risk factors and her low-density lipoprotein cholesterol (LDL) level was 203 mg/dL, the ATP [Adult Treatment Panel] III guideline suggested consideration of drug therapy (2). However, she and her primary care physician chose therapeutic lifestyle changes because of their understanding that her high HDL would confer protective benefits. Ms. T began walking regularly and tried to follow a heart-healthy diet. In 2012, total cholesterol was 283 mg/dL, HDL was 75 mg/dL, and LDL was 181 mg/dL. Again, after consultation with her physician, she planned to continue with lifestyle changes. At her most recent visit, total cholesterol was 293 mg/dL, HDL was 110 mg/dL, and LDL was 166 mg/dL. According to the pooled cohort equation in the new American College of Cardiology and the American Heart Association (ACC/AHA) guideline (3), Ms. T's 10-year risk for an atherosclerotic cardiovascular disease (ASCVD) event was 11.2%. According to the guideline, moderate-intensity statin therapy would be recommended.

Ms. T's medical history is noteworthy for hypertension since 2009, psoriasis, and a vitamin B_{12} deficiency. Current medications include hydrochlorothiazide, 25 mg daily; potassium chloride extended-release, 20 mEq

ABOUT BEYOND THE GUIDELINES

Beyond the Guidelines is an educational feature based on recent guidelines. Each one considers a patient who "falls between the cracks" of available evidence and for whom the optimal clinical course is unclear. Presented at Beth Israel Deaconess Medical Center Department of Medicine (BIDMC) Grand Rounds, each conference reviews the background evidence and 2 experts then discuss the patient and field audience questions. Videos of the patient and conference, slides, and a CME/MOC activity accompany each article. For more information, visit www.annals.org/GrandRounds.

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daily; cyanocobalamin, 1000 mcg/mL monthly; clobetasol cream 0.05% as needed; and vitamin D_3, 1000 units once daily. At her most recent examination, blood pressure was 144/86 mm Hg and body mass index was 21.4 kg/m^2. The remainder of the examination was normal.

Ms. T is retired and lives alone. She eats a heart-healthy diet and walks regularly. She does not smoke or drink alcohol.

She is wondering how to proceed in light of the new recommendations.

Ms. T's Story

I first learned I had high cholesterol about 15 years ago. The good cholesterol is relatively high, but the bad cholesterol is also high, so I worried about it initially. It is scary, and I have taken some other medications like red yeast to see if I can get it lower, but I am not very good about taking medication. Because the good cholesterol was high, my doctor was not necessarily concerned immediately, but I think now might be the time to do something about it.

We really have not talked about a particular type of medication. We talked about diet, like limiting cheese and things like that. I am Italian, so it is very difficult to get away from that type of food, but I try. As far as exercise, I used to walk about 18 miles a week back and forth to work. Since I have retired that has changed a bit, but I am back to walking probably about 15 miles a week. I have never kept track of whether exercise affects my cholesterol levels.

I know stroke and heart attack could be caused by my high cholesterol. In the back of my mind I am always concerned that they are going to happen no matter what, though I looked at my family history and we do not necessarily have a history of stroke—we are very healthy people. My mom is still alive, and she is 89.

In talking with my doctor about how to go forward, we have just kind of waited a little bit. I do not know why, but I think the issue is that she felt good that the good cholesterol was high. I would have to look into medication before taking it, naturally, but I would be willing to try it. I would think about what my risk would be if medication were prescribed and what effect it would have on me, if any.

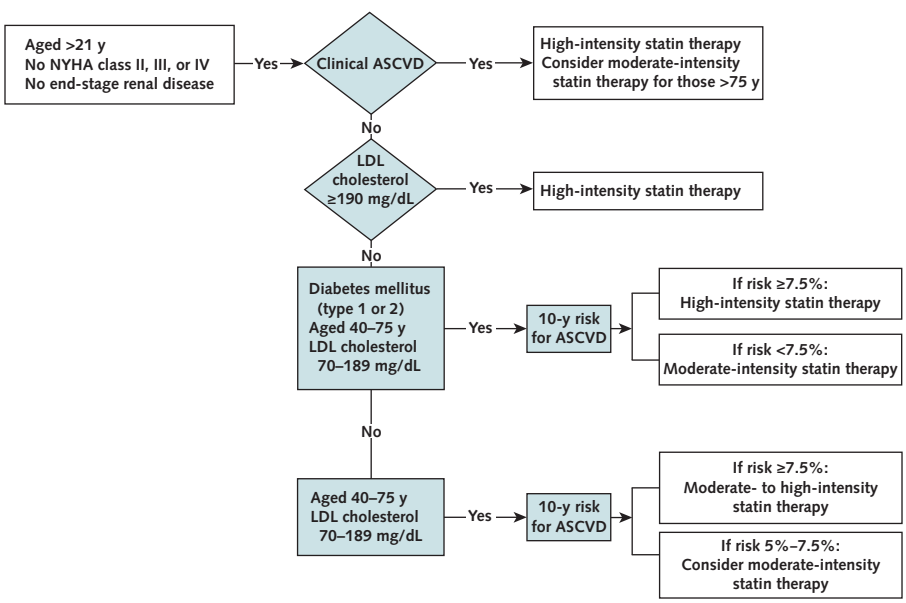
See the **Patient Video** (available at www.annals.org) to view the patient telling her story.

Context, Evidence, and Guidelines

In 2013, the ACC/AHA issued an updated guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. The National Heart, Lung, and Blood Institute (NHLBI) initiated this collaboration and charged an expert panel with the goal of reviewing the highest-quality evidence from randomized, controlled trials (RCTs); systematic reviews; and meta-analyses of RCTs to update the clinical practice guidelines. The panel addressed treatment of blood cholesterol levels to reduce risk for ASCVD, including risk for coronary heart disease, stroke, and peripheral vascular disease. The recommendations are intended to provide a strong evidence-based foundation for primary and secondary prevention of ASCVD (4).

The expert panel recommended that lifestyle modification, including adhering to a heart-healthy diet, exercising regularly, avoiding tobacco products, and maintaining an ideal weight, form the foundation of ASCVD risk reduction efforts and should be initiated before, or in concert with, cholesterol-lowering drug

Figure 1. Algorithm for high- and moderate-intensity statin therapy for various risk groups.



From reference 3. ASCVD = atherosclerotic cardiovascular disease; LDL = low-density lipoprotein; NYHA = New York Heart Association.

Table 1. Statin Therapy*

Statin	High-Intensity†	Moderate-Intensity‡	Low-Intensity§
Atorvastatin	40–80	10–20	–
Rosuvastatin	20–40	5–10	–
Simvastatin	–	20–40	10
Pravastatin	–	40	10–20
Fluvastatin	–	40 twice daily or 80 XL	20–40
Pitavastatin	–	2–4	1

XL = extended-release.
* Adapted from reference 3. Values are in milligrams. Only moderate-intensity statin therapy should be used in persons aged ≥75 y or in those with safety concerns.
† Low-density lipoprotein cholesterol level decreased by ≥50%.
‡ Low-density lipoprotein cholesterol level decreased by 30% to <50%.
§ Low-density lipoprotein cholesterol level decreased by <30%.

therapies. Drug therapy for other related risk factors, such as hypertension and diabetes, should also be initiated if necessary.

The eligible RCTs found a consistent reduction in ASCVD events from statin therapy for primary and secondary prevention, with the exception of persons with New York Heart Association class II to IV heart failure or those receiving maintenance hemodialysis. As the RCTs compared fixed doses of statins and were not designed to evaluate titrated (that is, dose-adjusted) statin treatment, the expert panel's recommendations focus on choosing the most appropriate intensity of therapy (low, moderate, or high) to reduce ASCVD events. The expert panel also found that nonstatin therapies do not appreciably reduce ASCVD risk and have the potential for adverse effects.

The panel identified the following 4 groups for which strong RCT evidence indicates that reduction in ASCVD events from statin therapy exceeds adverse events: persons needing secondary prevention of ASCVD; persons needing primary prevention for LDL cholesterol levels of 190 mg/dL or greater; persons aged 40 to 75 years with comorbid diabetes needing primary prevention for LDL cholesterol levels of 70 to 189 mg/dL; and persons aged 40 to 75 years who do not have comorbid diabetes needing primary prevention for an estimated 10-year ASCVD risk of 7.5% or greater and LDL cholesterol levels of 70 to 189 mg/dL. According to the guideline, moderate evidence supports the use of statins for primary prevention in persons with a 10-year ASCVD risk of 5% to less than 7.5%, whereas selected individuals with a 10-year risk less than 5% may potentially benefit.

For primary prevention, the panel suggested using the pooled cohort equation to estimate 10-year ASCVD risk, to guide initiation of statin therapy, and to determine intensity of statin therapy. This new risk assessment tool was developed from studies that reflected the risk profile of the general population rather than selected groups. In addition, the equation assesses risk for death from nonfatal and fatal myocardial infarction and nonfatal and fatal stroke (5). It is intended to advance ASCVD risk estimation by providing sex- and race-specific estimates and including stroke as an outcome; however, some studies have observed overestimation of ASCVD risk using this new equation (6).

For persons who would benefit from ASCVD risk reduction with a statin, the panel recommends basing the intensity of therapy on the average LDL cholesterol response to a specific dose. For secondary prevention in persons who have had an ASCVD event, high-intensity statin therapy has greater benefit (that is, reduction in ASCVD events) than moderate-intensity therapy, although therapy should be individualized in persons older than 75 years and those with safety concerns, in whom moderate-intensity statin therapy should be considered (**Figure 1**).

For primary prevention, the absolute benefit in ASCVD risk reduction depends on the absolute baseline ASCVD risk. As shown in **Figure 1**, the guideline recommends initiating high-intensity statin therapy for persons with an LDL cholesterol level of 190 mg/dL or greater, and for persons with diabetes aged 40 to 75 years who have an LDL cholesterol level of 70 to 189 mg/dL and 10-year ASCVD risk of 7.5% or greater. The guideline recommends moderate- to high-intensity statin therapy for patients with diabetes aged 40 to 75 years with an LDL cholesterol level of 70 to 189 mg/dL whose 10-year ASCVD risk is less than 7.5%, as well as for those without diabetes whose 10-year ASCVD risk is 7.5% or greater. Lastly, the guideline suggests considering initiation of moderate-intensity statin therapy for patients whose 10-year ASCVD risk is 5% to less than 7.5%. Although statin therapy increases the risk for type 2 diabetes, the expert panel believed that in persons with a 10-year ASCVD risk of 5% or less, the reduced ASCVD risk was sufficient to outweigh the increased diabetes risk. Options for high-, moderate-, and low-intensity statin therapies are shown in **Table 1**.

Once the appropriate therapy is initiated, a fasting lipid panel is recommended. However, it should no longer be used as a treatment goal or performance measure. "Treating to goal" could result in treatment with suboptimal statin intensity, or adding nonstatin therapy in the absence of RCT evidence (4). Routine monitoring of hepatic aminotransferase level or creatinine kinase level is also not recommended.

The expert panel encourages clinicians to use the guideline as a starting place for conversations with patients, especially those for which a statin is being initiated for primary prevention. Physicians and patients are encouraged to discuss the potential for benefits, adverse effects, drug interactions, and patient preferences. This dialogue can also serve as an opportunity to discuss lifestyle habits and other efforts to reduce risk.

CLINICAL QUESTIONS

To help decide how to balance these factors and to structure a debate between the 2 discussants, we focused on consideration of the following key questions when applying this guideline to clinical practice in general and to Ms. T in particular.

Question 1: How would you suggest assessing this patient's risk for an ASCVD event?

Question 2: What do you think are the risks and benefits of starting this patient on a statin? How would you present this information to the patient?

Question 3: If starting this patient on a statin, would you treat to target or institute a moderate- or high-intensity statin?

DISCUSSION

A Cardiologist's Perspective (Dr. Murray Mittleman)

Question 1: How do you suggest assessing this patient's risk for an ASCVD event?

In thinking about the risk for an ASCVD event, the AHA/ACC risk calculator is an excellent starting point (3), but it does not tell the whole story. The risk calculator is designed to estimate the average *expected* risk in a population with the characteristics entered into the risk equation. However, the equation does not take all known risk factors into account. In Ms. T's case, we are told that there is no family history of cardiovascular events, let alone early-onset events that seem to convey the most information about elevated risk. While it could be argued that some of the association between family history and ASCVD events flows through risk factors that are included in the risk calculator, such as total cholesterol and HDL cholesterol levels and systolic blood pressure, these pathways do not account for the entire association. Another important aspect of the history is that Ms. T has made lifestyle choices that are associated with a reduced risk for ASCVD events, including habitual physical activity, prudent dietary choices, not smoking, and maintaining a healthy weight. Like family history, some of the association between lifestyle factors and ASCVD events is mediated through changes in lipids and blood pressure, but these measurable physiologic changes do not fully account for the protective effect of lifestyle choices. Indeed, data from the Nurses' Health Study suggest that more than 80% of coronary heart disease events could be attributed to not smoking, not being overweight or obese, engaging in moderate or vigorous physical activity for at least 30 minutes daily, drinking at least one half of an alcoholic beverage daily, and scoring in the top 40% of a healthy diet score (7). On one hand, Ms. T adheres to all of these lifestyle choices except alcohol intake, so we can assume that her risk may be somewhat lower than the average woman with a similar profile entered into the risk calculator. On the other hand, we are told that she has a history of psoriasis, which has been associated with a higher risk for ASCVD events in the General Practice Research Database and in other studies (8).

To accurately gauge Ms. T's ASCVD risk, other health information may be useful. Some suggest measuring high-sensitivity C-reactive protein (CRP), which has been shown to predict ASCVD risk and is included in alternative risk calculators, such as the Reynold risk score (9). Some authors suggest obtaining cardiac computed tomography to measure coronary calcium score (10). Although both of these measures have been shown to predict risk, there is currently no clear evidence that further testing would improve the clinical outcome for a patient like Ms. T.

Table 2. 10-y Risk Estimation for Ms. T*

Pooled Cohort Equation (Atherosclerotic Cardiovascular Disease)	Framingham Risk Score (Coronary Heart Disease)	Reynolds Risk Score (Atherosclerotic Cardiovascular Disease)
11	4	2–4

* Values are percentages.

Another important consideration is whether the AHA/ACC ASCVD risk calculator is appropriately calibrated. The calculator was constructed using data collected over the past several decades, and there is some evidence in the literature that it may overestimate 10-year risk of ASCVD in contemporary populations (6, 11). To account for potential overestimation, some authors have recommended increasing the threshold for statin treatment among 40- to 75-year-olds without diabetes or ASCVD and LDL cholesterol levels between 70 to 189 mg/dL, from 7.5% to a 10-year risk of at least 15%, and expanding the range for assessing patient preferences before recommending statin therapy from a baseline risk of 5% to 7.5% to those with a baseline risk of 5% to 15% (10). Ms. T's estimated risk is 11.2%–even if it were overestimated by 30%, as suggested by the analysis of Cook and Ridker (11), 10-year risk would still be approximately 8.6%.

When the recommendation to treat with moderate-intensity statin therapy for primary prevention is being considered, it is important to determine the number needed to treat (NNT) to prevent 1 ASCVD event. A meta-analysis of the RCTs showed evidence that moderate-intensity statin therapy in primary prevention results in a relative risk reduction of approximately 20% (12). Thus, if we assume that, if untreated, Ms. T's risk is truly 11.2%, then we would need to treat 45 similar patients to prevent 1 ASCVD event. On the other hand, if we account for the potential 30% overestimation of risk, then the NNT to prevent 1 event would increase to 59 patients. This compares favorably with the number of patients with moderate hypertension needed to treat with thiazide diuretics to prevent 1 ASCVD event (13), the choice made by Ms. T and her physician.

Question 2: What do you think are the risks and benefits of starting this patient on a statin? How would you present this information to the patient?

The primary benefit of instituting treatment with a moderate-intensity statin in a patient like Ms. T is the expected reduction in her risk for an ASCVD event (3, 4). For some patients, this provides some peace of mind that they are taking action beyond lifestyle approaches to help lower their probability of having a potentially catastrophic cardiovascular event. Moderate-dose statin therapy comes with a small, finite risk for adverse effects, including the occurrence of type 2 di-

abetes (1 excess case per 1000 patients per year). Patients should be screened for diabetes according to current guidelines (3). Because statins can cause muscle symptoms, including pain, tenderness, stiffness, cramping, weakness or general fatigue, and very rarely rhabdomyolysis, it is important to inform patients of these risks and monitor for symptoms. Likewise, statins can rarely cause hepatotoxicity, so it is important to inquire about symptoms suggestive of liver dysfunction, including unusual fatigue, loss of appetite, abdominal pain, dark urine, or jaundice (3).

Although the risks of statin therapy are generally low and routine monitoring of levels of transaminase or creatinine kinase in asymptomatic patients is unnecessary, some patients may be at higher risk for adverse effects and should be monitored more closely. These include patients with multiple or serious comorbidities, such as impaired kidney or liver function; muscle disorders; history of statin intolerance; need for treatment with drugs that affect statin metabolism; and history of hemorrhagic stroke and those older than 75 years (3).

Question 3: If starting this patient on a statin, would you treat to target or institute a moderate- or high-intensity statin?

I would counsel Ms. T to maintain her active lifestyle and institute further dietary modifications. I would inform her of her predicted risk for an ASCVD event and the potential to lower the risk with statin therapy. I would also discuss the potential risks. If she elects to begin pharmacotherapy, I would take a detailed history regarding musculoskeletal and gastrointestinal symptoms and measure alanine transaminase and creatinine kinase levels at baseline before starting moderate-intensity statin therapy. Unless there were symptoms suggesting an adverse effect, I would not routinely monitor transaminase or creatinine kinase levels. I would not treat to a specific LDL goal. Rather, I would check her LDL at least once after 3 months of therapy to provide her with feedback on the results of treatment. As long as it was not extremely low (under 40 mg/dL), there would be no reason for routine monitoring unless her clinical situation changed.

A Primary Care Physician's Perspective (Dr. William Taylor)

Question 1: How would you suggest assessing this patient's risk for an ASCVD event?

Authors of the 2013 ACC/AHA guideline advocate greatly expanding the number of Americans treated with statins, claiming that their recommendations are based on evidence. The expansion derives largely from the application of a new risk estimator in primary prevention—that is, to those without clinically evident ASCVD (14). The guideline includes a recommendation to consider treatment with a statin when 10-year risk of ASCVD exceeds 5%, and a strong recommendation to treat when 10-year risk exceeds 7.5%. However, an examination of the evidence reveals serious shortcomings of the risk estimator and little support for the 5% and 7.5% thresholds (6, 10, 11, 15–18). The risk estimator has been shown repeatedly to overestimate risk in the range of 50% to 100% (6, 14). Overestimation probably results from the application of rates of development of ASCVD from cohorts assembled many years ago, thereby failing to account for decreasing rates of ASCVD in the United States in the past several decades. And overestimation for Ms. T (and everyone for whom risk is calculated today or in the future) may be greater than current studies show, since the estimation of risk involves prediction of future events, when rates of ASCVD will be lower if current trends continue.

Table 3. Problems With 10-y Risk for ASCVD as a Measure of Ms. T's Risk

Topic	Problem	Solution
Risk for ASCVD is a composite measure	Provides equal weight to outcomes of differing utility	Separate outcomes or weight based on patient's preferences*
10 y is an arbitrarily selected interval	10-y interval has no evidentiary support; most relevant trials (and meta-analyses) evaluate intervals ≤5 y	Select a shorter interval; make clear the implications of interval length on presentation of risk
Interval length influences risk calculation	If secular trends continue with declining rates of ASCVD, longer intervals will increasingly compound the calibration error shown for the estimator based on the pooled cohort equation and will lead to overestimation errors with other risk estimators, as well	Use a shorter interval; make clear the implications of uncertainties in risk prediction and opportunities for overestimation on presentation of risk
Calculation of risk at older ages	Calculation of risk over 10 y for a woman aged 67 y involves estimating risk for women aged >75 y, when less is known about the effect of statins on risk† and the effect of blood LDL-C level on risk may decrease (20)	Use a shorter interval; make clear the implications of uncertainties and opportunities for overestimation in risk prediction on presentation of risk
Timing of risk for an ASCVD event	The same event is more undesirable the sooner it occurs; the failure to consider this topic is compounded as the interval increases	Use a shorter interval; incorporate discounting based on patient's preferences*
Increase in risk for ASCVD with age	As the interval increases, most predicted ASCVD events occur later, when risk prediction is more uncertain and events have less effect/are less undesirable	Use a shorter interval; make clear the implications of uncertainties and opportunities for overestimation in risk prediction on presentation of risk

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
* "Patient preferences play an important role in all treatment decisions, especially for individuals with a 10-year ASCVD risk <7.5%" (19).
† " . . . few clinical trial data are available for primary prevention in women older than age 75" (19).

Table 2 shows Ms. T's 10-year risk using 3 estimators. Her risk ranges from 2% to 11%, depending on the estimator and outcome. All 3 estimators use 10-year risk, itself a concept rife with problems. Anyone using this measure of risk should understand its shortcomings or, better, provide patients, including Ms. T, with a less problematic risk estimate.

Table 3 lists some of the problems in conveying risk with a calculation of ASCVD expected in 10 years and identifies ways that a shorter interval, such as 1 year, would mitigate some of these problems (19, 20). To estimate yearly risk, the calculated risk of 11% over 10 years can be apportioned each year according to risk for death from all causes (21) as shown in Table 4. When 10-year risk is apportioned in this manner, 7 of 1000 women with Ms. T's risk characteristics would be expected to experience an ASCVD event in 1 year. To account for the pooled cohort equation's overestimate of risk (6, 14), the predicted number of ASCVD events in the first year must accordingly be adjusted downward, resulting in an estimate of 4 or possibly fewer events per 1000 women in the first year.

Table 4. Yearly Risk for an ASCVD Event Derived From 11% Risk in 10 y From Pooled Cohort Equation Calculator Apportioned According to Annual Risk for Death for Women*

Age, *y*	Risk for ASCVD, %
67–68	0.7
68–69	0.8
69–70	0.8
70–71	0.9
71–72	1.0
72–73	1.1
73–74	1.2
74–75	1.3
75–76	1.4
76–77	1.6
Total	11†

ASCVD = atherosclerotic cardiovascular disease.
* Adapted from reference 21.
† Numbers do not sum exactly due to rounding.

Question 2: What do you think are the risks and benefits of starting this patient on a statin? How would you present this information to the patient?

A careful reading of the guideline demonstrates the weakness of the evidentiary support for treatment with a moderate-intensity statin for women like Ms. T who do not have clinically evident ASCVD. Authors of the guideline recommend that treatment with a moderate-intensity statin be considered for primary prevention when 10-year risk for ASCVD is between 5% and 7.5%, the range most likely appropriate for Ms. T after adjustment for the estimator's overestimate of risk. Yet the recommendation to treat at this level of risk is based on a flawed analysis.

The recommendation to treat with a moderate-intensity statin is derived from the panel's conclusion that treatment would lower risk for an ASCVD event by 25% over 10 years in women as well as men. To reach this conclusion, the authors cited 2 primary prevention trials (22, 23). Each of these studies showed a benefit for all participants, yet neither demonstrated a benefit among women. The authors ascribed the failure to demonstrate benefit among women to lack of power. However, they neglected to include ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial) in their analysis (24). ALLHAT-LLT was an appropriately powered, randomized trial designed and conducted by the NHLBI specifically to answer several important questions, among them whether statin treatment benefits women without clinically evident ASCVD (24). In this trial, in which 5051 women with hypertension and LDL cholesterol levels of 120 to 189 mg/dL were treated over a period of 4.8 years, LDL cholesterol was reduced by 17% in those randomly assigned to pravastatin compared with those randomly assigned to usual care, but no significant benefit was found. Although authors of the study ascribed these results to crossover and argued that the negative findings could be ignored, the results speak for themselves. Despite the guideline's claim that evidence supports treating patients like Ms. T with a moderate-intensity statin, evidence from trials, as shown in Table 5, is weak—indeed, some might argue that it is nonexistent.

Although they found little or no direct evidence to support such treatment from trials, guideline authors argued that meta-analysis (12, 25–27) supported their recommendation to treat women like Ms. T. However, meta-analysis has known shortcomings that are compounded by potential biases, especially when available studies have been conducted or sponsored by industry, as were many statin trials other than ALLHAT-LLT (28–31). Even if these problems with meta-analysis are ignored and estimates of benefit from meta-analysis are accepted, the estimate of benefit of statin treatment must be adjusted downward from the 25% reduction in ASCVD events over 10 years claimed by guideline authors. The meta-analysis used by the authors found the reduction in ASCVD events among women to be 15%, not 25% (32). Of note, authors of the meta-analysis themselves emphasized the caveat that their data covered only a 5-year time span, because trials of statins rarely lasted longer (32).

What about the potential for harm from statin treatment for Ms. T? Authors of the guideline went to some length to develop an estimate of the harms of statin treatment against which to balance its benefits. They found insufficient evidence to consider risk from hemorrhagic stroke or rhabdomyolysis and settled on risk for new-onset diabetes, derived mainly from JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), a trial of a high-intensity statin therapy stopped after a mean duration of 1.9 years due to dramatic reductions in events (33). However, application of results from JUPITER to patients like Ms. T is based on little more than speculation because Ms. T's LDL cholesterol was not less than 130 mg/dL and her level of high-sensitivity CRP was not

Table 5. Primary Prevention Trials Using Moderate-Intensity Statin Therapy With Women Enrolled in Trial

Study (Reference)	Protocol	Results	Application to Ms. T
AFCAPS/TexCAPS (22)	Men and women in the United States with average LDL-C levels, low HDL-C levels, randomly assigned to lovastatin or placebo	After 5.2 y, significant reductions in CV events; no significant reductions in events among women	Ms. T. would not have met entry criteria
MEGA (23)	Men and women in Japan without clinically evident ASCVD, total cholesterol levels of 5.70–6.99 mmol/L (220–270 mg/dL), randomly assigned to pravastatin plus diet or diet alone	After 5.3 y, significant reductions in CV events; no significant reductions in events among women	Ms. T would not have met entry criteria
ALLHAT-LLT (24)	Men and women in the United States with hypertension and LDL-C levels of 3.10–4.89 mmol/L (120–189 mg/dL) randomly assigned to pravastatin or usual care	After 4.8 y, no significant reductions in CV events; no significant reductions in events among women	Ms. T would have met entry criteria

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese.

known to be 2 mg/L or greater, JUPITER's 2 major inclusion criteria.

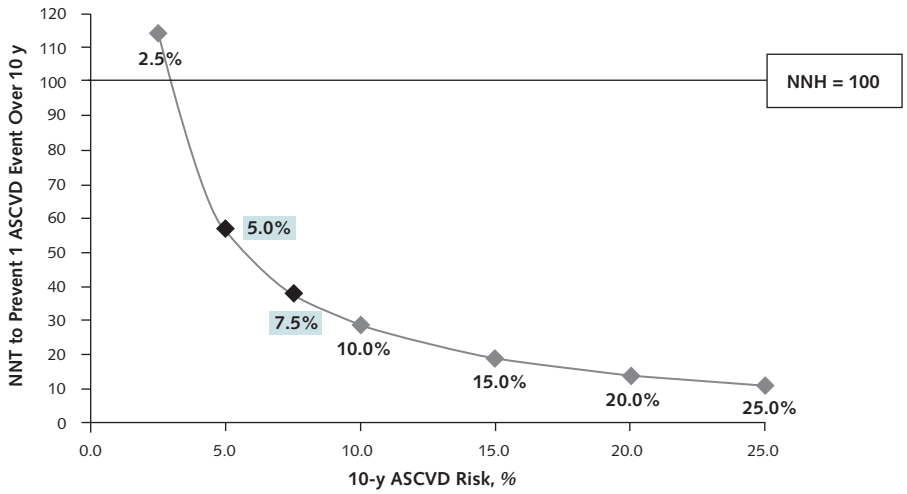
The guideline ignores more troublesome potential harms. Just as the ability to identify benefits of statin treatment is limited by inadequate power and short duration of trials as well as potential shortcomings and biases in meta-analyses, these same limitations impair the ability to identify harms with confidence. It has become clear that statins do much more than reduce blood cholesterol levels. Given the remarkable list of the pleiotropic effects of statins (34–38), it is naive and potentially dangerous to assume that they cannot cause adverse effects with long-term use. Problems like the U-shaped relationship between cholesterol level and mortality, and recurring concerns about the effect of cholesterol reduction on mortality, serve as cautionary tales (39, 40). In addition, although later trials provided sufficient reassurance to allay initial concerns (24, 41), the remarkably high rate of breast cancer in 1 trial of statin treatment (42) is a reminder that the harms of these drugs may not yet be fully appreciated.

Guideline authors contend that statin treatment is justified as primary prevention for women as well as men aged 40 to 75 years when the number needed to harm in 10 years exceeds the NNT and conclude, based on their analysis, that treatment should be considered when 10-year risk for ASCVD exceeds 5%. They contend that strong evidence supports treatment when 10-year risk for ASCVD exceeds 7.5% and that both thresholds can be derived from their analysis, summarized by Figure 2 reproduced from the ACC/AHA Full Panel Report Supplement (19). However, a decision to treat based on this analysis is flawed for several reasons. A mere arithmetic comparison of NNT and number needed to harm has no rational basis. For Ms. T and many others, such analysis fails to acknowledge important limitations. The lack of comparability of harms and benefits invalidates numerical comparison and does not account for the influence of time or explain the arbitrary use of a 10-year interval. It also fails to note that the major effect of hypothetical benefits occurs at the latter part of a 10-year interval, a time when benefits are least certain. It also does not account for the concept of "discounting," whereby benefits achieved later are worth less and risks faced sooner are more troublesome (43). Most important, it does not account for the unknowns regarding benefits and risks of statins for primary prevention. This is especially problematic in women Ms. T's age, when the computation of benefit extends into a period for which virtually no data from trials are available. Based on these arguments, there is more in question than the appropriateness of the 5% and 7.5% thresholds. Rather than demonstrating that benefits and harms of primary prevention can be predicted confidently over 10 years, current evidence supports a more modest approach to advising Ms. T about the potential benefits and harms of statin treatment. Table 6 shows the NNT based on Ms. T's 11% risk for an ASCVD event in 10 years from the pooled cohort equation estimator. Based on all the factors enumerated above, more accurate calculations would produce considerably higher NNTs, in other words, many more people would require treatment for one to benefit.

Question 3: If starting this patient on a statin, would you treat to target or institute a moderate- or high-intensity statin?

I would remind Ms. T that it is difficult to predict the future. If she were seen by a primary care physician today, I believe she should be told that a respected group of national experts has estimated the benefits and harms she might experience if she were to take a statin every day for the next 10 years and concluded that they believe the benefits in reduced occurrence of ASCVD outweigh the harms, including a risk that statin treatment might cause diabetes. These experts also acknowledged that use of the guideline should be flexible, leaving room for individualization based on the patient's characteristics and values and the physician's input and judgment. She should be reminded that she is doing a fine job in reducing her risk with her efforts to avoid tobacco use, maintain ideal body weight, exercise regularly, and eat a healthy diet. Blood pressure control will also contribute to keeping her risk down. If medical practice allowed time for a reasoned discussion (44) and if Ms. T were comfortable with numbers

Figure 2. Moderate-intensity statin treatment. Reproduced from the ACC/AHA Guidelines Full Panel Report Supplement, page 70 (19).



Assumes a 35% relative risk reduction in ASCVD. NNT to prevent 1 ASCVD event varies by baseline estimated 10-y ASCVD risk. The NNH is based on 1 excess case of incident diabetes per 100 individuals treated with statins for 10 y. ACC/AHA = American College of Cardiologists/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; NNH = number needed to harm; NNT = number needed to treat.

and would like to understand benefits and risk in such terms (45), she could be told that her risk for a stroke or heart attack in the next year is likely to be much less than 1 in 100, and probably closer to 1 in 1000. The experts who wrote the guideline believe that statins reduce that risk by about 25% based mainly on evidence from men—experience with women is much more limited. If her risk for a stroke or heart attack were 4 in 1000 in the next year, a 25% reduction would bring it down to 3 in 1000. She could be asked, "How does that sound to you?" Although fixed-dosed statin treatment has more evidentiary support than treating to goal as explained in the guideline, a fully informed patient might be more likely to take a different approach when presented with this information, an approach that might not include taking a statin at this time but rather waiting to see whether her physician has any new information on these issues next year when she returns for another discussion.

SUMMARY

Ms. T tells us that she "would have to look into medication before taking it, naturally, but I would be willing to try it. I would think about what my risk would be if medication were prescribed and what effect it would have on me, if any." While our discussants share many opinions with regard to Ms. T's risk for an ASCVD event, some important differences emerged in their presentations. Both agree that the new pooled risk calculator may overestimate risk by 30% to 50% or more (11). If this is the case, Ms. T's 10-year risk may be only 8.6% or less, rather than 11.2%. Dr. Mittleman points out that even if it is 8.6%, the guideline would still recommend moderate-intensity statin therapy. Dr. Taylor thinks that even 8.6% could be an overestimate and her risk could be as low as 2% to 4% if the Reynolds risk score was used (46). Although Dr. Mittleman did not think her risk was as low as 4%, he agreed that it may be lower than the average expected risk given her heart-healthy lifestyle, ideal body weight, family history, and lack of other cardiac risk factors aside from hypertension.

Our discussants also disagreed on the strength of evidence for initiating a statin. Dr. Mittleman believed that the available evidence was as good for women as for men, based on the work by Mora and colleagues (47), and that statins decrease the risk for an ASCVD event by 20% to 25% regardless of the baseline risk estimate. Dr. Taylor did not agree, especially given the ALLHAT-LLT findings that treatment effects for women were not well-established (24).

Table 6. Derivation of NNT Based on 11% Risk in 10 y From Pooled Cohort Equation Estimator

Age, *y*	Risk for ASCVD, %	Assume Statin Treatment Reduces Risk by 25%, %	Absolute Risk Reduction, %	NNT
67–68	0.69	0.52	0.17	588
68–69	0.75	0.56	0.19	526
69–70	0.82	0.61	0.21	476
70–71	0.89	0.67	0.22	454
71–72	0.97	0.73	0.24	417
72–73	1.06	0.80	0.26	384
73–74	1.16	0.87	0.29	345
74–75	1.28	0.96	0.32	313
75–76	1.41	1.06	0.35	286
76–77	1.55	1.16	0.39	256
Total	11*	7.94	2.64	38

ASCVD = atherosclerotic cardiovascular disease; NNT = number needed to treat.
* Numbers do not sum exactly due to rounding.

Both agreed that absolute risk reduction was important. For example, if Ms. T's risk was 11%, a 20% risk reduction would mean that, if she received treatment, her risk over the next 10 years would be about 9%. In other words, 45 patients like Ms. T would need to be treated to prevent an ASCVD event. However, if her risk was actually 8.6%, the NNT would be 59; if her risk was closer to 2%, the NNT would be 256. Dr. Taylor also pointed out that most of the calculated benefit occurs in the later years, whereas the potential harm occurs sooner.

Our discussants agreed that statins carry risk for harm, including muscle pain, hepatotoxicity, hemorrhagic stroke, and diabetes and that this risk is greatest in persons older than 75 years. Dr. Taylor also noted that several primary prevention trials failed to lower total mortality despite reductions in ASCVD events (48), raising questions about potential harm from longer-term statin use (39, 49). This contrasts with hypertension, in which treatment consistently decreases total mortality across a clinically relevant and wide range of target blood pressures.

Both discussants recommended a heart-healthy lifestyle and treatment of other cardiovascular risk factors. Dr. Mittleman believed that the evidence was strong enough to recommend a fixed dose of a moderate-intensity statin as suggested by the guideline. Dr. Taylor disagreed; he would wait for better evidence before treating. They both agreed, however, that the patient would benefit from better control of her hypertension.

This case presents several high-value care considerations. First, the pooled cohort equation may overestimate risk by 30% to 50%, leading to overtreatment. Second, there is disagreement over the strength of evidence for initiating statins in women, again potentially leading to overtreatment. It is important to consider all known risk factors, including family history, lifestyle, and other noncardiovascular comorbid conditions, and to understand how the patient values the potential for current drug-related harm versus the future benefit of ASCVD risk reduction. Finally, shared decision making is important when whether to initiate a statin is being considered.

Both discussants agreed that research is needed to develop more accurate risk prediction tools, to evaluate statins in women and in persons older than 75 years, to test alternative dosing regimens, and to evaluate nonstatin therapies for ASCVD risk reduction.

Of note, since this grand rounds presentation, a new study has compared cardiovascular risk scores (50); it showed that the pooled cohort equation overestimates risk in men by 37% to 154% and in women by 8% to 67%. Readers may want to review this new information when forming an opinion on the appropriateness of starting a statin. A transcript of the audience question-and-answer period is available in the **Appendix** (available at www.annals.org). To view the entire **Conference Video**, including the question-and-answer session, go to www.annals.org.

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Appendix: Questions and Comments

Dr. Smetana: Thank you to both of our discussants. Now think about the questions you would like to ask. I am going to take the license to ask the first question, but we will be passing around handheld microphones for those who would like to ask questions of our discussants. And my first question, for which the answer can be brief, is who actually wrote these guidelines? Were they written by cardiologists, primary care doctors, by epidemiologists? I wonder if that would have changed the outcome of the guideline.

Dr. Mittleman: It was a pretty broad panel, but probably more heavily weighted toward epidemiologists and cardiovascular specialists. Several of the epidemiologists are primary care physicians, like David Goff and a number of others.

Dr. Smetana: All right–let's take some time for questions from the audience. With your question, please introduce yourself by name and then ask your question.

Dr. Tom Delbanco: You usually only get one shot at a patient, and listening to this patient as carefully as I could, she said she doesn't like taking medicines very much, and I also noticed that her blood pressure was not so terrific, for one thing. I think it is far more important for her to have a good blood pressure than a lower cholesterol, and my suspicion is that if you throw another pill at her and it is a statin, there is a good chance she will take neither of them as much as she is now, which I am not sure she is taking. So I would push her hypertension and make a trade with her: I would say, "I will leave your statins alone if you got your blood pressure down." What do you think, Dr. Taylor?

Dr. Taylor: I think that Tom was my boss and teacher for many years and I would not disagree with him.

Dr. Mittleman: I also would use that as a starting point; once again, her risk equation is being driven by her hypertension. If her blood pressure were better controlled, that estimated risk might fall into the range where you would no longer recommend a statin. So that is not at all an unreasonable first approach.

Dr. Gordon Strewler: We haven't heard much about her HDL. How does that enter your thinking?

Dr. Mittleman: Her HDL is terrific and has even increased over time as she has increased her level of exercise. We are seeing the benefit of exercise. Her HDL is figured into a risk calculator–remember, it's total cholesterol and HDL–so the risk estimate is already incorporating the HDL.

Dr. Taylor: And it may be, this is speculation, that as time goes on, the LDL might be less predictive and the HDL might still be protective. There is some evidence from the Framingham Heart Study that total cholesterol, and therefore likely LDL, drops out as a predictor for men over 65 and women older than 75 years, but HDL continues to predict risk.

Dr. Smetana: Dr. Bates?

Dr. Carol Bates: First, let me unmask myself; I was the second person who voted no. One of the things that has really troubled me about the new guideline is the leap to high-intensity cholesterol treatment. My anecdotal experience is that the muscle side effects are dose-related. If exercise is important and people stop exercising because their muscles ache, it's troubling to me to jump to 40 to 80 milligrams of atorvastatin.

Dr. Mittleman: I agree with that concern. For a patient like Ms. T, the recommendation was moderate intensity, which was 10 to 20 milligrams of atorvastatin or 5 milligrams of rosuvastatin, for example. So you could use the lowest dose of a high-potency statin, which has far fewer muscle side effects. In the conclusion of my talk, I said one of the key points that we need for future research is to resolve that issue. There may be better methods, but based on the available evidence I think that these are very reasonable approaches.

Dr. Anthony Hollenberg: How about a biologic plausibility with recent genetic studies that correlate mutations that influence LDL levels with cardiac risk in terms of influencing whether you treat somebody with high LDL?

Dr. Mittleman: I agree. Randomized trials and Mendelian randomization studies support that LDL is likely on a causal pathway, whereas some other risk markers are not. Whereas similar Mendelian randomization studies of high-sensitivity CRP suggest that it may not be on a causal pathway, even though inflammation seems to be at the heart of pathobiology. Treatments specifically targeting CRP, for example, are not supported by these studies, whereas targeting LDL has biologic rationale.

Dr. Taylor: That is why you might ask Ms. T to come back in a year or two when you know a little more about those kinds of issues.

Dr. Bradley Crotty: She has made great efforts in exercise and diet and this is sort of curious. How much is good enough? Because Dr. Mittleman, at the end your counseling was still to continue doing that, which I think we would all agree with. At what point do you, if you are going to do that, say, okay enough is enough, let's make a decision. We could always go one more year more and one year more.

Dr. Mittleman: In our practice, we really push the lifestyle changes because they are the cornerstone of therapy. There are benefits that go above and beyond what we measure in blood tests. In her case, Ms. T has

done a terrific job, particularly with exercise, which is evident in terms of weight maintenance and the progressive increase of HDL over time. She discusses her diet in the extended video that was not shown today, and it's completely consistent with what we understand to be an excellent approach. A very good reference for that is the Predimed study that showed reductions in diabetes and cardiovascular disease incidence with a diet that had a pretty high plant-based fat content, primarily in the form of extra virgin olive oil and tree nuts. So, when I said I would tweak her diet, it is more in keeping with the current evidence, as opposed to hammering down on avoidance of dietary cholesterol, considering there is really no evidence that it reduces risk.

Dr. Taylor: I would start with her and her values, what this is for her in her life. We all know that emphasizing diet and exercise a little bit more, whether she is actually going to achieve it, if you calculate it, how much better off is she for doing that, it is pretty marginal. I would encourage her to do what she is doing, give her lots of support, and not push too hard and make her feel like Sisyphus–that no matter what she does she has to roll the rock further up the hill.