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CLINICAL GUIDELINE

Management of Dyslipidemia for Cardiovascular Disease Risk Reduction: Synopsis of the 2020 Updated U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline

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Description: In June 2020, the U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) released a joint update of their clinical practice guideline for managing dyslipidemia to reduce cardiovascular disease risk in adults. This synopsis describes the major recommendations.

Methods: On 6 August to 9 August 2019, the VA/DoD Evidence-Based Practice Work Group (EBPWG) 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 (English-language publications from 1 December 2013 to 16 May 2019), and developed 27 recommendations and a simple 1-page algorithm. The recommendations were graded by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Recommendations: This synopsis summarizes key features of the guideline in 7 crucial areas: targeting of statin dose (not low-density lipoprotein cholesterol goals), additional tests for risk prediction, primary and secondary prevention, laboratory testing, physical activity, and nutrition.

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Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the United States and globally (1). Reducing the burden of CVD is a priority area for the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD). In June 2020, the VA/DoD released an evidence-based update to their 2014 clinical practice guideline for managing dyslipidemia to reduce CVD risk (www.healthquality.va.gov/guidelines/CD/lipids) (2). This synopsis presents the guideline, which continues to emphasize CVD risk management over a short-term (10-year) horizon with more conservative dosing of statins in primary and stable secondary prevention, without targeting low-density lipoprotein cholesterol (LDL-C) goals. We provide new recommendations for stepped intensification for secondary prevention in higher-risk patients and a new emphasis on aerobic physical activity and Mediterranean-style diets. The **Figure** outlines the algorithm of these recommendations.

Guideline Development Process

To develop these recommendations, the VA/DoD followed the method developed by the VA/DoD Evidence-Based Practice Work Group (EBPWG) (3), which follows the standards described for trustworthy guidelines (4–6). The guideline project team completed conflict-of-interest disclosure forms for relationships in the previous 2 years and affirmed the disclosures verbally during the project. Web-based surveillance (such as through Centers for Medicare & Medicaid Services open payments or ProPublica) was used to screen for potential conflicts of interest among project team members, and action was taken to mitigate identified conflicts.

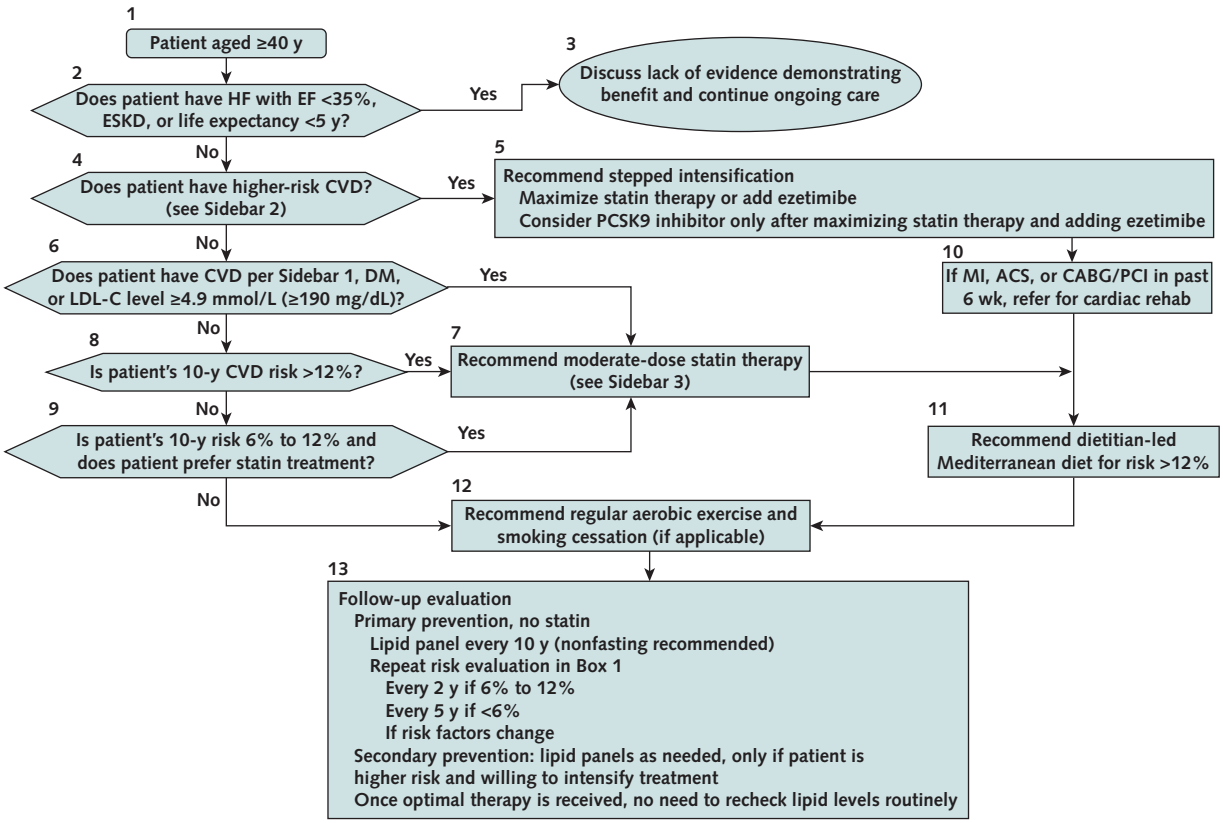
The EBPWG selected 2 guideline panel co-chairs, 1 from the VA and 1 from the DoD. The co-chairs then selected a multidisciplinary panel that comprised practicing clinician stakeholders, including primary care physicians (family medicine and internal medicine), cardiologists, dietitians, pharmacists, nurse practitioners, and physician assistants. The VA/DoD contracted with The Lewin Group, a third party with expertise in developing clinical practice guidelines, to facilitate meetings and develop key questions (KQs) using the PICOTS (population, intervention, comparator, outcomes, timing of outcomes measurement, and setting) format. (For a list of EBPWG members, see the **Appendix**, available at Annals.org.)

The guideline panel developed 12 KQs, many of which are similar to questions that the American College of Cardiology and American Heart Association used in developing their guideline on cholesterol management (7), and concerned evidence supporting LDL-C and non–high-density lipoprotein cholesterol levels as targets for treatment, treatment effectiveness in reducing clinically important CVD events (fatal and nonfatal myocardial infarctions [MIs] and strokes, and total mortality), and adverse effects of each drug class. Additional KQs addressed the timing and frequency of CVD risk assessments and lipid level testing; the cost-effectiveness of cholesterol-modifying drugs; the accuracy of risk assessments, as well as the added value of additional risk-stratifying tests; the efficacy of interventions to enhance statin tolerance and adherence; and

See also:

Editorial comment 1
Related article 2

Figure. Algorithm of the VA/DoD clinical practice guideline for managing dyslipidemia to reduce CVD risk.



Sidebar 1: CVD and Equivalents

MI or ACS
CABG/PCI
Stable CAD (angina or equivalent)
Stroke/TIA
PAD (claudication or AAA)
Does not include asymptomatic incidental finding of atherosclerosis (e.g., CAC)

Sidebar 2: High-Risk CVD Patients

MI or ACS in past 12 mo or
Recurrent ACS, MI, or stroke, or
Known CVD (see Sidebar 1) and any of the following: currently smoking, DM, CKD, PAD, CABG/PCI

Stepped intensification
- Maximize statin therapy or add ezetimibe
- If not already done, maximize statin therapy and add ezetimibe
- Consider PCSK9 inhibitor only after maximizing statin therapy and adding ezetimibe

Sidebar 3: Drug Doses

Generic Name	Moderate Dose, *mg*	High Dose, *mg*
Atorvastatin	10–20	40–80
Rosuvastatin	5–10	20–40
Simvastatin	20–40	N/A
Pravastatin	40–80	N/A
Lovastatin	40–80	N/A
Fluvastatin	80 (sustained release) or 40 (twice daily)	N/A
Pitavastatin	1–4	N/A

In patients who are intolerant of statins: after washout (e.g., 1 mo), rechallenge with same or another statin rather than switching medication class.
Intensified patient care (e.g., phone calls, e-mails, patient education, drug regimen simplification) may improve adherence to lipid-lowering medications.

Note that previously measured lipid levels may be used reliably in serial CVD risk assessments. We do not recommend rechecking lipid levels each time CVD risk is assessed, because lipid levels remain stable within each patient over time and contribute little to predicted risk relative to other factors.

the effectiveness of physical activity and dietary interventions (including nutraceuticals) on CVD outcomes.

A systematic search of the peer-reviewed English-language literature from 1 December 2013 through 16 May 2019 was conducted to find evidence relevant to the KQs and focused on randomized controlled trials (RCTs) and systematic reviews and meta-analyses of fair or better quality. Search methods and results are detailed in the full guideline (www.healthquality.va.gov/guidelines/CD/lipids). The guideline panel used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method to rate the recommendations (8–13), with the critical outcome of CVD mortality as the primary factor in rating grade strength.

The draft guideline was sent to more than 20 expert reviewers both within 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 10 June 2020 and released on 11 June 2020.

RECOMMENDATIONS

The guideline continues to focus on CVD risk reduction through management of lipid levels among persons most likely to benefit. The primary critical outcome of interest in grading the evidence was cardiovascular mortality, with cardiovascular morbidity considered an important but less critical outcome by which to grade evidence. The Table summarizes all 27 recommendations. Here, we highlight the 7 areas most relevant to practice. The full guideline report provides complete recommendations, rationale, and supporting evidence (www.healthquality.va.gov/guidelines/CD/lipids).

1. Continue to Treat to Target Dose Not LDL-C Level

Our updated systematic review did not identify any direct evidence to support a strategy of targeting cholesterol levels to improve outcomes. Post hoc and observational studies have consistently shown a graded association between LDL-C levels and cardiovascular morbidity and mortality. However, studies have not used an RCT design to directly compare LDL-C goal strategies. Most trials have compared a specific, fixed statin dose with placebo, and very few trials have directly compared relative doses of individual statins.

The EBPWG carefully considered whether to use target levels for LDL-C but noted that the evidence relating patient-oriented outcomes to LDL-C levels consisted of trial comparisons between therapy intensities, not LDL-C target levels. Because no study prospectively evaluated LDL-C goals, the EBPWG decided to focus on treatment intensity to match the evidence and simplify point-of-care decision making.

Because of the lack of direct evidence of benefit from using target LDL-C goals, we recommend the use of target medication doses consistent with the clinical trials, most of which used moderate statin doses. We believe the use of LDL-C targets is more likely to lead to harm associated with higher statin doses or combination medical therapy, for which there is little evidence.

2. Use of Additional Tests to Refine Risk Prediction: Evidence Is Still Insufficient

Despite their relative imprecision, current CVD risk assessment tools remain the cornerstone for risk stratification to direct risk reduction strategies (14). Much effort has been made to improve these tools with additional testing, such as coronary artery calcium (CAC), high-sensitivity C-reactive protein, ankle–brachial index, and apolipoprotein evaluations. However, our updated review of the literature on the added prognostic value of these tests indicates that they are limited in further refining risk (15, 16). Only CAC scoring provided a statistically significant net reclassification of risk of at least modest magnitude, although its impact on clinical outcomes is uncertain, even when it is applied to intermediate-risk populations, who would benefit most (17). Without prospective RCT evidence demonstrating improvement in critical outcomes, we do not believe the added cost and radiation risk of CAC scoring can be justified in refining risk assessment for primary prevention subpopulations (18). The decision to pursue such testing should be shared with the patient and include clear communication about the uncertain benefits and known harms, and the rationale for testing should be apparent before it is carried out. For example, these tests might be used in patients classified as intermediate risk, for whom there is uncertainty about treatment benefit or indifference about treatment. A "negative" test result might lower the probability across a threshold of "no treatment," whereas a "positive" result might raise the probability across a "treat" threshold. However, the rationale for the test should be clear before it is performed. Routine CAC testing is not recommended, because no evidence exists that it improves patient outcomes, it is costly, and it exposes patients to potentially harmful radiation.

3. Primary Prevention: Moderate-Dose Statin Therapy Is Still Emphasized; No to Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

The updated evidence review on the role of statins in primary prevention resulted in little change to the previous guidelines. For patients with a 10-year risk greater than 12%, clinical trials indicate that CVD risk may be decreased by 20% to 30% with moderate-dose statin therapy for 5 years (19). The rationale for using a threshold of 12% is that it most closely resembles that of the clinical trial populations in which the benefits clearly outweighed the risks (20, 21). A similar rationale is used for the 6% threshold; no clinical trial specifically addressed persons with a risk below this threshold. Once a patient's 10-year risk has been calculated, we recommend shared decision making to determine whether the potential benefits of medications outweigh the potential harms for that patient. This tradeoff varies by level of 10-year CVD risk because of differences in the 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

Table. VA/DoD List of Recommendations for Managing Dyslipidemia to Reduce CVD Risk

Recommendation, by Topic	Strength
Primary prevention: screening and assessment of CVD risk	
1. For primary prevention in patients aged >40 y who are not receiving statins and have not developed new CVD risk factors (e.g., diabetes, hypertension, tobacco use), we suggest against offering a CVD risk assessment more frequently than every 5 y.	Weak against
2. For primary prevention in patients not receiving statins, we suggest against routinely ordering a lipid panel more frequently than every 10 y.	Weak against
3. For CVD risk assessment in primary prevention, we suggest using a 10-y risk calculator.	Weak for
4. We suggest against the routine use of CAC testing.	Weak against
5. We suggest against the routine use of additional risk markers (e.g., high-sensitivity C-reactive protein, ankle–brachial index, CAC) when assessing CVD risk.	Weak against
Pharmacotherapy, supplements, and nutraceuticals	
Primary prevention	
6. We recommend moderate-dose statin therapy for patients with a 10-y CVD risk ≥12%, an LDL-C level ≥4.9 mmol/L (≥190 mg/dL), or diabetes.	Strong for
7. We suggest moderate-dose statin therapy for patients with a 10-y CVD risk between 6% and 12% after a discussion of the risks and benefits and an exploration of the patient's values and preferences.	Weak for
8. For patients receiving moderate-dose statin therapy, we suggest against maximizing the statin dose because of the lack of evidence proving added cardiovascular benefit and the risks of higher statin doses.	Weak against
9. Insufficient evidence exists to recommend for or against using ezetimibe with or without statins.	Neither for nor against
10. We recommend against offering PCSK9 inhibitors because their long-term safety is unknown, evidence for their benefit is inconclusive, and they are expensive.	Strong against
Secondary prevention	
11. We recommend using at least moderate statin doses.*	Strong for
12. For higher-risk patients† who are willing to intensify treatment, we suggest offering high-dose statin therapy to reduce nonfatal cardiovascular events after discussing the risk of high statin doses with the patient and exploring the patient's values and preferences.	Weak for
13. For higher-risk patients† who are willing to intensify treatment, we suggest adding ezetimibe to either moderate- or high-dose statin therapy to reduce nonfatal cardiovascular events after discussing the risk of high statin doses with the patient and exploring the patient's values and preferences.	Weak for
14. For higher-risk patients† who are willing to intensify treatment, we suggest offering a PCSK9 inhibitor in addition to a maximally tolerated dose of a statin with ezetimibe to reduce nonfatal cardiovascular events after discussing the uncertain long-term safety and additional benefits with the patient and exploring the patient's values and preferences.	Weak for
Other medications, supplements, and nutraceuticals	
15. For primary or secondary prevention, we recommend against using niacin (either supplements or prescription formulas).	Strong against
16. For primary or secondary prevention, we suggest against adding fibrates to statin therapy.	Weak against
17. Insufficient evidence exists to recommend for or against using bempedoic acid with or without statins for either primary or secondary prevention.	Neither for nor against
18. For primary prevention, insufficient evidence exists to recommend for or against icosapent ethyl for patients who are receiving statins and have persistently elevated fasting triglyceride levels.	Neither for nor against
19. For secondary prevention, we suggest offering icosapent ethyl to patients who are receiving statins and have persistently elevated fasting triglyceride levels >1.7 mmol/L (>150 mg/dL) to reduce cardiovascular morbidity and mortality.	Weak for
20. For primary or secondary prevention, we suggest against omega-3 fatty acids as a dietary supplement to reduce CVD risk.	Weak against
21. Insufficient evidence exists to recommend for or against fiber, garlic, ginger, green tea, or red yeast rice supplements to reduce CVD risk.	Neither for nor against
Monitoring and adherence	
22. We suggest against the routine monitoring of lipid levels in patients receiving statins.	Weak against
23. For patients who cannot tolerate a statin, we suggest a washout period followed by a rechallenge with the same or a different statin or a lower dose or, if that fails, a trial of intermittent (nondaily) dosing.	Weak for
24. We suggest offering intensified patient care (e.g., phone calls, e-mails, patient education, drug regimen simplification) to improve adherence to lipid-lowering medications.	Weak for
Lifestyle interventions	
25. For primary and secondary prevention of CVD, we suggest a dietitian-led Mediterranean diet.	Weak for
26. For primary and secondary prevention of CVD, we suggest regular aerobic physical activity of any intensity and duration.	Weak for
27. We recommend a structured, exercise-based cardiac rehabilitation program for patients with recent coronary heart disease (i.e., MI, diagnosis of coronary artery disease, CABG surgery, or PCI) to reduce cardiovascular morbidity and mortality.	Strong for

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAC = coronary artery calcium; CVD = cardiovascular disease; DoD = U.S. Department of Defense; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9; VA = U.S. Department of Veterans Affairs.
* "Moderate-dose" statin therapy is equivalent to moderate-intensity therapy; "high-dose" statin therapy is equivalent to high-intensity therapy.
† Higher-risk patients include those with an MI or ACS in the past 12 mo; recurrent ACS, MI, or stroke; or established CVD with additional risk factors (e.g., currently smoking, diabetes, peripheral artery disease, or CABG/PCI).

than 12% (strong evidence). These thresholds represent rationally defined inflection points of increasing risk and increasing congruency with clinical trial populations that derived a benefit from statin therapy. No RCT directly compared high-dose with moderate-dose statin therapy in primary prevention. Given the higher risk for adverse effects with high-dose statin treatment and the absence of evidence for added benefit compared with moderate doses, we believe the appropriate goal dose for primary prevention should be moderate (same as moderate intensity). We therefore recommended against the use of high-dose (or high-intensity) statin therapy in primary prevention.

No clinical trial of nonstatin therapies has directly proved a reduction in cardiovascular mortality in primary prevention populations. Nonstatin treatments include ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. One systematic review of PCSK9 inhibitor trials showed that of the primary prevention patients included in the studies ($n > 10\,000$), none obtained a benefit in any cardiovascular outcome (22). Given the uncertain safety of long-term use, lack of evidence of benefit, and high cost of PCSK9 inhibitors, we strongly recommend against their use for primary prevention.

4. Secondary Prevention: Moderate Statin Doses Initially, Then Stepped Intensification in Higher-Risk Patients

A large body of clinical trial evidence supports moderate-dose statin therapy in secondary prevention populations, with demonstrated reductions in cardiovascular and all-cause mortality over approximately 5 years (23, 24). The preponderance of evidence is derived from trials of moderate statin doses, with very few trials directly comparing the effectiveness of high- versus moderate-dose statin treatment. Given the substantial benefit and limited harms, we believe that moderate statin doses form the foundation of pharmacologic treatment for secondary prevention.

Substantial evidence exists that high- versus low- or moderate-dose statin therapy reduces cardiovascular morbidity but not mortality (25). This evidence is derived mostly from higher-risk secondary prevention populations, such as those with recent MI or acute coronary syndrome (in the past 12 months); recurrent acute coronary syndrome, MI, or stroke; or established CVD with additional major risk factors (such as current tobacco use, diabetes, peripheral artery disease, or previous coronary artery bypass graft surgery or percutaneous coronary intervention). Evidence also exists that high-dose statin therapy is associated with higher rates of adverse outcomes (such as treatment discontinuation, myopathy, and incident diabetes) (25, 26). We thus concluded that without a benefit in the predefined critical outcome of cardiovascular mortality, but with an increased risk for adverse events, high-dose statin therapy should be offered through shared decision making with patients, and preferentially to higher-risk populations (such as those with recurrent events or those with known multivessel obstructive coronary or peripheral artery disease and active tobacco use or diabetes), from which the evidence was derived.

For higher-risk patients, evidence supports the addition of ezetimibe or PCSK9 inhibitors to moderate- or high-dose statin therapy, with demonstrated improvement in the important outcome of cardiovascular morbidity but not in the critical outcome of cardiovascular mortality (27, 28). Because "add-ons" to high-dose statin therapy have not been compared directly, and the decision to pursue such a strategy tends to be event driven in higher-risk populations, we recommend a stepwise approach to intensification based on relative cost-effectiveness and safety as well as the patient's event history and degree of atherosclerotic burden. Because of the high cost and uncertain long-term safety of PCSK9 inhibitors, we recommend that this medication class be reserved as a last choice.

5. Laboratory Testing: No Routine Fasting or Monitoring Is Needed; Less Is More

As in our 2014 guideline, we continue to recommend the evaluation of nonfasting lipid levels for risk assessment and monitoring, on the basis of further evidence that fasting lipid levels add no clinical value to risk prediction compared with nonfasting levels and are considerably more burdensome in terms of patient inconvenience and cost (29).

Because the focus on managing lipid levels has evolved from cholesterol values themselves to therapy based on CVD risk, the need for lipid testing should diminish considerably. The calculation of CVD risk is affected only minimally by lipid levels and depends much more on other major risk factors, such as age; sex; and the presence of hypertension, diabetes, or tobacco use.

In our systematic review, we found that lipid levels vary little in a patient over time and that true variation exceeds random variation only if testing is spaced by 9 to 10 years (30, 31). Thus, given the small contribution of lipid values to calculating a cardiovascular risk score, the focus on targeted dosing (as opposed to target cholesterol levels), and the minimal within-patient variation over time, we recommend measuring lipid levels no more than every 10 years. One can reliably use the previously measured lipid value in assessing CVD risk. We do not recommend rechecking lipid levels each time CVD risk is assessed, because lipid levels remain stable within persons over time and contribute only a small amount to predicted risk relative to other factors. Once moderate-dose statin therapy is prescribed (the therapeutic goal for managing lipid levels in primary CVD prevention), we see no rationale for monitoring lipid levels thereafter.

We recognize that circumstances may exist in which clinicians wish to measure lipid levels more frequently, such as in assessing adherence to therapy or for intensification strategies in secondary prevention to avoid excessively low LDL-C levels. However, we recommend against routine lipid level testing for risk assessment and monitoring, unless it is specifically intended to guide decision making.

6. Physical Activity: Increased Aerobic Exercise for All and Cardiac Rehabilitation After a Recent CVD Event

Our rationale for including physical activity recommendations in this dyslipidemia guideline is based on the well-described effects of physical activity on both lipid levels and CVD, as well as the reasonable hypothesis that the benefit of physical activity on CVD may be mediated by its effects on lipid levels.

On the basis of mostly observational evidence for primary and secondary CVD prevention, we recommend regular aerobic physical activity of any intensity and duration. This is a weak recommendation based on the observational nature of the data. Although the widely propagated recommendations from the *Physical Activity Guidelines for Americans* specify 150 minutes of moderate-intensity or 75 minutes of vigorous physical activity per week (32), our systematic review discovered only observational data supporting a graded association between physical activity and reduction in cardiovascular and all-cause mortality. The largest difference in risk was observed between persons who exhibited sedentary behavior compared with those at the lowest levels of regular physical activity. The lack of RCT data limited our grading of this evidence to make any further specific recommendation. Thus, we believe that recommending regular physical activity of any duration and at any intensity is most consistent with the available evidence. This broader recommendation has implications for generalizability and feasibility, specifically in patients who are elderly or have poor physical function.

For secondary prevention in patients with recent CVD events, we strongly recommend a structured, exercise-based rehabilitation program, on the basis of robust evidence of improvement in nonfatal MI and both cardiovascular and all-cause mortality. A systematic review and meta-analysis of 69 mostly moderate-quality clinical trials of cardiac rehabilitation reported a 26% relative risk reduction in cardiovascular mortality over a median of 10 years (33). Although the characteristics of these programs were somewhat heterogeneous, common elements included early initiation relative to the event (within 2 to 8 weeks) and the structured nature of the exercise programs.

7. Nutrition, Supplements, Niacin, and Fibrates: Suggest a Mediterranean Diet for High-Risk Patients, Limit Icosapent Ethyl to Secondary Prevention, Avoid Supplements and Niacin, and Avoid Adding Fibrates to Statin Therapy

For primary and secondary CVD prevention, we suggest a dietitian-led Mediterranean diet. A systematic review of 30 RCTs found only low-quality evidence but did show that a Mediterranean diet reduced composite events, stroke, MI, and both cardiovascular and all-cause mortality. The benefit was limited to high-risk primary prevention and secondary prevention populations (34). The Mediterranean diet includes a high unsaturated–saturated fat ratio, high proportion of caloric intake from plant-based foods (fruits, vegetables, nuts, legumes, and grains), moderate consumption of fish and low-fat dairy products, and low intake of lean meat and red wine. Although it is reasonable to consider other diets that comprise the same elements, the only specific diet studied in an RCT and powered for CVD outcomes is the Mediterranean diet.

For primary CVD prevention, the evidence is insufficient to recommend for or against icosapent ethyl in patients who are receiving statins and have persistently elevated fasting triglyceride levels. However, for secondary prevention, we suggest offering icosapent ethyl to patients receiving statins who have fasting triglyceride levels persistently greater than 1.7 mmol/L (150 mg/dL) to reduce cardiovascular morbidity and mortality. These recommendations are based on a single, large RCT (35). In that study, treatment with 4 g of icosapent ethyl resulted in a 25% reduction in the primary end point, defined as a combination of vascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina over 5 years. This effect was evident only among patients with known CVD, who comprised the majority of the study participants. The recommendation was graded as weak because of a lack of corroborating trials; the study's industry sponsorship; and other idiosyncratic features of the trial, such as its use of mineral oil as the placebo.

For primary or secondary prevention, we recommend against the use of omega-3 fatty acids as a dietary supplement to reduce CVD risk. The evidence showed no effect of omega-3 supplements (ranging from 0.5 to >5 g/d) on cardiovascular mortality, composite cardiovascular events, MI, stroke, or all-cause mortality in studies ranging from 12 to 72 months. In the RCTs evaluated, the results were inconclusive regarding the risk for adverse effects, including bleeding and thrombosis, and the risk of bias was substantial (36). Thus, the EBPWG decided to issue a "weak against" recommendation.

Insufficient evidence exists to recommend for or against the use of fiber, garlic, ginger, green tea, or red yeast rice supplements to reduce CVD risk. No studies evaluated the long-term effects of fiber, garlic, ginger, green tea, or red yeast rice supplements on CVD morbidity or mortality. Instead, only the safety of these interventions has been evaluated. Most of these substances were evaluated in their supplemental form, not as they naturally occur in foods, where they may have different effects.

We strongly recommend against the use of niacin in prescription or supplement doses, alone or in combination with statins, for primary or secondary prevention because of increased adverse events and lack of CVD risk reduction (37–39).

We recommend against adding fibrates to statin therapy for either primary or secondary prevention, on the basis of evidence of adverse effects (elevated liver aminotransferase and creatinine levels and a possible increase in CVD risk in women) and no known benefit. However, because of the lack of robust evidence, this recommendation was graded as weak (37, 40–43).

CONCLUSION

We present a pragmatic, patient-centered approach to managing lipid levels to reduce CVD risk, applying evidence for treatment that is concordant with the risk in the populations studied. Although our guideline is similar to that of the American College of Cardiology and American Heart Association (7), there are several important differences. First, we are less confident that the trial data support lower LDL-C target levels and higher dosing of statins, especially in primary prevention. Second, we extended the literature review through May 2019. Third, although we continue to support the use of calculators to estimate CVD risk for primary prevention, we do not believe the evidence supports the routine use of additional tests for risk prediction, even in intermediate-risk populations. Fourth, safety concerns (particularly with higher statin doses and combination therapy) influenced our pharmacologic treatment recommendations, which start with more conservative and safer moderate-dose statin therapy for both primary and secondary prevention, reserving upward titration for secondary prevention in higher-risk patients on the basis of shared decision making and recurrent events. Fifth, we believe that the evidence supports a more assertive stance on aerobic activity, cardiac rehabilitation, nutrition, and supplements. Sixth, we take a stronger position on limiting the use of laboratory testing to a more judicious, decision-oriented approach. Specifically, we recommend nonfasting lipid profiles, which should be repeated only every 10 years (given limited variability over time), and not at all once a goal statin dose is achieved.

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References

1. **Virani SS, Alonso A, Benjamin EJ, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020;141:e139-e596. [PMID: 31992061] doi:10.1161/CIR.0000000000000757

2. **Downs JR, O'Malley PG.** 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. Ann Intern Med. 2015;163:291-7. [PMID: 26099117] doi:10.7326/M15-0840

3. **U.S. Department of Veterans Affairs, U.S. Department of Defense.** Guideline for Guidelines. Accessed at www.healthquality.va.gov/policy/index.asp on 27 August 2020.

4. **Andrews JC, Schünemann HJ, Oxman AD, 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

5. **Newberry SJ, Ahmadzai N, Motala A, et al.** Methods Research Report. Surveillance and Identification of Signals for Updating Systematic Reviews: Implementation and Early Experience. Agency for Healthcare Research and Quality; 2013. AHRQ publication no. 13-EHC088-EF.

6. **Guirguis-Blake J, Calonge N, Miller T, et al; 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]

7. **Grundy SM, Stone NJ, Bailey AL, et al.** 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;139:e1082-e1143. [PMID: 30586774] doi:10.1161/CIR.0000000000000625

8. **National Institute for Health and Care Excellence.** The Guidelines Manual. Process and Methods Guides No. 6. Accessed at www.ncbi.nlm.nih.gov/books/NBK395866 on 27 August 2020.

9. **Martínez García L, McFarlane E, Barnes S, et al.** Updated recommendations: an assessment of NICE clinical guidelines. Implement Sci. 2014;9:72. [PMID: 24919856] doi:10.1186/1748-5908-9-72

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

11. **Institute of Medicine.** Clinical Practice Guidelines We Can Trust. National Academies Pr; 2011.

12. **Atkins D, Best D, Briss PA, et al; GRADE Working Group.** Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490. [PMID: 15205295]

13. **Andrews J, Guyatt G, Oxman AD, 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

14. **Lloyd-Jones DM, Braun LT, Ndumele CE, et al.** Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2019;73:3153-3167. [PMID: 30423392] doi:10.1016/j.jacc.2018.11.005

15. **Lin JS, Evans CV, Johnson E, et al.** Nontraditional risk factors in cardiovascular disease risk assessment: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;320:281-297. [PMID: 29998301] doi:10.1001/jama.2018.4242

16. **Graversen P, Abildstrøm SZ, Jespersen L, et al.** Cardiovascular risk prediction: can systematic coronary risk evaluation (SCORE) be improved by adding simple risk markers? Results from the Copenhagen City Heart Study. Eur J Prev Cardiol. 2016;23:1546-56. [PMID: 26976846] doi:10.1177/2047487316638201
17. **Yeboah J, Young R, McClelland RL, et al.** Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. J Am Coll Cardiol. 2016;67:139-147. [PMID: 26791059] doi:10.1016/j.jacc.2015.10.058
18. **Kim KP, Einstein AJ, Berrington de González A.** Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med. 2009;169:1188-94. [PMID: 19597067] doi:10.1001/archinternmed.2009.162
19. **Yebyo HG, Aschmann HE, Kaufmann M, et al.** Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: a systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. Am Heart J. 2019;210:18-28. [PMID: 30716508] doi:10.1016/j.ahj.2018.12.007
20. **Downs JR, Clearfield M, Weis S, et al.** Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615-22. [PMID: 9613910]
21. **Taylor F, Huffman MD, Macedo AF, et al.** Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013:CD004816. [PMID: 23440795] doi:10.1002/14651858.CD004816.pub5
22. **Du H, Li X, Su N, et al.** Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: a systematic review and meta-analysis. Heart. 2019;105:1149-1159. [PMID: 30842207] doi:10.1136/heartjnl-2019-314763
23. **Baigent C, Keech A, Kearney PM, 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]
24. **Koskinas KC, Siontis GCM, Piccolo R, et al.** Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. Eur Heart J. 2018;39:1172-1180. [PMID: 29069377] doi:10.1093/eurheartj/ehx566
25. **Silva M, Matthews ML, Jarvis C, et al.** Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther. 2007;29:253-60. [PMID: 17472818]
26. **Wang S, Cai R, Yuan Y, et al.** Association between reductions in low-density lipoprotein cholesterol with statin therapy and the risk of new-onset diabetes: a meta-analysis. Sci Rep. 2017;7:39982. [PMID: 28071756] doi:10.1038/srep39982
27. **Zhan S, Tang M, Liu F, et al.** Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database Syst Rev. 2018;11:CD012502. [PMID: 30480766] doi:10.1002/14651858.CD012502.pub2
28. **Schmidt AF, Pearce LS, Wilkins JT, et al.** PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017;4:CD011748. [PMID: 28453187] doi:10.1002/14651858.CD011748.pub2
29. **Mora S, Chang CL, Moorthy MV, et al.** Association of nonfasting vs fasting lipid levels with risk of major coronary events in the Anglo-Scandinavian Cardiac Outcomes Trial-lipid lowering arm. JAMA Intern Med. 2019;179:898-905. [PMID: 31135812] doi:10.1001/jamainternmed.2019.0392
30. **Angelow A, Schmidt CO, Dörr M, et al.** Utility of repeat serum cholesterol measurements for assessment of cardiovascular risk in primary prevention. Eur J Prev Cardiol. 2016;23:628-35. [PMID: 26170419] doi:10.1177/2047487315595583
31. **Perera R, McFadden E, McLellan J, et al.** Optimal strategies for monitoring lipid levels in patients at risk or with cardiovascular disease: a systematic review with statistical and cost-effectiveness modelling. Health Technol Assess. 2015;19:1-401, vii-viii. [PMID: 26680162] doi:10.3310/hta191000
32. **Piercy KL, Troiano RP, Ballard RM, et al.** The physical activity guidelines for Americans. JAMA. 2018;320:2020-2028. [PMID: 30418471] doi:10.1001/jama.2018.14854
33. **Abell B, Glasziou P, Hoffmann T.** The contribution of individual exercise training components to clinical outcomes in randomised controlled trials of cardiac rehabilitation: a systematic review and meta-regression. Sports Med Open. 2017;3:19. [PMID: 28477308] doi:10.1186/s40798-017-0086-z
34. **Rees K, Takeda A, Martin N, et al.** Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2019;3:CD009825. [PMID: 30864165] doi:10.1002/14651858.CD009825.pub3
35. **Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators.** Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11-22. [PMID: 30415628] doi:10.1056/NEJMoa1812792
36. **Abdelhamid AS, Brown TJ, Brainard JS, et al.** Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018;11:CD003177. [PMID: 30521670] doi:10.1002/14651858.CD003177.pub4
37. **Keene D, Price C, Shun-Shin MJ, et al.** Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. BMJ. 2014;349:g4379. [PMID: 25038074] doi:10.1136/bmj.g4379
38. **Schandelmaier S, Briel M, Saccilotto R, et al.** Niacin for primary and secondary prevention of cardiovascular events. Cochrane Database Syst Rev. 2017;6:CD009744. [PMID: 28616955] doi:10.1002/14651858.CD009744.pub2
39. **Kaur N, Pandey A, Negi H, et al.** Effect of HDL-raising drugs on cardiovascular outcomes: a systematic review and meta-regression. PLoS One. 2014;9:e94585. [PMID: 24728455] doi:10.1371/journal.pone.0094585
40. **Jakob T, Nordmann AJ, Schandelmaier S, et al.** Fibrates for primary prevention of cardiovascular disease events. Cochrane Database Syst Rev. 2016;11:CD009753. [PMID: 27849333]
41. **Shao K, Tang Y, Zhou D, et al.** Comparison of the safety of statin monotherapy and coadministration with fenofibrate in patients with mixed hyperlipidemia: a meta-analysis. International Journal of Clinical and Experimental Medicine. 2016;9:5291-300.
42. **Murray AM, Hsu FC, Williamson JD, et al; Action to Control Cardiovascular Risk in Diabetes Follow-On Memory in Diabetes (ACCORDION MIND) Investigators.** ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. Diabetologia. 2017;60:69-80. [PMID: 27766347]
43. **Ginsberg HN, Elam MB, Lovato LC, et al; ACCORD Study Group.** Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563-74. [PMID: 20228404] doi:10.1056/NEJMoa1001282

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