The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA* Guidelines on the Management of Blood Cholesterol in Diabetes

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The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines recently published its 2018 recommendations on management of LDL cholesterol (LDL-C) in people with diabetes. For primary prevention, moderate-intensity statin therapy is recommended for those aged 40–75 years, with a preference for high-intensity statin treatment for older subjects and for those with higher estimated risk or risk-enhancing factors following a patient-clinician discussion. Statin therapy may be reasonable in adults <40 years or >75 years of age where there is less evidence for benefit. For people with diabetes and established atherosclerotic cardiovascular disease, high-intensity statin therapy is recommended. The majority of these subjects have very high risk, and an LDL-C goal of <70 mg/dL is recommended. If this target is not achieved, ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 inhibitor may be added.

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines published its first guidelines on the management of blood cholesterol in people with diabetes in 2013 and has now updated and modified these recommendations in the 2018 guidelines (1). The guidelines were developed by a writing committee consisting of medical experts including cardiologists, internists, interventionists, a nurse practitioner, pharmacists, a physician assistant, a pediatrician, a nephrologist, a diabetologist (American Diabetes Association [ADA] representative), and a lay/patient representative, and all members were required to have no relationships with industry. The development of recommendations was based on all available evidence, based on a literature search of randomized controlled trials (RCTs), registries, nonrandomized comparative and descriptive studies, and systematic reviews from May 1980 through July 2017 using relevant keywords as well as considering the results of an independent evidence review committee that assessed the magnitude of benefits and harms from the addition of nonstatin medications to statin therapy in those with clinical atherosclerotic cardiovascular disease (ASCVD). Recommendations were based on ACC/AHA criteria that designate both a class of recommendation (COR) and a level of evidence (LOE). COR describes the estimated magnitude and certainty of benefit in proportion to risk, and LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources.

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OVERVIEW

ASCVD is the leading cause of morbidity and mortality in diabetes, and diabetes is a major contributor to the development of ASCVD in the population. The principal focus of the 2018 guidelines section on diabetes is on primary prevention of ASCVD in adults using pharmacotherapy to lower LDL cholesterol (LDL-C) in addition to a healthy lifestyle. Other sections of relevance to diabetes that are dealt with in the guidelines include secondary prevention of ASCVD, hypertriglyceridemia, and chronic kidney disease (CKD). As in the 2013 guidelines, the 2018 guidelines recommend moderate-intensity statin therapy for most adults for primary prevention, but the 2018 guidelines extend the recommendations for risk assessment in the 40–75-year age-group to upgrade statin therapy decision-making through consideration of an expanded list of risk-enhancing factors in addition to major risk factors in a clinician-patient discussion. Though evidence remains incomplete, greater attention is given in the 2018 guidelines to adults <40 years of age and those >75 years. For secondary prevention, the 2018 guidelines continue to recommend high-intensity statins but now recommend ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors added to maximally tolerated statin therapy for a subgroup of very high-risk patients who do not achieve an LDL-C below a threshold value of 70 mg/dL with statin therapy alone.

PRIMARY PREVENTION

There is a wide spectrum of risk among individuals with diabetes (2–5) that varies with age, duration of diabetes, and the presence of traditional risk factors and risk enhancers common to the general population, as well as those specific to the population with diabetes (Fig. 1).

Age 40–75 Years

RCTs of statin therapy included adults with diabetes aged 40–75 years. Therefore, evidence for benefit is principally derived from studies in this age-group. Most adults with diabetes in this age range are at intermediate or high risk for their first ASCVD event (2–5). A large meta-analysis of 14 RCTs of moderate-intensity statin therapy (30–50% LDL-C lowering) that included people with type 1 diabetes (n = 1,466) and type 2 diabetes (n = 17,220) demonstrated a 21% reduction in major vascular events per 1 mmol/L (~39 mg/dL) reduction in LDL-C (6). The benefit was similar for type 1 and type 2 diabetes patients and whether or not they had a history of ASCVD. Of these studies, there were four primary prevention RCTs of statin therapy conducted exclusively in cohorts with diabetes, three of which showed significant reductions in ASCVD events (7–10). A meta-analysis of these four trials found that moderate-intensity statin therapy is associated with a risk reduction of 25% (11), similar to that found in people without diabetes or ASCVD. In addition, a large registry study (n = 24,230) in people with type 1 diabetes without a history of ASCVD found a 40% reduction in cardiovascular disease (CVD) death among those receiving lipid-lowering therapy compared with those who did not (12). Therefore, moderate-intensity statin treatment is indicated in such individuals on the basis of a high level of evidence and without the need for prior risk assessment.

Refinement of Risk Assessment

Strong general evidence indicates that the benefit from statin therapy is related to both global risk and intensity of treatment and is supported by meta-analyses comparing high-intensity versus moderate-intensity statin therapy (13), although no RCTs of high-intensity statin therapy have been carried out in cohorts of patients exclusively with diabetes. Because the level of ASCVD risk influences the decision to upgrade statin treatment from moderate to high intensity, evaluation of risk using the pooled cohorts equations (PCE) derived from studies of cohorts that included a large number of subjects who had diabetes will help refine risk estimates and therapeutic decision-making. However, this three-tiered ASCVD risk score, which categorizes individuals into borderline (5–7.4%), intermediate (7.5–19.9%), and high (≥20%) 10-year risk for ASCVD, does not determine whether statin intensity should be increased. Rather, it begins an evaluation that includes clinician judgment of the individual's global risk, including an assessment of risk-enhancing factors as well as the potential for benefit from a high-intensity statin versus the potential for adverse effects or drug-drug interactions, and the evaluation should also take into account patient preferences and values.

Risk Enhancers

Although the PCE is the most robust tool for estimating 10-year risk in U.S. adults 40–75 years of age based on its inclusion of major independent risk factors, it has limitations when applied to individuals. One purpose of the clinician-patient risk discussion is to individualize risk status based on PCE as well as other risk enhancing factors prevalent in the general population that may be present in people with diabetes, as well as those specific to diabetes (14–20) (Table 1).

Coronary Calcium Scoring

The coronary artery calcium (CAC) score may be used in primary prevention among the general population in borderline or intermediate-risk individuals to identify lower-risk individuals with a CAC score of 0 for derisking purposes. Nonetheless, a study of adults with type 2 diabetes and without ASCVD who had a CAC score of 0 found a mean ASCVD 10-year risk of 8.0% (21), indicating that they were not at low risk or soon would not be at low risk. Recent data in adults with type 1 diabetes without ASCVD and with a CAC score of 0 showed that their mean ASCVD 10-year risk was 5.6% (22). Therefore, CAC scoring in people with diabetes aged 40–75 years is not recommended for derisking or revising risk assessment below the treatment threshold.

High-Intensity Statin Therapy (>50% LDL-C Lowering)

People with diabetes have a higher trajectory of lifetime risk than do those without diabetes. Furthermore, morbidity and mortality associated with a first event is increased in diabetes, and the residual risk among the statin-treated groups in the primary prevention trials of people with diabetes remained high (e.g., overall 8.5% had major cardiovascular events in 3.8 years [11]). In addition there is evidence of benefit from high-intensity statin treatment in primary prevention among men >50 years of age and women >60 years of age (23). On the basis of these considerations, high-intensity statin therapy to maximize risk reduction is preferred in patients with diabetes as they age or develop risk enhancers. In those who have a high ASCVD risk score of >20%, a risk discussion may be held on the benefits of achieving ≥50% LDL-C lowering, and in those in whom

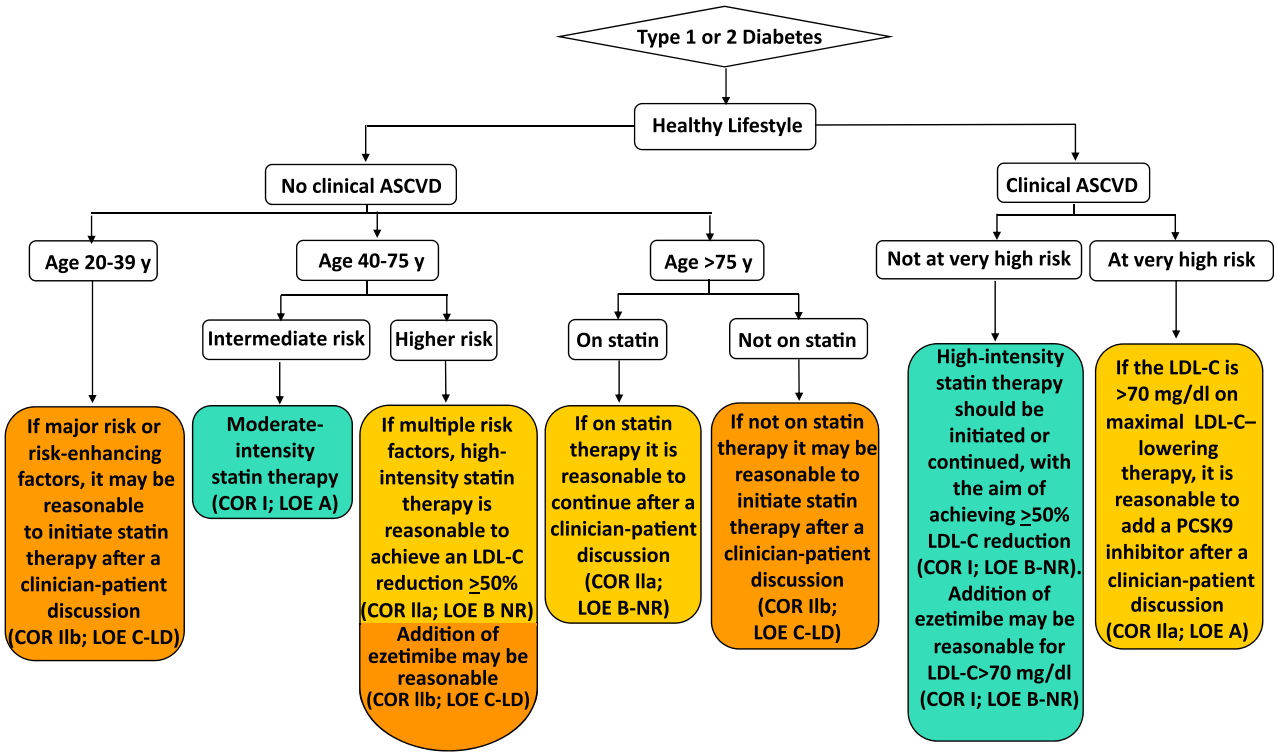

Figure 1—AHA/ACC MultiSociety 2018 guidelines for cholesterol management in people with diabetes. The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources. COR I – strong (green); COR IIa – moderate (yellow); COR IIb – weak (orange). LOE A – high quality: multiple high-quality RCTs/meta-analyses; LOE B-R – moderate quality: at least one RCT/meta-analysis; LOE B-NR – moderate quality: one or more well-designed nonrandomized studies; LOE C-LD – limited data.

high-intensity statin cannot be tolerated or does not lower LDL-C as expected by ≥50%, addition of ezetimibe 10 mg/day to moderate-intensity statin therapy can achieve the same percent LDL-C lowering as that achieved with high-intensity statin therapy (24).

Age <40 Years

There is limited information on ASCVD rates among individuals 20–39 years of age and even less in children and adolescents with diabetes, and there is no information on whether statin therapy is beneficial in these age-groups. Available evidence indicates that although rates of ASCVD are low in people <30 years of age, they increase with time (3,14,25). They may reach intermediate risk levels by 30–39 years of age, especially in individuals with long-standing type 2 diabetes (3,25), who may have more advanced subclinical coronary atherosclerosis than do subjects without diabetes (26), and in those with type 1 diabetes of >20 years' duration (15). ASCVD rates will also be influenced by hypertension and diabetic microvascular complications that may be prevalent in these age-groups (15,27). Thus, it may be reasonable to have a discussion about initiating moderate-intensity statin therapy with patients <40 years of age who have had type 2 diabetes for at least 10 years or type 1 diabetes for at least 20 years and in patients with one or more major CVD risk factor or diabetic complications (Table 1).

Age >75 Years

ASCVD risk increases incrementally with age in diabetes (2–4). In one long-term cohort study of people with type 2 diabetes without ASCVD, incident rates of myocardial infarction averaged 25.6 per 1,000 person-years in those >75 years of age (2), while another study in a type 1 diabetes cohort found the 10-year fatal CVD risk in those >75 years of age was 70% in men and 40% in women (4). Although no RCTs of statin therapy in people >75 years of age have been undertaken, a meta-analysis of two recent statin trials in older subjects demonstrated similar benefits in ASCVD reduction among those >70 versus ≤70 years of age (28). A recent large retrospective study found that statin therapy in new users without preexisting ASCVD was associated with reduced ASCVD events in people with type 2 diabetes aged 75–84 years but not in those ≥85 years of age, nor in those without diabetes (29). These studies do support the continuation of moderate- or high-intensity statin therapy for primary prevention in people >75 years of age with diabetes, who comprise about 20% of the population in this age category. The clinician should note that the benefit may be offset by limited life span or increased susceptibility to adverse events in patients in this age-group. This becomes even more relevant in adults >75 years of age with diabetes who are not receiving statin therapy, in whom the diagnosis of diabetes may be recent or its duration unknown. It may therefore be reasonable to have a clinician-patient discussion in which the potential benefits and risks of initiating statin therapy in this age-group are reviewed.

CKD

The 2018 guidelines recommend that CKD be considered a risk-enhancing factor, and evidence indicates albuminuria

Table 1—Risk enhancers in primary prevention

Specific to diabetes	General
Long duration (≥10 years for type 2 diabetes (3,14) or ≥20 years for type 1 diabetes (15)	Family history of premature ASCVD
Albuminuria ≥30 μg of albumin/mg creatinine (16)	LDL-C levels ≥160 mg/dL
eGFR <60 mL/min/1.73 m^2 (16)	Metabolic syndrome
Retinopathy (17)	CKD
Neuropathy (18)	History of preeclampsia or premature menopause in women
Ankle brachial index <0.9 (19,20)	Chronic inflammatory disorders
	High-risk ethnicity such as South Asian ancestry
	Triglyceride levels persistently >175 mg/dL
	If measured:
	Apolipoprotein B levels with elevations >130 mg/dL (may be useful if hypertriglyceridemia >200 mg/dL to rule out genetic disorders such as Type III or clarify ASCVD risk)
	hs-CRP ≥2 mg/L
	Lipoprotein(a) levels with elevations >50 mg/dL (>125 nmol/L). Elevated lipoprotein(a) levels especially useful in those with a family history of ASCVD
	Reduced ankle brachial index

(≥30 mg/g creatinine) or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 increases risk for ASCVD in diabetes independent of major risk factors (16). Trials show absolute benefit from statin use in subjects with CKD, and this benefit is consistent across eGFR stages (30). However, the relative risk reduction per unit of LDL-C lowering may be lower with more advanced CKD. Although people on dialysis have the highest absolute risk of events, the proportion of deaths thought to be due to atherosclerotic events is lower and the lack of benefit in RCTs with statin initiation among people on dialysis (31) raises the question of competing risks.

Hypertriglyceridemia

Patients with type 2 diabetes frequently have hypertriglyceridemia. The 2018 guidelines recommended that in adults 40–75 years of age with moderate (150–499 mg/dL) or severe (≥500 mg/dL) hypertriglyceridemia and ASCVD risk ≥7.5%, after considering lifestyle and secondary factors, it is reasonable to consider a persistently elevated triglyceride level (≥175 mg/dL) as a factor favoring initiation or intensification of statin therapy. In adults with persistently elevated or increasing severe hypertriglyceridemia and especially if ≥1,000 mg/dL, it is further reasonable to reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of n-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy. A recent RCT found that addition of high doses of a synthetic n-3 fatty acid preparation (icosapent ethyl) to statin therapy in patients with ASCVD and/or diabetes plus at least one other CVD risk factor, and with triglyceride levels 135–499 mg/dL and LDL-C levels 41–100 mg/dL, reduced ASCVD events by 25% (32). The U.S. Food and Drug Administration has approved icosapent ethyl for those with ASCVD or diabetes with at least two additional ASCVD risk factors and triglyceride levels >150 mg/dL. Based on this finding, the ADA has recommended that in patients with diabetes and ASCVD or other cardiac risk factors on a statin and with controlled LDL-C but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl should be considered to reduce cardiovascular risk (33).

SECONDARY PREVENTION

A meta-analysis of RCTs supports high-intensity statins for patients with ASCVD (13) (Fig. 1). The goal of therapy is to reduce LDL-C by >50%. If high-intensity statins are not tolerated, moderate-intensity statins are acceptable. For the latter, addition of ezetimibe may achieve >50% reduction in LDL-C and provide additional risk benefit (24). RCT data in patients >75 years of age are limited, but initiation or continuation of moderate-/high-intensity statin therapy is reasonable. Conservatively, up to one-fourth of patients with ASCVD have a very high-risk status (34). This condition is defined as a history of multiple major ASCVD events or one major ASCVD event plus multiple high-risk conditions: age ≥65 years, heterozygous familial hypercholesterolemia, prior percutaneous coronary intervention/coronary artery bypass grafting, diabetes, hypertension, CKD, current smoking, history of heart failure, and LDL-C ≥100 mg/dL on maximal statin plus ezetimibe. Most patients with diabetes and ASCVD fall into this category. Furthermore, in an RCT, addition of ezetimibe to moderate statin therapy in patients diagnosed with an acute coronary syndrome demonstrated significant additional benefit in the subgroup with diabetes and in those aged ≥75 years (35). In very high-risk patients, the goal for LDL-C on maximal statin therapy is a level <70 mg/dL. If this goal is not achieved with statins alone, adding ezetimibe is the next step. Then, if this combination does not reduce LDL-C to <70 mg/dL, adding a PCSK9 inhibitor can be considered. The latter is supported by two recent RCTs, which showed significant reductions of ASCVD events when PCSK9 inhibitors were added to maximal LDL-C–lowering therapy in patients with LDL-C ≥70 mg/dL (36,37). The relative risk reduction has been shown to be similar in people with or without diabetes (38,39). In these trials, although ezetimibe added to a statin was allowed, <10% of participants were taking ezetimibe at baseline. The rationale for ezetimibe before PCSK9 inhibitor is supported by simulation analyses indicating most patients treated with statin and ezetimibe achieve LDL-C <70 mg/dL (40,41). Recruitment criteria for PCSK9 inhibitor trials excluded patients with LDL-C <70 mg/dL; hence, no RCT evidence demonstrates that starting PCSK9 inhibitors in patients with LDL-C <70 mg/dL is either statistically or clinically efficacious. Moreover, in very high-risk patients recruited with LDL-C ≥70 mg/dL, adding ezetimibe to statin therapy incrementally reduces ASCVD events (24). The guidelines did not exclude using PCSK9

inhibitors without ezetimibe, but this approach was not favored. It should further be noted that RCTs with PCSK9 inhibitors lasted less than 3 years and thus did not exclude longer-term side effects, and unlike ezetimibe, PCSK9 inhibitors are not available in generic form.

It must be noted that cost-effectiveness analysis does not support widespread use of PCSK9 inhibitors when costs are at mid-2018 prices. Recently, prices have begun to decline, but cost-effectiveness at current prices is still relatively low by conventional analyses. As prices decline more, the use of these drugs may become acceptably cost-effective. If so, for patients at very high risk, PCSK9 inhibitors could enhance clinical utility when added to maximal therapy with statins and ezetimibe.

CONCLUSIONS

Although adults with diabetes vary in their risk for a first ASCVD event, diabetes is a major risk factor for ASCVD. Based on the results of multiple RCTs, those aged 40–75 years will benefit from statin therapy. Moderate-intensity statin therapy is recommended without the need for evaluation of ASCVD risk, but high-intensity statin therapy is preferred in older subjects and those with higher estimated risk or with risk-enhancing factors following a clinician-patient discussion. Although there have been no RCTs in subjects $<$40 years or $>$75 years, based on a consideration of risks versus benefits, statin therapy may be reasonable in these groups. The majority of patients with diabetes and ASCVD have a very high risk for a recurrent event and an LDL-C goal of $<$70 mg/dL is recommended for them. This may require the addition of ezetimibe to maximal-intensity statin therapy, which is likely to achieve this goal in the majority of those with LDL-C $>$70 mg/dL on statin therapy alone; if not, addition of a PCSK9 inhibitor may then be considered. The 2018 ACC/AHA guidelines are very similar to the ADA 2019 guidelines for lipid management (32), and the unanimity between the two sets of guidelines adds weight to these conclusions.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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