Annals of Internal Medicine

CLINICAL GUIDELINE

Management of Dyslipidemia for Cardiovascular Disease Risk Reduction: Synopsis of the 2014 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline

John R. Downs, MD, and Patrick G. O'Malley, MD, MPH

Description: In December 2014, the U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) approved a joint clinical practice guideline for the management of dyslipidemia for cardiovascular disease risk reduction in adults. This synopsis summarizes the major recommendations.

Methods: On 30 September 2013, the VA/DoD Evidence-Based Practice Work Group convened a joint VA/DoD guideline development effort that included clinical stakeholders and conformed to the Institute of Medicine's tenets for trustworthy clinical practice guidelines. The guideline panel developed key questions, systematically searched and evaluated the literature, developed a simple 1-page algorithm, and rated each of 26 recommendations by using the Grading of Recommendations Assessment, Development, and Evaluation system.

Recommendations: This synopsis summarizes key features of the guideline in 5 areas: elimination of treatment targets, additional tests for risk prediction, primary and secondary prevention, and laboratory testing.

Ann Intern Med. 2015;163:291-297. doi:10.7326/M15-0840 **www.annals.org**

For author affiliations, see end of text.

This article was published online first at www.annals.org on 23 June 2015.

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the United States and globally (1). Addressing CVD is a priority for the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD). In December 2014, the VA/DoD approved an evidence-based clinical practice guideline about the management of dyslipidemia for CVD risk reduction (www.healthquality.va.gov/guidelines/CD/lipids). This synopsis summarizes the guideline, which largely concerns the overall risk for CVD over a short-term (10-year) horizon.

Guideline Development Process

To develop these recommendations, the VA/DoD followed methods developed by the VA/DoD Evidence-Based Practice Working Group (EBPWG) (2) that adhere to the standards described for trustworthy guidelines (3–5). (For a list of EBPWG members, see the Appendix, available www.annals.org.) The guideline project team completed conflict-of-interest disclosures for relationships in the prior 2 years and affirmed the disclosures verbally during the project. Web-based surveillance (for example, ProPublica) was used to screen for potential conflicts of interest among project team members, and action was taken to mitigate identified conflicts.

The EBPWG selected 2 guideline panel co-chairs—1 each from the VA and DoD. The co-chairs then selected a multidisciplinary panel of practicing clinician stakeholders, including primary care physicians (family and internal medicine), cardiologists, medical nutritionists, pharmacists, nurse practitioners, and physician assistants. The VA/DoD contracted with The Lewin Group, a third party with expertise in clinical practice guideline development, to facilitate meetings and develop key questions (KQs) using the population, intervention, comparison, outcome, time, and setting (PICOTS) format.

The guideline panel developed 7 KQs. Three were identical to questions that the American College of Cardiology and American Heart Association (ACC/AHA) used in developing their guideline on cholesterol treatment (6) and concerned evidence supporting low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) levels as targets of treatment, treatment effectiveness in reducing clinically important CVD events (fatal and nonfatal myocardial infarctions [MIs], strokes, and total mortality), and adverse effects of each drug class. The 4 additional KQs dealt with cost-effectiveness of cholesterol-modifying drugs, additional risk-stratifying tests, frequency of laboratory testing, and effects of dietary intervention on CVD outcomes.

A systematic search of the peer-reviewed literature through February 2014 was conducted to find evidence relevant to the KQs that focused on randomized trials and systematic reviews and meta-analyses of fair or better quality. The search methods and results are detailed in the full guideline (www.healthquality.va.gov/guidelines/CD/lipids). The guideline panel rated recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (7–9).

The draft guideline was sent to more than 20 expert reviewers inside and outside the federal sector. Comments were considered and incorporated according to panel consensus into the final guideline, which the VA/DoD EBPWG approved on 1 December 2014 and released on 7 January 2015.

See also:

Web-Only
CME quiz

RECOMMENDATIONS

The guideline focuses on CVD risk reduction through the management of lipids among adults who are most likely to benefit. The guideline panel developed a simple 1-page algorithm (**Figure**), and the **Appendix Table** (available at www.annals.org) summarizes all 26 recommendations. Here we highlight 5 areas of most relevance to general practice. The full guideline report provides complete recommendations, rationale, and supporting evidence (www.healthquality.va.gov/guidelines/CD/lipids).

1. Elimination of Treatment Targets

Our literature review updated the 2013 ACC/AHA review (6) which concluded that the available evidence does not support the use of LDL-C or non–HDL-C levels as treatment targets. We did not identify any trials that showed the benefit of using LDL-C or non–HDL-C targets. Although some use the 2010 Cholesterol Treatment Trialists' Collaboration to justify treatment goals, this meta-analysis included statin trials that were not designed as treat-to-target studies (10). Analyses about treatment goals were post hoc and should be regarded as hypothesis-generating and not proof of benefit. Further, these analyses included the soft end point of revascularization in the composite primary end point. This fundamentally changed the results of the individual trials in patients with the acute coronary syndrome (ACS) and stable coronary artery disease and was a different primary end point than the original Cholesterol Treatment Trialists' Collaboration analyses of 90 056 patients in 2005 and 18 686 diabetic patients in 2008 (11, 12). These issues raise serious concerns about the validity of inferences about treatment targets based on these data (13).

Because of the lack of direct evidence about target cholesterol goals, which can lead to physicians prescribing escalating doses of statins and combinations of drugs with higher rates of adverse effects without known benefit in outcomes, the VA/DoD recommends against the use of cholesterol levels as treatment targets. However, clear evidence shows that moderate fixed-dose statin monotherapy improves total mortality and results in fewer CVD events.

2. Use of Additional Tests to Refine Risk Prediction

Although there has been strong interest in new genetic, serologic, physiologic, anatomical, and psychosocial risk markers to improve CVD risk prediction in populations in which there is relative indifference to treatment (such as adults at "intermediate" risk [10-year CVD risk of 6% to 12%]), only C-reactive protein and coronary artery calcium testing have shown minimal additive predictive risk beyond conventional risk factors. High-sensitivity C-reactive protein adds marginal additive strength to prediction models (increase in area under the curve of 0.004 and improved net reclassification of 1.5%) (14). Coronary artery calcium adds more to risk prediction (increase in area under the curve of 0.05 and improved net reclassification of 5% to 16%) (15–17), but this is generally considered to be a small effect. Both factors tend to add more predictive power among men, smokers, and adults at intermediate risk. No randomized trial has shown that incorporating such testing into practice improves CVD outcomes. The VA/DoD concluded that evidence is insufficient to recommend for or against either of these tests in patients at any level of risk for CVD.

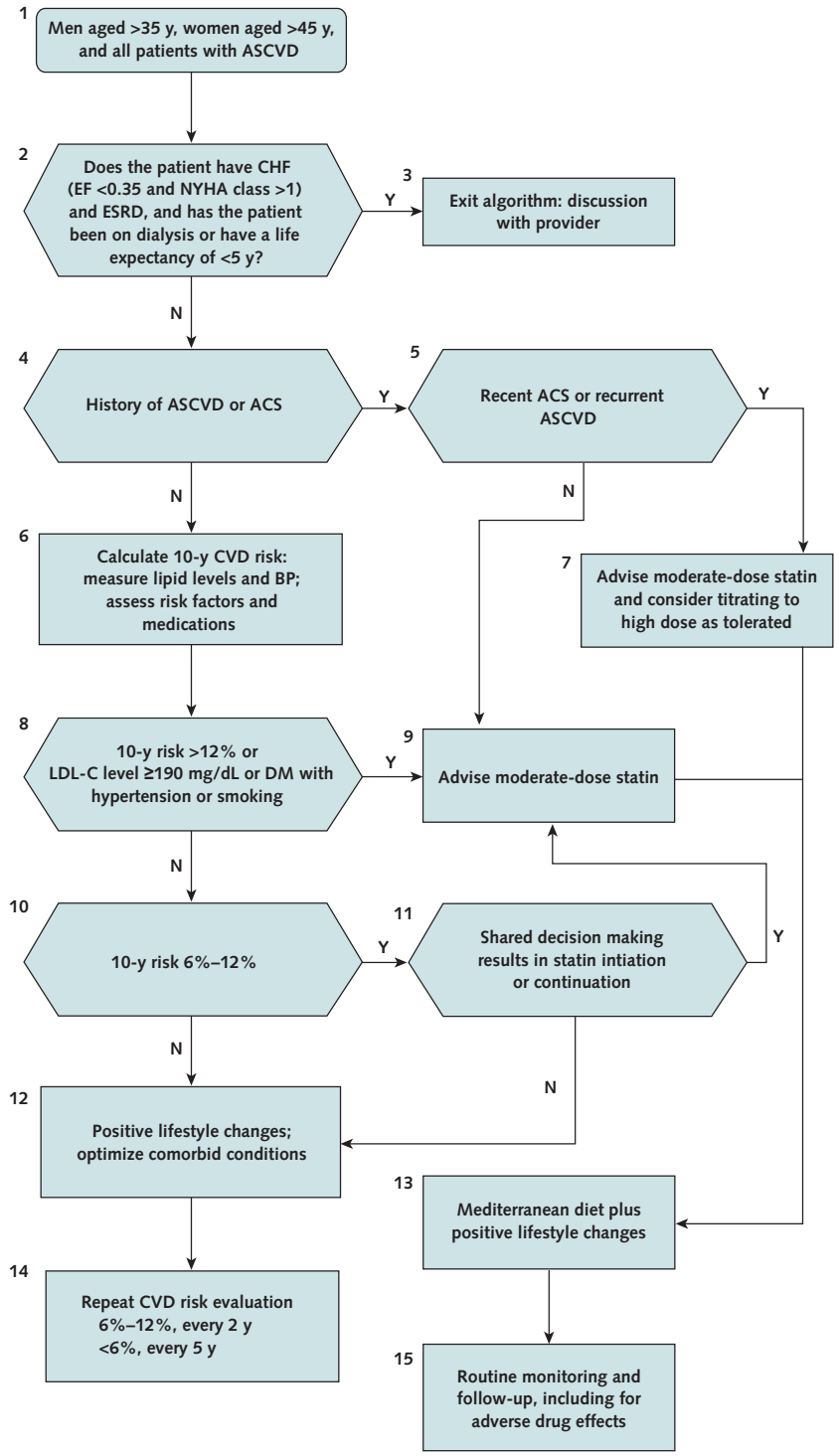
In theory, these tests might be used in intermediate-risk patients for whom there is uncertainty about treatment benefit or indifference about treatment. A "negative" test result could decrease the probability across a threshold of "no treatment," and a "positive" test result could increase the probability across a "treat" threshold. However, such testing should be a shared decision with the patient, and the rationale for the test should be clear before it is used. Routine use of these tests is not recommended because of the lack of evidence that testing improves patient outcomes, the costs of testing, and exposure to potentially harmful radiation during coronary artery calcium testing.

3. Primary Prevention: More Nuanced

Once a patient's 10-year risk has been calculated, the VA/DoD recommends shared decision making to decide whether the potential benefits of medications outweigh the potential harms for each patient. This tradeoff varies by the level of 10-year risk for CVD largely because of the varying level of evidence of benefit weighed against a constant risk for adverse events: less than 6% (no evidence of benefit), 6% to 12% (limited evidence), and greater than 12% (convincing evidence). For patients with a 10-year risk greater than 12%, clinical trials indicate that CVD risk can be decreased by 20% to 30% with use of a moderate-dose statin for 5 years. The rationale for a 12% risk threshold is that it most closely resembles the populations in the clinical trials for which the benefits clearly outweighed the risks (18, 19). A similar rationale is used for the threshold of 6%; no clinical trials specifically address patients in this category. The mean 10-year risk from the very few primary prevention trials that included patients in an intermediate-risk group (6% to 12%) was approximately 8%, but these trials had idiosyncratic inclusion criteria (20, 21). The thresholds represent rationally defined inflection points of increasing risk and increasing congruency with the populations included in clinical trials that showed benefit from statin therapy. Current risk calculators may overestimate risk (especially in lower risk cohorts, such as 10-year predicted risk <12%), which adds further uncertainty to this decision (22).

Although the absolute benefit of statin therapy depends on the patient's risk for CVD, the potential for harm is the same regardless of risk. Muscle-related symptoms were the most frequent adverse effects of statins seen in trials in 10% to 20% of patients (23–26), and the frequency is thought to be higher in community cohorts. These adverse effects are usually benign and resolve with treatment interruption but often lead to reluctance to resume statin treatment. Rhabdomyol-

Figure. VA/DoD clinical practice guideline algorithm for managing dyslipidemia for cardiovascular risk reduction.



ASCVD and Equivalents*

All ACS or MI
CABG or PCI
Stable obstructive CAD (stable symptoms of angina or equivalent)
CVA or TIA
Atherosclerotic PVD (claudication or AAA)

Statin Dose, by 10-Year CVD Risk

10-Year Risk	Statin Dose
ASCVD (second prevention)	Moderate to high
>12%	Moderate
6%–12% (with shared decision making)	Moderate
<6%	None

Drug Doses†

Statin	Moderate, *mg*	High, *mg*
Generics available		
Atorvastatin	10–20	40–80
Simvastatin	20–40	
Pravastatin	40–80	
Lovastatin	40–80	
Fluvastatin	80‡	
Brand formulation only		
Rosuvastatin	5–10	20–40

AAA = abdominal aortic aneurysm; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebral vascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; DoD = U.S. Department of Defense; EF = ejection fraction; ESRD = end-stage renal disease; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; N = no; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack; VA = U.S. Department of Veteran Affairs; Y = yes.

* Does not include asymptomatic atherosclerosis (coronary artery calcium, exercise test, intima–media thickness, ankle–brachial index, or brachial reactivity).

† For patients unable to tolerate the appropriate moderate- or high-dose statin, the highest tolerable statin dose is an option according to their risk.

‡ 80 mg once a day or 40 mg twice a day.

ysis is a more severe adverse effect related to statins, but it is relatively rare and generally limited to patients receiving high-dose statins or with factors that predispose them to muscle toxicity, such as drug–drug interactions, impaired hepatic or renal function, hypothyroidism, advanced age, rheumatic disorders, vitamin D deficiency, or alcohol misuse (10, 11, 27). Statins increase the risk for type 2 diabetes mellitus by 0.5%, and this risk seems to be higher in women and persons receiving high-dose statins (28, 29).

Although the decision to start statins should always be shared with patients, the VA/DoD guideline panel concluded that, for patients with a risk of 12% or greater, the benefits in CVD risk reduction substantially outweigh the risks. Thus, in such patients, the guideline strongly advocates offering treatment with a moderate-dose statin. In patients at intermediate risk (10-year CVD risk of 6% to 12%), the decision to initiate therapy should be based on an individual patient assessment and is nuanced; there is uncertainty about benefit because of the limited number of trials, the tendency for risk calculators to overestimate risk, and the more tenuous balance between benefit and risk.

4. Secondary Prevention: Moderate-Dose Statin First, Then Titrate to a High Dose in Patients at the Highest Risk

The recommendation to initiate statin therapy at a moderate dose and titrate to a high dose (where appropriate; for example, ACS, recurrent atherosclerotic CVD events, or multiple uncontrolled risk factors) for secondary prevention is based on a high level of evidence from 3 meta-analyses from the Cholesterol Treatment Trialists' Collaboration (10, 11, 28). All dosing regimens in the secondary prevention trials included in these meta-analyses reduced all-cause mortality, nonfatal MI, coronary death, and nonfatal stroke compared with placebo. Statin doses were primarily fixed moderate doses (simvastatin, 20 to 40 mg; pravastatin, 40 to 80 mg; lovastatin, 20 to 80 mg; and atorvastatin, 10 mg).

The recommendation to consider a high-dose statin in patients with acute ACS and those with multiple uncontrolled risk factors or recurrent atherosclerotic CVD events is based on a low level of evidence from a 2010 meta-analysis of 10 trials (n = 41 778) comparing high-dose with low- to moderate-dose statins for secondary prevention (30). No significant difference was found in overall mortality (relative risk [RR], 0.92 [95% CI, 0.83 to 1.03]; P = 0.14) or CVD deaths (RR, 0.89 [CI, 0.78 to 1.01]; P = 0.07) between high-dose statins and lower doses. Significant differences in nonfatal MI (RR, 0.82 [CI, 0.76 to 0.89]; P < 0.001) and combined nonfatal and fatal stroke (RR, 0.86 [CI, 0.77 to 0.96]; P = 0.006) favored higher doses. The meta-analysis included a subgroup analysis of 3 trials in patients with ACS that found a statistically significant reduction in all-cause mortality and CVD death with higher statin doses. Limitations of this meta-analysis were that 5 of the 10 trials randomly assigned fewer than 1000 patients who were followed for less than 2 years, and some included surrogate end points, such as arteriosclerotic progression, as their primary end point.

A second meta-analysis included 5 studies of low- or moderate-dose versus high-dose statins and found that new-onset diabetes occurred more frequently in the high-dose group (odds ratio [OR], 1.12 [CI, 1.04 to 1.22]; number needed to harm, 498); there were an estimated 2 additional diabetes diagnoses per 1000 patients treated with high-dose statins for 5 years (31). Cardiovascular events (composite of all-cause mortality, cardiovascular death, nonfatal MI, nonfatal stroke, and coronary revascularization) occurred less often in the high-dose statin group (OR, 0.84 [CI, 0.75 to 0.94]), which translated into an estimated 6.5 fewer CVD events per 1000 patients treated with high-dose statins for 5 years (31). Another meta-analysis examined data from 4 of the trials comparing moderate- to high-dose statins and found that treatment with high-dose atorvastatin or simvastatin was associated with a higher risk for any adverse event (OR, 1.44 [CI, 1.33 to 1.55]; P < 0.001) and events leading to withdrawal of the statin (OR, 1.28 [CI, 1.18 to 1.39]) (32). High-dose regimens were also associated with more abnormalities in liver function tests and creatine kinase levels (32).

In summary, improvement in the primary outcome of major cardiovascular events was not consistently seen with a higher-dose statin compared with a moderate-dose statin because only 2 of the 5 original trials showed greater efficacy of the higher dose, and differences were limited to a reduction in nonfatal events. Although the risk for serious adverse events related to statins is low, other less severe adverse events, such as muscle symptoms (for example, myalgias), occur more often with higher-dose statins and may lead to decreased adherence and reluctance to continue statin therapy. None of the individual studies or meta-analyses addressed back titration from a high-dose to a low-dose statin or vice versa. On the basis of this evidence, the VA/DoD recommends that if high-dose statins are considered, clinicians and patients should carefully consider the known added harms and small additional benefits of such therapy and limit high-dose statins to patients at greatest risk for CVD.

5. Laboratory Testing: No Need to Fast or Monitor

A nonfasting lipid profile provides measures of total cholesterol and HDL-C levels that differ little from measures after a 9- to 12-hour fast (33). Compared with fasting measures, nonfasting LDL-C level may be 10% lower and triglyceride levels may be as much as 20% higher. Lipid measures are necessary to enable risk calculation based only on measures of total cholesterol and HDL-C levels, and the small variance in LDL-C level is unlikely to affect classification of risk or therapeutic decisions (34, 35). Thus, a nonfasting lipid profile provides acceptably accurate measures for risk calculation.

If triglyceride levels are greater than 4.52 mmol/L (>400 mg/dL), the Friedewald equation commonly used to calculate LDL-C levels may not be accurate. In this uncommon scenario, the nonfasting lipid profile

may need to be remeasured after fasting. Fasting lipid measures are also indicated if the purpose is to measure or monitor triglyceride levels. Routine fasting lipid measures burdens patients and laboratories. Most patients do not come to clinic visits while fasting; thus, they are required to take time away from work or family and bear the expense and bother of a second visit after fasting. Some patients are unwilling to fast or to return and avoid lipid testing altogether. Laboratories can be burdened by the large number of patients who present early in the morning after an overnight fast. Thus, the small gain in accuracy of a fasting lipid profile over random measurement is outweighed by these burdens.

In addition, because the efficacy of statins is based on a target dose, not lipid levels, we do not recommend routine monitoring of lipids once a statin is initiated (36). If adherence is a concern, it may be reasonable to measure lipids to assess a patient's adherence. For patients receiving high-dose statins, it may also be reasonable to assess lipids because there are known adverse effects associated with very low LDL-C levels that can occur with high-dose therapy (37).

Measuring baseline creatine kinase levels and using liver function tests are clinically prudent to interpret potential future laboratory results or symptoms. All clinical trials that studied the efficacy of statins excluded patients with elevated levels of liver aminotransferases, and there is a concern that statins may exacerbate hepatotoxicity; therefore, the VA/DoD suggests assessing for evidence of liver damage before initiating statin therapy and avoiding statins in patients with evidence of worsening liver damage or fluctuating results on liver function tests. Once low- or moderate-dose statins have been initiated, the traditional recommendation is to do liver function tests on a regular basis to detect asymptomatic liver damage and measure creatine kinase levels if muscular symptoms occur. However, this practice is not based on studies specifically designed to test the effectiveness of frequent monitoring. No direct evidence shows that laboratory monitoring improves detection of myopathy or liver dysfunction (except at higher doses of statins). Further, in 2012, the U.S. Food and Drug Administration announced revisions in periodic liver monitoring in persons receiving statin therapy and concluded that serious liver injury with statins is rare and unpredictable in individual patients; also, routine periodic monitoring of liver enzyme levels does not seem to be effective in detecting or preventing this rare adverse effect (38).

The risk for serious liver injury while receiving moderate-dose statin therapy is extremely rare and did not differ from placebo in clinical trials. Patients with aspartate or alanine aminotransferase levels less than 3 times the normal levels do not warrant an immediate change in dose but should continue to follow up and consider repeated testing with their health care provider. Patients with aspartate and alanine aminotransferase levels greater than 3 times the normal levels should consult with their providers to evaluate the net benefit of continuing statin therapy versus adjusting or discontinuing medication (29, 39). Frequent laboratory testing has negative consequences from both patient (such as septic thrombophlebitis, cellulitis, pain at the blood draw site, and inconvenience) and provider (such as excess workload and opportunity costs) perspectives.

SUMMARY

The VA/DoD guideline differs from the ACC/AHA guideline in several aspects. Although we agree with the ACC/AHA that the data support the elimination of targets, we extend the literature review through February 2014. Further, we support the use of risk calculators to estimate risk in primary prevention populations, call for a more nuanced shared-decision approach, and suggest the use of additional tests for risk prediction in a more conservative manner than the ACC/AHA advocates. Likewise, safety concerns influenced our pharmacologic treatment strategy that recommends starting with the more conservative and safer moderate-dose statin for both primary and secondary prevention, with upward titration in secondary prevention based on shared decision making. Laboratory testing is based on clinical need for monitoring the results of liver function tests and nonfasting lipid profiles. Lastly, our guideline group contained members with no conflict of interest.

Hayward and Krumholz (40) stated the following in 2012 about lipid targets: "Changing long-held beliefs is never easy, even when the need for change is based on strong evidence. Change is especially difficult when prior beliefs are firmly embedded in culture, accepted as dogma, and codified in books, articles, guidelines, public service announcements and performance measures." This guideline will undoubtedly provoke criticism. However, as some have suggested (41), we hope to have brought some "order to the chaos" of clinical guidelines by providing a rigorous, simple, transparent, and high-quality guideline that providers can use to efficiently care for their patients and improve patient-centered clinical outcomes.

From South Texas Veterans Health Care System, San Antonio, Texas, and Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Disclaimer: The views expressed here are not to be construed as those of the U.S. Department of Veterans Affairs or the U.S. Department of Defense.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-0840.

Requests for Single Reprints: John R. Downs, MD, South Texas Veterans Health Care System, Medicine Service (111), 7400 Merton Minter, San Antonio, TX 78229; e-mail, john.downs@va.gov.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics–2013 update: a report from the American Heart Association. Circulation. 2013;127:e6-e245. [PMID: 23239837] doi:10.1161/CIR.0b013e31828124ad

2. **U.S. Department of Veteran Affairs, U.S. Department of Defense.** VA/DoD clinical practice guidelines: CPG policy guidance: guideline for guidelines. Revised 10 April 2013. Washington, DC: Veterans Health Administration, Office of Quality and Performance, Evidence Review Subgroup; 2013. Accessed at www.healthquality.va.gov/policy/index.asp.

3. **Agency for Healthcare Research and Quality.** Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ publication no. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012.

4. **Guirguis-Blake J, Calonge N, Miller T, Siu A, Teutsch S, Whitlock E; U.S. Preventive Services Task Force.** Current processes of the U.S. Preventive Services Task Force: refining evidence-based recommendation development. Ann Intern Med. 2007;147:117-22. [PMID: 17576998]

5. **Institute of Medicine.** Clinical practice guidelines we can trust. Washington, DC: National Academies Pr; 2011. Accessed at www.iom.edu/~/media/Files/Report%20Files/2011/Clinical-Practice-Guidelines-We-Can-Trust/Clinical%20Practice%20Guidelines%202011%20Insert.pdf on 1 June 2015.

6. **Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, 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. J Am Coll Cardiol. 2014;63:2889-934. [PMID: 24239923] doi:10.1016/j.jacc.2013.11.002

7. **Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al; GRADE Working Group.** Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490. [PMID: 15205295]

8. **Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al.** GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66:719-25. [PMID: 23312392] doi:10.1016/j.jclinepi.2012.03.013

9. **Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al.** GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66:726-35. [PMID: 23570745] doi:10.1016/j.jclinepi.2013.02.003

10. **Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al; Cholesterol Treatment Trialists' (CTT) Collaboration.** Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-81. [PMID: 21067804] doi:10.1016/S0140-6736(10)61350-5

11. **Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267-78. [PMID: 16214597]

12. **Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371:117-25. [PMID: 18191683] doi:10.1016/S0140-6736(08)60104-X

13. **Sniderman A, Thanassoulis G, Couture P, Williams K, Alam A, Furberg CD.** Is lower and lower better and better? A re-evaluation of the evidence from the Cholesterol Treatment Trialists' Collaboration meta-analysis for low-density lipoprotein lowering [Editorial]. J Clin Lipidol. 2012;6:303-9. [PMID: 22836065] doi:10.1016/j.jacl.2012.05.004

14. **Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, et al; Emerging Risk Factors Collaboration.** C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med. 2012;367:1310-20. [PMID: 23034020] doi:10.1056/NEJMoa1107477

15. **Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al; Heinz Nixdorf Recall Study Investigative Group.** Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol. 2010;56:1397-406. [PMID: 20946997] doi:10.1016/j.jacc.2010.06.030

16. **Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, et al.** Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med. 2012;156:438-44. [PMID: 22431676] doi:10.7326/0003-4819-156-6-201203200-00006

17. **Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al.** Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308:788-95. [PMID: 22910756] doi:10.1001/jama.2012.9624

18. **Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al.** Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615-22. [PMID: 9613910]

19. **Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al.** Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816. [PMID: 23440795] doi:10.1002/14651858.CD004816.pub5

20. **Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al; JUPITER Study Group.** Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-207. [PMID: 18997196] doi:10.1056/NEJMoa0807646

21. **Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al; MEGA Study Group.** Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368:1155-63. [PMID: 17011942]

22. **DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al.** An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162:266-75. [PMID: 25686167] doi:10.7326/M14-1281

23. **Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B.** Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403-14. [PMID: 16453090]

24. **Hippisley-Cox J, Coupland C.** Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197. [PMID: 20488911] doi:10.1136/bmj.c2197

25. **Naci H, Brugts J, Ades T.** Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes. 2013;6:390-9. [PMID: 23838105] doi:10.1161/CIRCOUTCOMES.111.000071

26. **Nichols GA, Koro CE.** Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. Clin Ther. 2007;29:1761-70. [PMID: 17919557]

27. **Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, et al; Cholesterol Treatment Trialists' (CTT) Collaboration.** Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One. 2012;7:e29849. [PMID: 22276132] doi:10.1371/journal.pone.0029849

28. **Yan YL, Qiu B, Hu LJ, Jing XD, Liu YJ, Deng SB, et al.** Efficacy and safety evaluation of intensive statin therapy in older patients with coronary heart disease: a systematic review and meta-analysis. Eur J

Clin Pharmacol. 2013;69:2001-9. [PMID: 23942733] doi:10.1007/s00228-013-1570-0
29. **Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP.** What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. Eur J Prev Cardiol. 2014;21:464-74. [PMID: 24623264] doi:10.1177/2047487314525531
30. **Mills EJ, O'Regan C, Eyawo O, Wu P, Mills F, Berwanger O, et al.** Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. Eur Heart J. 2011;32:1409-15. [PMID: 21385791] doi:10.1093/eurheartj/ehr035
31. **Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al.** Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305:2556-64. [PMID: 21693744] doi:10.1001/jama.2011.860
32. **Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M, et al.** Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther. 2007;29:253-60. [PMID: 17472818]
33. **Sidhu D, Naugler C.** Fasting time and lipid levels in a community-based population: a cross-sectional study. Arch Intern Med. 2012;172:1707-10. [PMID: 23147400]
34. **Khera AV, Mora S.** Fasting for lipid testing: Is it worth the trouble? Arch Intern Med. 2012;172:1710-2. [PMID: 23405395]
35. **Gaziano JM.** Should we fast before we measure our lipids? [Editorial]. Arch Intern Med. 2012;172:1705-6. [PMID: 23401886]
36. **McConnell M, Downs JR, Good CB.** Decrease the incentives to order lipid panels [Letter]. JAMA Intern Med. 2014;174:473. [PMID: 24590082] doi:10.1001/jamainternmed.2013.12872
37. **Everett BM, Mora S, Glynn RJ, MacFadyen J, Ridker PM.** Safety profile of subjects treated to very low low-density lipoprotein cholesterol levels (<30 mg/dl) with rosuvastatin 20 mg daily (from JUPITER). Am J Cardiol. 2014;114:1682-9. [PMID: 25439449] doi:10.1016/j.amjcard.2014.08.041
38. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. Accessed at www.fda.gov/Drugs/DrugSafety/ucm293101.htm on 4 June 2015.
39. **McKenney JM, Davidson MH, Jacobson TA, Guyton JR; National Lipid Association Statin Safety Assessment Task Force.** Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97:89C-94C. [PMID: 16581336]
40. **Hayward RA, Krumholz HM.** Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health [Letter]. Circ Cardiovasc Qual Outcomes. 2012;5:2-5. [PMID: 22253366] doi:10.1161/CIRCOUTCOMES.111.964676
41. **Laine C, Taichman DB, Mulrow C.** Trustworthy clinical guidelines [Editorial]. Ann Intern Med. 2011;154:774-5. [PMID: 21646561] doi:10.7326/0003-4819-154-11-201106070-00011

Current Author Addresses: Dr. Downs: South Texas Veterans Health Care System, Medicine Service (111), 7400 Merton Minter, San Antonio, TX 78229.
Dr. O'Malley: Department of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814.

Author Contributions: Conception and design: J.R. Downs, P.G. O'Malley.
Analysis and interpretation of the data: J.R. Downs, P.G. O'Malley.
Drafting of the article: J.R. Downs, P.G. O'Malley.
Critical revision of the article for important intellectual content: J.R. Downs, P.G. O'Malley.
Final approval of the article: J.R. Downs, P.G. O'Malley.
Administrative, technical, or logistic support: J.R. Downs, P.G. O'Malley.
Collection and assembly of data: J.R. Downs, P.G. O'Malley.

Appendix: VA/DoD Evidence-Based Practice Work Group

John R. Downs, MD (*VA Co-Chair*); Patrick G. O'Malley, MD, MPH (*DoD Co-Chair*); Ernest Degenhardt, MSN, FNP; Deborah Grady MD, MPH; Edward Hulten, MD, MPH; Cathy Kelley, PharmD; Azra Khan, PharmD; Amanda Logan, RD; Mark McConnell, MD; Michelle Pino, RD, LD; M. Eric Rodgers, PhD, FNP; James L. Sall, PhD, FNP; Robert Sylvester, MD; ECRI Institute; The Lewin Group; and Sigma Health Consulting.

Appendix Table. 2014 VA/DoD Cholesterol Recommendations and Their Strength, Grouped by Clinical Management Category*

Number	Recommendation	Grade
Assessment of cardiovascular risk and pharmacotherapy for primary prevention		
1	We recommend CVD risk screening for men aged >35 y and women aged >45 y, including a lipid profile and risk assessment.	Strong
2	We recommend against routine screening for dyslipidemia outside of the context of a cardiovascular risk assessment.	Strong
3	For risk calculation, we suggest a 10-y risk calculator.	Weak
4	We suggest that patients being considered for statin therapy be assessed for other CVD risk factors (such as diabetes and hypertension).	Weak
5	We suggest against the routine use of hsCRP testing.	Weak
6	We suggest against the routine use of CAC testing.	Weak
7	We suggest shared decision making about pharmacologic treatment for patients with an estimated 10-y CVD risk ≥12% that considers the known minimal harms and substantial benefits of moderate-dose therapy in this group of patients.	Weak
8	We suggest initiation of a moderate-dose statin for patients with an estimated 10-y CVD risk ≥12%.	Weak
9	We suggest considering a moderate-dose statin for patients with a 10-y CVD risk between 6% and 12% after a discussion of the known minimal harms and benefits derived from limited evidence and an exploration of the patient's values and preferences.	Weak
10	For primary prevention, we recommend a moderate-dose statin as the agent of choice to reduce CVD risk if the patient chooses pharmacologic therapy.	Strong
11	For patients intolerant of statins: a. We suggest reinforcing lifestyle changes. b. For patients who prefer pharmacotherapy, we suggest considering gemfibrozil or bile acid sequestrants, although we note small CVD risk reduction in limited populations.	Weak
12	We suggest establishing baseline LFTs and creatine kinase before initiation of drug therapy.	Weak
13	We recommend against routinely doing LFTs or measuring creatine kinase levels after a moderate-dose statin is initiated.	Strong
Management of pharmacotherapy for secondary prevention		
14	In patients with established ASCVD, we recommend use of a moderate-dose statin after a discussion of the minimal harms and substantial benefits and an exploration of the patient's values and preferences.	Strong
15	In patients with ASCVD who are able to tolerate statins, we recommend against the routine use of nonstatin lipid-lowering drugs either as monotherapy or added to statins.	Strong
16	In patients with ASCVD who are unable to tolerate statins, we suggest reinforcing lifestyle changes and offering niacin or gemfibrozil, although we note only a small CVD risk reduction in limited populations.	Weak
17	We strongly recommend against the routine monitoring of LDL-C and non–HDL-C goals for the secondary prevention of ASCVD.	Strong
18	We suggest offering a high-dose statin only in select patient populations (e.g., ACS, multiple uncontrolled risk factors, or recurrent CVD while receiving moderate-dose statin) after a discussion of the added harms and small additional benefits and an exploration of the patient's values and preferences.	Weak
19	We suggest measuring LFTs 4–12 wk after the initiation of a high-dose statin.	Weak
Nonpharmacologic approaches		
20	We recommend all adults adopt healthy lifestyles to reduce CVD risk, including: 1. Tobacco cessation for all smokers 2. Optimal nutrition 3. Optimal physical activity	Strong
21	We suggest offering high-risk patients a Mediterranean diet.	Weak
22	We suggest that each patient's diet be individualized on the basis of a nutrition assessment, other CVD risk factors, other disease conditions, and lifestyle.	Weak
23	We recommend treating the common secondary causes of elevated triglyceride levels: dietary (e.g., refined sugars), alcohol use, hypothyroidism, and hyperglycemia.	Strong
24	For patients with triglyceride levels >5.65 mmol/L (>500 mg/dL), we suggest diet therapy, including avoidance of alcohol, restriction of dietary fat, and avoidance of refined sugars. For patients with triglyceride levels >11.3 mmol/L (>1000 mg/dL), we suggest a very-low-fat diet to reduce chylomicronemia and the risk for acute pancreatitis.	Weak
Monitoring and follow-up		
25	We suggest CVD risk assessment every 5 y for patients with 10-y CVD risk <6%.	Weak
26	We suggest CVD risk assessment every 2 y for patients with 10-y CVD risk between 6% and 12% or with the appearance of a new CVD risk factor (e.g., diabetes mellitus or hypertension).	Weak

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CVD = cardiovascular disease; DoD = U.S. Department of Defense; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; VA = U.S. Department of Veterans Affairs.
* For the full guidelines, evidence base, and rationale, see www.healthquality.va.gov/guidelines/CD/lipids/.