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Lipid management beyond the guidelines☆

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ABSTRACT

The 2018 AHA/ACC cholesterol guideline builds on the 2013 ACC/AHA cholesterol guideline statin recommendations to provide more detailed recommendations for the use of nonstatin therapy risk stratification for primary prevention statin use. New information has become available after the development of the 2018 AHA/ACC cholesterol guideline that can further inform clinical practice. Proprotein convertase subtilisin kexin type-9 (PCSK9) monoclonal antibodies are now a reasonable or even good value following over 60% reductions in their acquisition price, and the identification of high risk patient groups most likely to benefit from further low-density lipoprotein cholesterol (LDL-C) lowering. Meta-analyses and clinical trial data now show that patients with LDL-C ≥ 100 mg/dl are more likely to experience progressively greater reductions in the risk of cardiovascular and total mortality and coronary heart disease events for progressively higher LDL-C levels. Icosapent ethyl, a highly concentrated form of modified EPA has been shown to reduce cardiovascular events in high risk patients with moderate hypertriglyceridemia on statin therapy. Comparisons with other statin guidelines revealed that statin initiation for those with ≥7.5% 10-year atherosclerotic cardiovascular disease (ASCVD) risk is the most effective strategy for reducing the most ASCVD events for the proportion of the population treated. Data from younger populations finally became available for coronary artery calcium (CAC) scoring (mean age of 51 years) which confirmed the value of CAC > 0 for identifying individuals at increased ASCVD risk most likely to benefit from statin initiation. This analysis also found that statins could keep CAC = 0 in those with risk factors. Epidemiologic pooling studies now clearly show that LDL-C and non-high-density lipoprotein cholesterol levels in young adulthood confer excess risk for ASCVD later in life. Accumulating data support earlier risk factor intervention trials as the next research priority.

Contents

Abbreviations and acronyms: AHA, American Heart Association; ACC, American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium scoring; CKD, chronic kidney disease; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EAS, European Atherosclerosis Society; EPA, eicosapentaenoic acid; ESC, European Society for Cardiology; HDL-C, high density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; MESA, multi-ethnic study of atherosclerosis; NICE, National Institute for Health and Care Excellence; NNT, number-needed-to-treat; PCE, Pooled Cohort Equations; PCSK9 mAbs, proprotein convertase subtilisin/kexin type 9 inhibiting monoclonal antibodies; QALY, quality adjusted life year; REDUCE-IT, reduction of cardiovascular events with icosapent ethyl-intervention trial; TG, triglyceride; US, United States of America; USPTF, US Preventive Services Task Force.

☆ Statement of conflict of interest: see page XX.

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Introduction

The most recent cholesterol guideline in the United States (US) comes from the 2018 AHA/ACC/Multispecialty Guideline on the Management of Blood Cholesterol.[1] This guideline builds on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[2] The 2013 ACC/AHA cholesterol guideline was initially controversial due to a new treatment paradigm focused on the appropriate statin intensity in 4 statin benefit groups and a move away from the treat-to-goal approach in the earlier Adult Treatment Panel 3 guideline and still recommended by some groups inside and outside the US.[3–5] Much of the controversy surrounding the 2013 ACC/AHA cholesterol guideline can be understood as a reaction to paradigm change, which occurs when sufficient new data and advances in methodology require a new treatment paradigm (Fig 1).[6] The scientific enterprise continues to move forward and continually generates new evidence and improves methods. The 2013 ACC/AHA cholesterol guideline recommendations arose from strict adherence to evidence from cardiovascular disease (CVD) outcomes trials and systematic reviews of epidemiologic studies and made few expert recommendations.

Summary of 2018 guideline major recommendations

The 2018 AHA/ACC cholesterol guideline incorporates new evidence from nonstatin CVD outcomes trials and epidemiologic studies to move toward more individualization of cholesterol lowering therapy in the setting of shared decision-making (see paper by Grundy & Stone in this issue). As in the 2013 guideline, in the 2018 AHA/ACC guideline, lifestyle remains the foundation for drug therapies to reduce the risk of atherosclerotic CVD (ASCVD). Statins continue to receive strong, Class I "must do" recommendations for patients with ASCVD, low-density lipoprotein cholesterol (LDL-C) levels ≥190 mg/dl, and diabetes aged 40–75 years, with the addition of primary prevention patients with ≥20% 10-year ASCVD risk as estimated by the Pooled Cohort Equations (PCE). Shared decision-making continues to be recommended for primary prevention statin therapy in patients aged 40–75 years with 5 to <20% 10-year ASCVD risk, with a number of new characteristics that can may influence ASCVD risk assessment. When a treatment decision is uncertain, calcium scoring can be used to up- or down-classify risk.

Once statin and lifestyle therapy are maximized, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be considered in selected high risk patients, such as those with ASCVD and other high risk characteristics, familial or severe genetic hypercholesterolemia, or diabetes with other high risk characteristics.

What's new after the 2018 guideline for secondary prevention?

Greater cost-effectiveness for PCSK9 inhibitors

For the first time, the 2018 AHA/ACC cholesterol guideline formally incorporated cost considerations into a lipid guideline.[7,8] Two CVD outcome trials found benefit from proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibodies (mAbs) added to high or moderate intensity statin therapy in patients with chronic ASCVD or acute coronary syndromes. Typically, two good quality randomized trials demonstrating a CVD risk reduction benefit would be considered sufficient evidence to support a Class I A "must do" recommendation. However, the high wholesale list price of >$14,000 per year, even with discounting, and moderate risk reductions of 15–20% in ASCVD events, resulted in a determination that PCSK9 mAbs were "low value", or >$150,000/quality of life year (QALY). Therefore, a Class IIa "consider" recommendation was made for PCSK9 mAbs added to maximal statin and ezetimibe therapy only in very high risk patients.

In October 2018, both PCSK9 mAb manufacturers reduced the original list price by 60%, to about $5450–5600 per year. A previous analysis by the Institute for Clinical and Economic Review suggested that with discounts of 60%, that when the 5-year number-needed-to-treat (NNT) to prevent one ASCVD event were 21–28, PCSK9 mAbs have incremental cost effectiveness of <$100,000/QALY in patients with ASCVD or familial hypercholesterolemia (FH).[9] A recent statement from the National Lipid Association identified 3 patient groups for which 60% discounted PCSK9 mAbs could provide a reasonable value at $100,000/QALY (Fig 2).[10] In addition, some groups with extremely high ASCVD risk or with FH could receive a high value (<$50,000/QALY) from discounted PCSK9 mAbs. The statement was based on a systematic review of subgroup analyses of moderate versus high intensity statin and PCSK9 mAb trials found that several patient phenotypes emerged that could inform shared decision-making for PCSK9 mAbs based on LDL-C levels on maximal statin ± ezetimibe therapy. PCSK9 mAbs would provide at least a reasonable value for extremely high risk (≥40% 10-year ASCVD risk) patients with an extensive or active

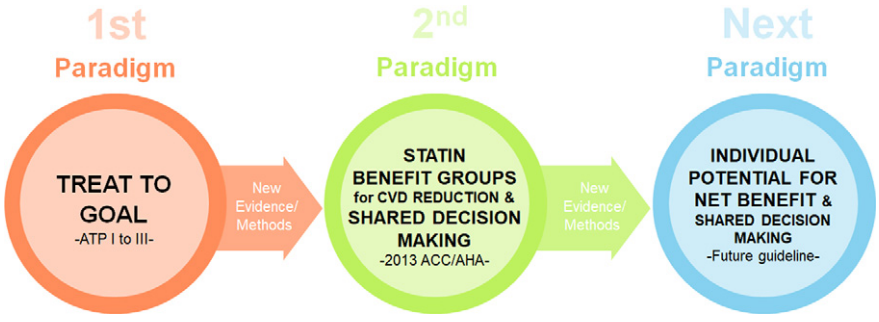

Fig 1. Paradigm change in cholesterol guidelines as new evidence and better methods are developed. Adapted from Robinson JG, Ray KK. Circulation. 2016;133:1533–1536.

burden of ASCVD and poorly controlled risk factors, or less extensive ASCVD with a high burden of poorly controlled cardiometabolic risk factors (including diabetes and FH) when LDL-C levels are ≥70 mg/dl on maximal statin ± ezetimibe therapy. Patients with less extensive ASCVD and some poorly controlled risk factors had a 30–39% 10-year ASCVD risk, and could experience at least a reasonable value from PCSK 9 mAbs when LDL-C levels are ≥100 mg/dl. High risk patients (20–29% 10-year ASCVD risk) had single vessel ASCVD and well controlled risk factors, or primary prevention FH with CVD risk factors could have at least reasonable value from PCSK9 mAbs when LDL-C levels are ≥130 mg/dl.

More ASCVD and mortality risk reduction benefits when LDL-C ≥ 100 mg/dl

A meta-analysis of statin, ezetimibe, and PCSK9 mAb trials found when baseline LDL-C levels were <100mg/dl, no cardiovascular or total mortality benefits were observed from LDL-C lowering therapy.[11] When baseline LDL-C were ≥100 mg/dl, for each 40 mg/dl higher baseline LDL-C, an additional 10% reduction in total mortality and 14% reduction in the relative risk of CVD-mortality emerged. The relative risk of major CVD events, myocardial infarction and revascularizations also increased with each 10 mg/dl higher increment in baseline LDL-C. Notably, in the PCSK9 mAb trial ODYSSEY OUTCOMES, a total morality benefit was observed when baseline LDL-C levels were ≥100 mg/dl on high or moderate intensity statin therapy.[12] In addition, the coronary intravascular ultrasound trials found LDL-C = of about 100 mg/dl to be an important cut-point for response to LDL-C lowering from high intensity or PCSK9 mAb therapy.[13,14] The lower the achieved LDL-C is below 100 mg/dl, the greater the regression. Conversely, the higher the achieved LDL-C is above 100 mg/dl, the greater the plaque progression. LDL-C levels also have effects on plaque composition, and LDL-C ≥ 100 mg/dl is more likely to be associated with unstable plaque characteristics.[15,16]

These findings support a log linear association between LDL-C lowering and ASCVD event reduction that is amplified in the setting of higher CVD risk, as was suggested in an analysis of subgroups from the statin versus placebo trials.[17] In the flatter portion of the log linear curve when LDL-C levels are below 100 mg/dl, ASCVD events continue to occur at high rates. These recurrent events are more likely to be due to plaque erosions, which have become increasingly common causes of acute coronary syndromes in statin-treated patients.[16] This may also be the explanation for the diminished reduction in fatal ASCVD events when LDL-C levels are <100 mg/dl, since plaque erosions are more likely to be nonfatal CVD, while occlusive plaque ruptures may be more likely to cause fatal events.

Clinical implications of log linear association LDL-C and ASCVD event reduction

The log linear shape of the LDL-C/CVD event curve has important implications for clinical practice since it places a high priority on intensifying LDL-C lowering therapy when LDL-C levels are ≥100 mg/dl in order to maximize the mortality and ASCVD risk reduction benefits (Fig 3 conceptual diagram). Once LDL-C levels are <100 mg/dl, further LDL-C lowering may be beneficial in some patients, or attention can turn to other CVD prevention therapies. It should be noted that all recent trials of the newer diabetes drugs, antithrombotic agents, and omega-3 fatty acids that have shown a reduction in ASCVD events have been performed in the setting of well-controlled risk factors, including statin therapy and LDL-cholesterol levels <100 mg/dl. This includes trials of SGLT2 and GLP-1 inhibitors in diabetes patients, icosapent ethyl in patients with ASCVD or high risk diabetes and triglycerides 135–499 mg/dl (discussed below), and rivaroxaban in patients with stable ASCVD.[18–21]

REDUCE-IT

Up until recently, omega-3 fatty acid supplementation trials in the statin era have been negative in non-Japanese populations.[22] The recent REDUCE-IT trial of icosapent ethyl, a highly purified form of modified EPA, for the first time found a 25% reduction in CVD events and a 20% reduction in CVD death in very high risk statin-treated patients with triglyceride (TG) levels 135–499 mg/dl.[21] Earlier negative trials used 1 g

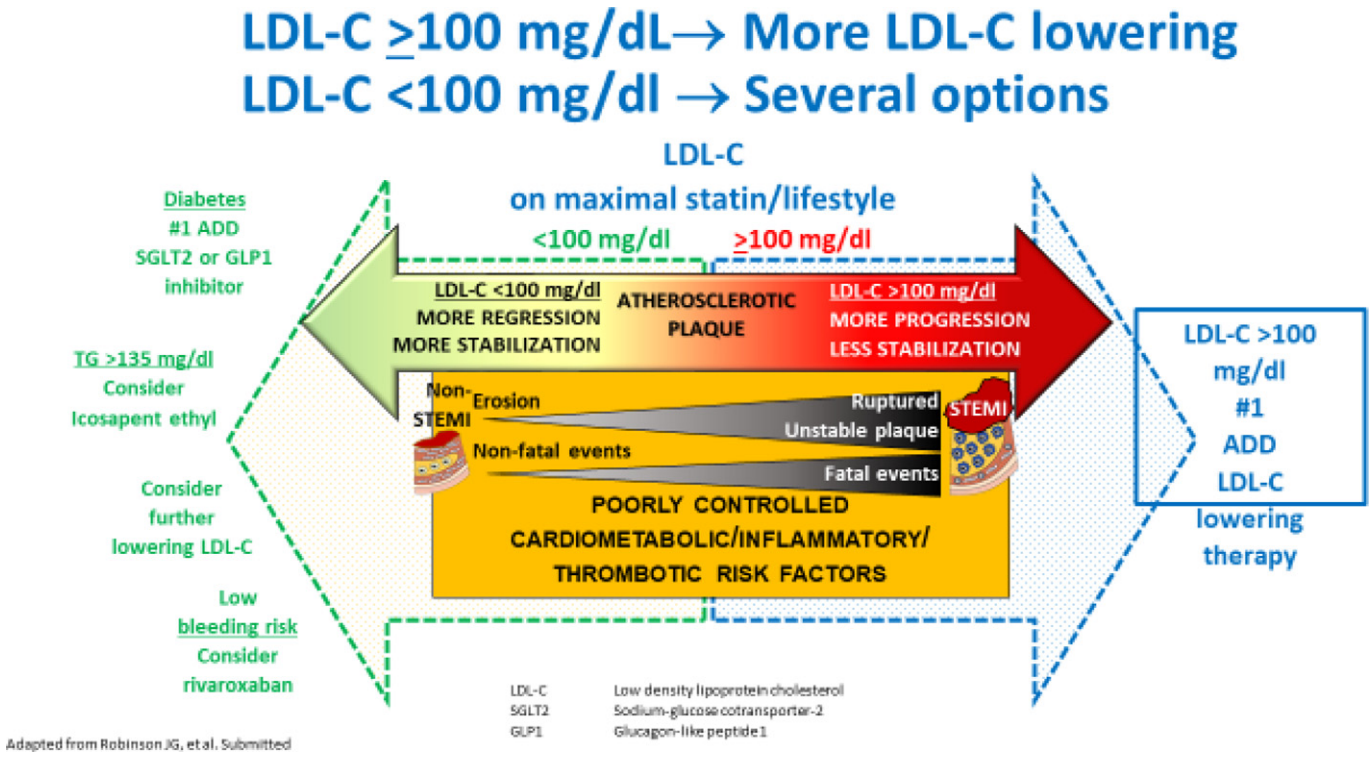

Fig 2. LDL-C level on maximal statin therapy can guide the next choice of preventive therapy.

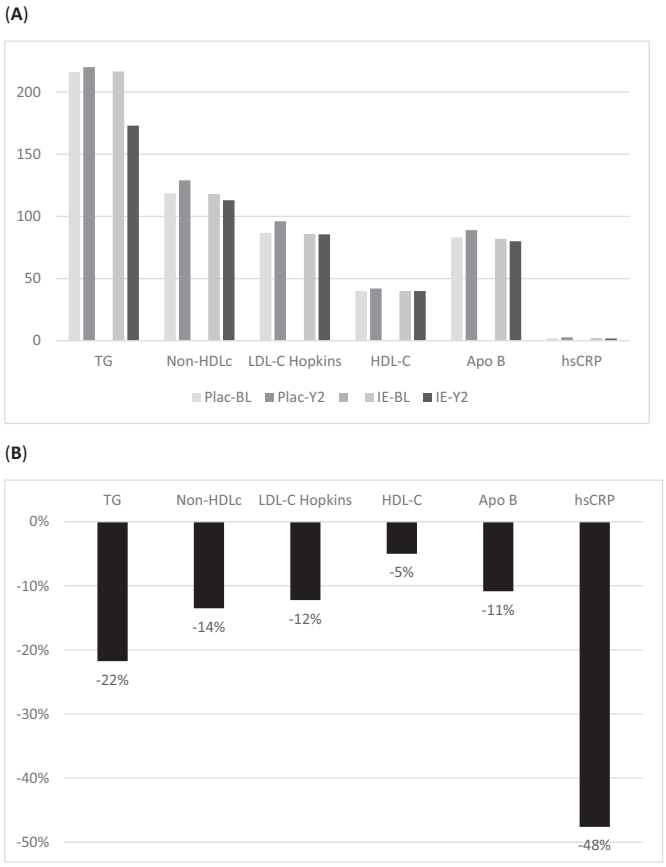

Fig 3. Median triglyceride (TG), non-HDL-C, LDL-C by the Hopkins-Martin method, HDL-C, apo B, and high sensitivity C-reactive protein (hs-CRP) levels at baseline and year 2 (A) and between group differences in lipid and C-reactive protein (CRP) levels in icosapent ethyl compared to placebo groups at year 2 (B) in the REDUCE-IT trial. (Data from Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. 2019;380(1):11–22).

doses of eicosapentaenoic acid (EPA) combined with docosahexaenoic acid (DHA), although a recent trial using 1 g of EPA/DHA did demonstrate a reduction in nonfatal myocardial infarction in the recent VITAL trial (although the primary and composite endpoints were negative).[22,23] Notably, JELIS, an earlier trial of 1.8 g of EPA, also demonstrated a CVD risk reduction benefit in a hypercholesterolemic (but not hyperTG) population of Japanese patients treated with statins.[24]

There is evidence that high risk patients with elevated TGs, especially when high-density lipoprotein cholesterol (HDL-C) levels are low, benefit from fibrate therapy.[25,26] This observation led to the most recent omega-3 fatty acid trials using higher doses of 4 g daily, REDUCE-IT (icosapent ethyl) and STRENGTH (carboxylated forms of EPA and DHA), in high risk patients with elevated TG levels. The results of both trials will be needed to inform clinical practice regarding the preferential use of one or the other preparation.

The mechanisms underlying the ≈25% CVD risk reductions in REDUCE-IT are not entirely clear. It does not appear that the lipid effects entirely explain the 20–25% relative risk reductions in REDUCE-IT (Fig 3). TGs were reduced by 22% compared to the mineral oil placebo, although this was in small part due to the increase in TGs in the placebo group. The magnitude of relative risk reduction was consistent across the range of triglyceride levels. Median LDL-C was 86 mg/dl and non-HDL-C was 118 mg/dl. LDL-C, non-HDL-C, and apo B were modestly reduced with icosapent ethyl compared to the mineral oil placebo, but this is in larger part because LDL-C, non-HDL-C, and apo B increased in the placebo group. High-sensitivity C-reactive protein (hs-CRP) levels increased by ≥30% in the mineral oil group during the trial, resulting in a 48% difference in hs-CRP between the two treatment groups. Whether the worsening lipid and hs-CRP levels in the placebo group were due to adverse effects of the mineral oil, or to weight gain during the trial, is unknown. Nonetheless, icosapent ethyl did reduce hs-CRP, which may reflect an anti-inflammatory effect and have contributed to the reduction in CVD risk. Also notable was an increase in bleeding events, which could also have beneficial effects on cardiothrombotic risk.

If mineral oil have increased CVD risk, this may have magnified a more modest risk reduction from icosapent ethyl. In contrast, the STRENGTH trial is using a polyunsaturated oil placebo, which could have beneficial lipid effects and thereby reduce the magnitude of a risk reduction from carboxylated EPA/DHA. In addition, a better understanding of the adverse effect profile of the 2 drugs may inform decision-making. In addition to the increase in serious bleeding events, icosapent ethyl also increased the risk of atrial fibrillation and peripheral edema.[21]

Although the exact mechanisms and magnitude of CVD risk reduction may never be clear, icosapent ethyl 4 g provides another prevention option for very high risk patients with ASCVD or diabetes with multiple comorbidities who have an LDL-C < 100 mg/dl on statin therapy and moderately elevated TG levels. Icosapent ethyl should probably be avoided in patients at risk for atrial fibrillation, especially if they have intermittent atrial fibrillation. A cost-effectiveness analysis by the Institute for Clinical and Economic Review based on the REDUCE-IT trial suggests icosapent ethyl 4 g would provide a very good value at $18,000 per quality adjusted life year if used in very high risk patients with greater than a 4% risk of an ASCVD event per year.[27]

What's New after the 2018 guideline for primary prevention?

More confirmation of ≥7.5% 10-year ASCVD risk threshold

A comparison of 5 international guideline approaches to treatment strategies for primary prevention statin therapy confirms the superiority of the 2013 AHA/ACC and 2018 AHA/ACC guideline strategies (age 40–75 years with ≥7.5% 10-year ASCVD risk calculated by the PCE, diabetes or LDL-C ≥ 190 mg/dl) for preventing more ASCVD events than other approaches using higher treatment thresholds (Table 1).[28] The USPTF guideline (≥10% 10-year ASCVD risk plus one risk factor) treats about 25% fewer people but also prevents 20% fewer events. The Canadian guideline treats and prevents similar proportions to the ACC/AHA approach, adding chronic kidney disease age ≥ 50 years and a ≥10% 10-year ASCVD risk cut-point. The EAS/ASC guideline using fatal ASCVD risk cut-points in persons aged 40–65 years and higher LDL-C thresholds treats fewer people but also prevents many fewer events.

More confirmation of PCE accuracy

The PCE were derived from 4 representative US epidemiologic cohorts of non-Hispanic whites and African Americans.[29,30] Several analyses performed after the release of the 2013 cholesterol guideline found the PCE over-predicted 10-year ASCVD risk in lower risk populations of health professionals, northern Californians in the Kaiser Permanente health maintenance organization, and a contemporary US epidemiologic cohort treated with statins.[31–33] The PCE perform well in representative US cohorts such as REGARDS, and in when Medicare claims data are included.[34,35] The PCE also outperforms the Reynolds Risk equations that include hs-CRP and strategies using trial inclusion criteria.[34] Recalibration to the same endpoints and risk factors equalizes the performance of the various risk prediction equations and improved modeling for risk stratification for treatment.[36]

Coronary artery calcium (CAC) = 0 may not mean low ASCVD risk or low benefit

In the 2018 AHA/ACC guideline, when a decision to initiate statins is uncertain and 10-year ASCVD risk is estimated to be 5% to <20%, and risk

Table 1
Percentage of population eligible for statins and estimated percentage of ASCVD events prevented by using a high intensity statin for 10 years.

	ACC/AHA	USPTF	Canadian	EAS/ESC	NICE
	Age 40–75 years & ≥7.5% 10-year ASCVD risk[a]; Diabetes LDL-C ≥ 70 mg/dl; LDL-C ≥ 190 mg/dl	10% 10-y ASCVD risk + 1 risk factor (LDL-C ≥ 130 mg/dl, HDL-C < 40 mg/dl), hypertension, smoking or diabetes	Age 40–75 years & ≥20% 10-y CVD risk[b] or 10–19% with LDL-C ≥ 135 mg/dl; diabetes; LDL-C ≥ 193 mg/dl; CKD age ≥ 50 y	Age 40–65 y & 5–9% 10-fatal ASCVD[c] & LDL-C ≥ 155 mg/dl; or 40–65 y & ≥10% 10-y fatal ASCVD risk & LDL-C ≥ 97 mg/dl; diabetes; non-dialysis CKD; LDL-C > 232 mg/dl or total cholesterol ≥309 mg/dl	Age 40–75 y & 10% 10-y ASCVD risk[d]; non-dialysis CKD; LDL-C ≥ 190 mg/dl or total cholesterol ≥290 mg/dl
Eligible for statin	42	31	44	15	40
Events prevented	34	27	34	13	32

[a] Nonfatal and fatal ASCVD calculated by Pooled Cohort Equations.
[b] Nonfatal and fatal ASCVD calculated by the Framingham Risk Score.
[c] Fatal ASCVD calculated by the SCORE prediction model.
[d] Nonfatal and fatal ASCVD calculated by the QRISK prediction model.

enhancing factors can be considered, as can the results of CAC scoring. However, CAC scoring is note recommended for current smokers, patients with diabetes mellitus, or a strong family history of ASCVD, all of whom remain at increased ASCVD risk despite a CAC = 0. If these characteristics are absent, then the guideline recommends that if the CAC score is zero, risk is low and statin therapy may be delayed 5 to 10 years.

Unfortunately, there are a number of problems with the nonselective use of CAC = 0 to "de-risk" patients recommended in the 2018 guideline. The CAC data have been largely derived from European ancestry cohorts with mean ages in the 7th decade. Notably, African Americans are at higher ASCVD risk than whites before age 50 years, ages at which CAC is more likely to be zero even in those with high lifetime ASCVD risk.[37] One US cohort includes African Americans and Chinese Americans but is inadequately powered to address reclassification of risk by race or ethnicity.[38] Only one reclassification analysis has been performed for women, which showed that CAC = 0 did not indicate reduced risk in Japanese women.[39] It will be important to confirm the value of CAC for reclassification in non-white populations, since failure to appropriately treat high risk African Americans and women may worsen already widening disparities in ASCVD risk and mortality.[40]

The first study to evaluate younger adults was a recent observational analysis from the Walter Reed Army Medical Center that reported data for individuals with a mean age of 51 years on a statin (75% men) and 48 years not on a statin (66% men).[41] Over 12 years, similar low rates of ASCVD events of about 5% occurred in statin-treated and in untreated individuals, which was interpreted as no benefit from statins over 5-years in lower risk persons with CAC = 0 at baseline. This interpretation is not correct since the statin-treated group had higher risk factor levels at baseline, including more likely to be older, male, hypertensive, have diabetes, smoke, and take aspirin. Moreover, in the discussion section of the paper, the authors noted that those with CAC = 0 and LDL-C ≥ 130 mg/dl were not low risk, which is a critical amendment needed to the long list of those who should not undergo CAC scoring, as noted in the 2018 guideline. A more accurate interpretation of the Walter Reed study would be that statin therapy keeps CAC = 0 in individuals with risk factors.

Additional issues arise regarding the generalizability of findings from a healthier armed forces cohort to the general population of obese, sedentary women and men from a range of races and ethnicities is questionable without more data. Notably body mass index was not reported in the Walter Reed study for comparison to the US population.

An additional problem arising around interpreting CAC = 0 as "low risk" (which is not quantified in the 2018 guideline) may not be the same as "low benefit". In the analysis from MESA on which the 2018 guideline CAC strategy was based, in the 7.5% to 20% 10-year ASCVD risk group, 45% had CAC = 0 and a 4.6% 10-year ASCVD risk, about half that of the CAC > 0 group (10% 10-year ASCVD risk). However, there may still be a meaningful potential to benefit from the addition of statin therapy in lower risk persons, especially if they have higher LDL-C levels.[42] In the Cholesterol Treatment Trialists individual meta-analysis of primary prevention patients in statin CVD outcomes trials, the relative risk reduction was significantly greater (34% per 39 mg/dl reduction in LDL-C) in those with <10% 5-year risk of major vascular events than in those with ≥10% 5-year risk (18%).[43] Calculating the NNT (e.g. the inverse of the absolute risk reduction) yields a 5-year NNT = 38 for a high intensity statin for the CAC = 0 group, and an 5-year NNT = 27 for the CAC > 0 group. Both NNTs would be considered of reasonable benefit.[44]

Importance of lifetime risk factor exposure on ASCVD risk

Long term follow-up of several epidemiologic cohorts is revealing that earlier life risk factor exposure, including elevated LDL-C, non-HDL-C and blood pressure, predicts later life ASCVD events over and above CVD risk factor levels measured in mid-life.[45] Recent evidence in the US shows that there are as many ASCVD events before age 65 as after age 65, and that ASCVD rates and mortality are rising in younger non-white populations and women.[46,47] Taken together, this is a call to action to begin risk factor control earlier in life if there is to be further progress in reducing preventable premature deaths from ASCVD. This will require updates to the PCE to better predict ASCVD risk in adults <40 years, and in non-white populations. Randomized trials of lifestyle modification, statin and blood pressure-lowering therapies will also be needed to inform treatment guidelines.[48]

Conclusions

Good guidelines summarize the best evidence available at the time of the panel's deliberations. Important new studies and trials are often published that may outdate some recommendations by the time they are finally published. Class I recommendations with a high level of evidence are the least likely to change, such as those recommending high and moderate intensity statins, representing best practices that should be the focus of clinical implementation efforts. Lower levels of recommendations may evolve to incorporate new evidence in future guidelines. Future cholesterol guidelines will need to be updated to incorporate new evidence regarding use of PCSK9 mAbs, omega-3 fatty acid preparations, and primary prevention risk stratification approaches.

Statement of conflict of interest

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