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Approach to the Patient

Approach to Lipid Management in the Patient With Diabetes

Stephanie Kim[1] **and Savitha Subramanian**[2]

[1]Assistant Professor of Clinical Practice Division of Metabolism, Endocrinology and Nutrition, University of Washington, Seattle, WA 98109, USA
[2]Professor of Medicine Division of Metabolism, Endocrinology and Nutrition, University of Washington, Seattle, WA 98109, USA

Correspondence: Savitha Subramanian, MD, Professor of Medicine Division of Metabolism, Endocrinology and Nutrition, University of Washington, 850 Republican St, Box 358064, Seattle, WA 98109, USA. Email: ssubrama@uw.edu.

Abstract

Diabetes is associated with increased atherosclerotic cardiovascular disease (ASCVD) risk, a leading cause of morbidity and mortality. Disordered lipid metabolism is a major contributor to ASCVD risk in diabetes. Dyslipidemia in type 2 diabetes is characterized by hypertriglyceridemia, low high-density lipoprotein cholesterol and the presence of small, dense low-density lipoprotein particles. Statins have demonstrated longstanding benefit for reducing ASCVD risk in individuals with diabetes. Newer agents for add-on therapies to statins are now available for additional cardiovascular risk reduction. In this clinical overview, we review the pathogenesis of dyslipidemia in both type 1 and 2 diabetes and provide an update on the management of lipids in the individual with diabetes. We discuss the importance of appropriate risk stratification and individualized treatment selection and the need to avoid therapy inertia to mitigate cardiovascular risk. We also address lipid-related effects of glycemic-lowering therapies.

Key Words: cardiovascular disease, hypertriglyceridemia, HDL cholesterol, LDL cholesterol, type 1 diabetes, type 2 diabetes, statins, fibrates, fish oil, SGLT2 inhibitors, GLP-1 receptor agonists

Abbreviations: ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ANGPTL3, angiopoietin like 3; apo B, apolipoprotein B; apo C-III, apolipoprotein C-III; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; DHA, docosahexanoic acid; eGFR, estimated glomerular filtration rate; EPA, eicosapentanoic acid; ESC, European Society of Cardiology; FCS, familial chylomicronemia syndrome; GLP-1RA, glucagon like peptide 1 receptor agonist; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme-A; HTG, hypertriglyceridemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LPL, lipoprotein lipase; MACE, major adverse cardiovascular outcomes; NICE, National Institute of Health and Care Excellence; PCSK9, proprotein convertase subtilisin/kexin type-9; RCT, randomized controlled trial; SAMS, statin-associated muscle symptoms; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TG, triglyceride.

Clinical scenarios: Patient 1 is a 45-year-old man with a 14-year history of type 2 diabetes mellitus (T2D) and microalbuminuria who presents for a visit. Diabetes is treated with metformin and empagliflozin, and he takes losartan for hypertension. He consumes up to 21 alcoholic beverages a week. His A1C levels range between 6.9% and 7.5%. His body mass index (BMI) is 33 kg/m^2. A recent lipid panel reveals a total cholesterol 206 mg/dL, triglycerides (TGs) 362 mg/dL, low-density lipoprotein cholesterol (LDL-C) 103 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 42 mg/dL. Lipoprotein (a) [Lp(a)] is 10 nmol/L. TSH, creatinine, and estimated glomerular filtration rate (eGFR) are within normal range. Lipid-lowering therapy is recommended but he is hesitant to start a new medication.

Patient 2 is a 39-year-old woman with a 21-year history of type 1 diabetes mellitus (T1D) and no complications who has a lipid panel as follows: total cholesterol 253 mg/dL; TGs 96 mg/dL; HDL-C 64 mg/dL, LDL-C 170 mg/dL. She is on an automated insulin delivery device system, and her last A1C was 6.4%. She does not take any medications besides insulin. She does not smoke cigarettes or drink alcoholic beverages. She is married with 2 children and an avid runner. There is a family history of coronary artery disease in her father at age 62 and paternal grandfather at age 58. BMI is 22 kg/m^2 and blood pressure 118/78 mmHg. TSH, creatinine, and eGFR are within normal range. Lipid-lowering therapy for cardiovascular risk reduction is discussed but she is concerned about side effects.

Diabetes mellitus is a complex chronic and progressive metabolic disease characterized by hyperglycemia and often accompanied by complications. T2D is the most common form, accounting for over 90% of all diabetes, and is characterized by insulin resistance and gradual functional β cell failure (1). The rest are autoimmune (T1D), secondary, and

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atypical forms of diabetes. Atherosclerotic cardiovascular disease (ASCVD)—which includes coronary artery disease, stroke, and peripheral arterial disease—is the leading cause of morbidity and mortality in T2D, and the risk of death from ASCVD is increased 2- to 3-fold (2).

T1D, an autoimmune disorder with loss of beta cell function and absolute insulin deficiency, is also associated with a 2-to 8-fold increased risk of ASCVD and death (3-6). ASCVD in T1D predominantly manifests as coronary heart disease. ASCVD is more aggressive in individuals with T1D than in individuals without diabetes, and earlier onset of T1D significantly increases ASCVD risk (5). Women with T1D have an excess risk of fatal and nonfatal coronary artery disease (5, 7).

Hyperglycemia alone does not account for diabetes-associated increased ASCVD risk (8). Dyslipidemia is a well-established major risk factor for ASCVD. Individuals with T2D often have coexistence of features of increased cardiovascular risk including lipid abnormalities, central adiposity, hypertension, and hepatic steatosis, many of which may predate development of T2D. In T1D, dyslipidemia occurs when diabetes is untreated or suboptimally managed and corrects with improved glucose management. On occasion, correction of insulin deficiency can reveal underlying genetic dyslipidemias or metabolic syndrome (9). Herein, we review the pathophysiology of dyslipidemia in diabetes and discuss management strategies. Case scenarios are discussed at the end.

How Does Diabetes Alter Lipids?

Lipid abnormalities are commonly observed in T2D even with optimal glycemic management. The hallmark of dyslipidemia in diabetes includes increased plasma TGs and decreased HDL-C. LDL-C concentrations are normal or only slightly elevated, but LDL particles are small and dense and enriched with TGs. These lipid changes (especially elevated TGs and low HDL-C) are often present for years before the development of overt diabetes, as part of metabolic syndrome. Suboptimal glycemic control in T2D can further increase TG levels.

Accentuation of postprandial lipemia occurs in T2D due to accumulation of chylomicrons (large TG-rich particles secreted by the intestines following ingestion of dietary fat) and chylomicron remnants after a meal (10). Postprandial lipemia is believed to be a contributory factor to increased cardiovascular risk (11).

The dyslipidemia complex of T2D arises from several mechanistic processes, including increased production and secretion of both intestinal and hepatic TG-rich lipoproteins and their reduced clearance. Overproduction of very low density lipoproteins, which are liver-derived TG-enriched apolipoprotein B (apo B) containing lipoproteins, is a key contributor to dyslipidemia in T2D. Peripheral insulin resistance increases the availability of circulating free fatty acids, which are a substrate for TG synthesis by the liver and eventual very low density lipoproteins production. Delayed clearance of TG-rich lipoproteins can also contribute to elevated TGs. Lipoprotein lipase (LPL) is the rate-limiting enzyme that catabolizes TGs in the circulation. LPL activity is regulated by several proteins including apolipoprotein C-III (apo C-III) and angiopoietin like 3 (ANGPTL3), both of which inhibit LPL. Apo C-III circulates in plasma as a component of TG-rich lipoproteins. ANGPTL3 circulates in plasma and suppresses lipolysis at the endothelial surface in response to physiological stimuli such as fasting. LPL activity is decreased in T2D due to insulin resistance; this decreases hydrolysis of TGs in the circulation. In T2D, levels of apo C-III are increased, which can result increased plasma TGs. Loss of function mutations in apo C-III are associated with low TGs (12); thus, this apolipoprotein is a drug target and therapeutic approaches using gene silencing to decrease TGs are actively being pursued. Similar approaches targeting the protein ANGPTL3 to lower TGs are also in active development (see section on newer therapies). Proprotein convertase subtilisin/kexin type-9 (PCSK9), a circulating liver-derived protein, is a negative regulator of LDL clearance by binding to the LDL receptor and targeting it for premature intracellular degradation. Higher circulating levels of PCSK9 have been found in people with insulin resistance, metabolic syndrome, and diabetes (13). Thus, PCSK9 inhibition using currently available drug therapies have the potential to modify cardiovascular risk in diabetes.

Individuals with T1D with optimal glycemic management often have a lipid profile similar to the general population (14), often with better lipid profiles than their counterparts without diabetes (15) with average total and LDL-C levels that are lower and HDL-C levels that are higher than individuals without diabetes (16, 17). The lipid profile in individuals with T1D is significantly different with suboptimal diabetes management. Quantitative lipid abnormalities in T1D primarily occur in the setting of abnormal glycemia. In severe insulin deficiency due to untreated T1D or when diabetic ketoacidosis is present, hypertriglyceridemia (HTG) with low HDL-C is often observed (18), which improve with treatment with insulin. When glycemic control is suboptimal without ketoacidosis, TG and LDL-C levels may be increased (15, 19). Plasma TGs are often lower in men and women with T1D than compared to those without diabetes (20); plasma LDL-C is normal or slightly decreased and HDL-C normal or slightly elevated (21). When individuals with T1D have a higher BMI, abdominal adiposity, and/or insulin resistance, higher plasma TGs and lower HDL-C can be observed, similar to metabolic syndrome and T2D. Qualitative and functional changes in lipoproteins unrelated to glycemia have been observed in T1D, which can promote atherogenesis (21). Despite higher HDL-C levels in individuals with T1D, some studies have demonstrated decreased macrophage HDL cholesterol efflux capacity in vitro (22-24), the mechanism by which HDL removes cholesterol from peripheral cells. This suggests that elevated HDL-C levels may not be protective in this population. When diabetic kidney disease is present, total cholesterol, TG, and LDL-C are elevated and HDL-C is decreased (21). Elevated LDL-C levels and plasma TGs can be independently associated with progression of nephropathy in T1D (25).

Lp(a) is a modified LDL particle with an apolipoprotein (a) protein moiety covalently bound to its apo B component. Epidemiologic, Mendelian randomization, and genome-wide association studies have established Lp(a) as an independent, causal risk factor for ASCVD. Levels are genetically determined, are not different between men and women, and are mostly remain stable through adulthood. Lp(a) levels should be measured at least once in all adults, including people with diabetes, as recommended by several guidelines and/or position statements (26, 27).

Addressing Cardiovascular Risk in Diabetes

ASCVD is the leading cause of morbidity and mortality in individuals living with diabetes. Diabetes confers a higher risk of different forms of ASCVD, including ischemic heart disease,

stroke, and peripheral artery disease. In the past 2 decades, ASCVD mortality has decreased in people with both T1D and T2D likely due to improved care organization and delivery, more stringent risk factor targets, better risk factor control through both lifestyle intervention and pharmacological therapy, and the emergence of new LDL-C–lowering and antihyperglycemic therapies (28-30). Nevertheless, the risk of ASCVD in people with diabetes remains 2- to 4-fold higher than in age- and sex-matched subjects without diabetes. ASCVD risk is high in individuals with well-managed T1D even in the absence of quantitative lipid abnormalities. Mechanisms involved in development and progression of atherosclerosis in diabetes are complex and broadly include hyperglycemia, insulin resistance, dyslipidemia, chronic inflammation, and oxidative stress, which can influence the atherothrombotic process and result in clinical events such as myocardial infarction and stroke (31). Screening for lipid disorders and risk stratification are important steps in addressing cardiovascular risk and are elaborated next.

Lipid Screening in Individuals With Diabetes

A standard lipid panel, fasting or nonfasting, reveals the presence of any lipid abnormality. LDL-C levels are not reported for TG >400 mg/dL using the Friedewald formula due to inaccuracy of the equation. Newer lipid panel equations (Martins-Hopkins and NIH Sampson) overcome the inaccuracy of LDL-C measurement when TG levels are as high as 800 mg/dL. Testing should rule out secondary causes of dyslipidemia such as hypothyroidism, nephrotic syndrome, or chronic kidney disease (CKD). Elevated liver enzymes often indicate the presence of steatotic liver disease. Apo B (the structural protein on all atherogenic lipoproteins) is a useful and widely available marker for assessing cardiovascular risk. It may more accurately measure cardiovascular risk and determine the adequacy of lipid-lowering therapy than LDL-C or non-HDL-C and is recommended in European guidelines (27). Lp(a) levels, if elevated, add to cardiovascular risk and therefore should be measured. Primary lipid disorders such as familial hypercholesterolemia or polygenic forms of hyperlipidemia may coexist with diabetes and increase cardiovascular risk.

What Guidelines Are Available for Lipid and Cardiovascular Risk Management in Diabetes?

Guidance for approach to lipid management in diabetes has been developed by several worldwide organizations. The most comprehensive and widely accepted guidelines for cardiovascular risk reduction in all individuals are those offered by the European Society of Cardiology (ESC)/European Atherosclerosis Society widely followed in Europe (27), and the American College of Cardiology (ACC)/American Heart Association (AHA) (2018), used in US adults (32). There are other country-specific guidelines such as the National Institute of Health and Care Excellence (NICE) for the United Kingdom (https://www.nice.org.uk/guidance/ng238) and Canadian guidelines (33), which also offer guidance for cardiovascular risk reduction. Country-specific guidelines are available for China (34), India (35), and other parts of the world. Guidelines specific for individuals with diabetes were recently updated by the European Society of Cardiology (2023) (36), and specific recommendations have been published by ACC/AHA (2020) and the American Diabetes Association (ADA) (2024) (37) in the United States. A comparison of the most recent updated US and European guidelines is provided in Table 1. A summary of similarities and differences are described next.

Lifestyle Interventions

All available guidelines for lipid and cardiovascular risk reduction universally recommend the importance of adopting a heart healthy lifestyle in all individuals, with or without diabetes.

Risk Assessment

The ACC/AHA guidelines (2018) use the pooled cohort equations to assess 10-year ASCVD risk in US adults with use of diabetes-specific risk enhancing factors for further risk stratification ((32), Table 1). Diabetes-specific risk-enhancing factors include long duration (10 years of T2D and 20 years of T1D), albuminuria ≥30 mcg albumin/mg creatinine, eGFR <60 mL/min/1.73 m^2, presence of retinopathy or neuropathy, and ankle brachial index <0.9. The ADA recommendations are overall in line with those of the ACC/AHA and are updated annually, while European guidelines use the SCORE calculator derived from European cohort data sets and the updated SCORE2-Diabetes calculator, further refined for people with diabetes. SCORE integrates traditional risk factors such as age, systolic blood pressure, total and HDL-C cholesterol, and smoking status. SCORE2-Diabetes incorporates diabetes specific information such as duration of diabetes, hemoglobin A1c, and eGFR. The UK NICE guidelines use the QRISK3 calculator for refining cardiovascular risk.

Risk Categories

Guidelines vary in their categorization of risk. The ACC/AHA categorizes adults ages 40 to 75 years with diabetes based on 10-year ASCVD risk as intermediate or higher risk to allow for therapy intensification. ESC guidelines categorize individuals with diabetes into cardiovascular risk groups including very high risk, high risk, or moderate risk (Table 1).

Therapy Goals

Overall, guidelines are similar in LDL-C goals for ASCVD risk reduction. All organizations recognize secondary prevention as high or very high risk. An LDL-C goal of <55 mg/dL or 1.4 mmol/L is recommended by the ESC, ADA, and NICE guidelines. The ACC/AHA guidelines recommend a decrease in LDL-C by ≥50% from baseline. Table 2 shows the degree of lipid lowering offered by various targeted pharmacologic agents. Figure 1 offers a multipronged approach to cardiovascular risk and lipid management in diabetes based on available guidelines.

How Do We Utilize Guidelines to Guide Lipid Management in Diabetes?

Nonpharmacologic Interventions on Dyslipidemia of Diabetes

Lifestyle adjustments are integral to the management of diabetes. Body weight loss of >5% improves glycemia, blood pressure, and lipids in overweight or obese adults with T2D. The ADA, ACC/AHA, and ESC recommend eating patterns that emphasize foods with health benefits: consumption of vegetables, fruits, whole grains, legumes, and healthy protein

Table 1. Comparison of guidelines available for lipid lowering and ASCVD risk reduction in people with diabetes

	ADA (2024)	ESC (2023) and ESC/EAS (2019)	NICE (2023)	ACC/AHA (2018, 2020)
Diabetes specific?	Yes	ESC (2023)—yes ESC/EAS (2019)—no, but guidance for people with diabetes included	No, but guidance for people with diabetes included	No, separate guidance for people with diabetes published in 2020
Risk calculator used	Pooled cohort equations https://tools.acc.org/ascvd-risk-estimator-plus	SCORE-2 Diabetes (app available)	QRISK (qrisk.org)	Pooled cohort equations https://tools.acc.org/ascvd-risk-estimator-plus
Age range, years	40-75, 20-39	≥40 −70	25-84	40-75
Categories for 10-year ASCVD risk	High: ≥20% Intermediate: ≥7.5–<20% Borderline: 5–<7.5% Low: <5% (n/a for diabetes)	Very high: known ASCVD or ≥20% High: 10-<20% Moderate: 5-<10% Low: <5% (n/a for diabetes)	High: ≥20% Moderate: 10-<20% Low: <10%	High: ≥20% Intermediate: ≥7.5–<20% Borderline: 5–<7.5% Low: <5% (n/a for diabetes)
LDL-C therapy goals for people with ASCVD (secondary prevention)	LDL-C reduction of at least 50% and LDL-C target <55 mg/dL (<1.4 mmol/L)	LDL-C target <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50%	LDL-C goal <2.0 mmol/L (<77 mg/dL)	LDL-C target -≥50% from baseline and LDL-C target <70 mg/dL (<1.8 mmol/L)
LDL-C therapy goals for people without ASCVD (primary prevention)	LDL-C reduction of at least 50% from baseline and LDL-C target <70 mg/dL (<1.8 mmol/L)	Very high: LDL-C target <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% High: LDL-C target <1.8 mmol/L (<70 mg/dL) Moderate: LDL-C target <2.6 mmol/L (<100 mg/dL)	None given	LDL-C reduction of at least 50% from baseline and LDL-C target <70 mg/dL (<1.8 mmol/L)
Secondary therapy goals	None given	Very high: non-HDL-C target <2.2 mmol/L (<85 mg/dL) High: non-HDL-C target <2.6 mmol/L (<100 mg/dL)	People with ASCVD—non-HDL-C < 2.6 mmol/L (<100 mg/dL) People without ASCVD—> 40% reduction in non-HDL-C	None given
Preferred treatment for type 2 diabetes	People with ASCVD—high-intensity statin People without ASCVD—moderate-intensity statin Higher CV risk with 1 or more ASCVD risk factors—high-intensity statin[a] Age <40—with additional risk factors, consider moderate intensity statin[b]	Very high and high risk to high-intensity statin[a] Moderate risk to moderate-intensity statin[b]	People with ASCVD—offer atorvastatin 80 mg whatever starting LDL-C level, unless drug interaction, risk of adverse effects or patient preference People without ASCVD—10-year QRISK3 score ≥10%—offer atorvastatin 20 mg	People with ASCVD—high intensity statin[a] People without ASCVD—moderate-intensity statin[b] Higher CV risk with 1 or more ASCVD risk factors—high-intensity statin Age <40—with additional risk factors, consider moderate intensity statin Age >75—continuing statin reasonable; if not on statin, discuss initiation
Addition of non-statin therapies	People with ASCVD—add ezetimibe or a PCSK9 inhibitor if goal LDL-C not achieved on maximum tolerated statin therapy If intolerant to statin therapy, consider PCSK9 inhibitor monoclonal antibody, bempedoic acid, or PCSK9 inhibitor siRNA inclisiran as an alternatives People without ASCVD—if intolerant to statin therapy, bempedoic acid recommended to reduce CV event rates	Very high CV risk and LDL-C above target despite treatment with maximum tolerated statin or statin intolerance—PCSK9 inhibitor in combination with ezetimibe recommended People without ASCVD—if statin-based regimen not tolerated, consider ezetimibe and/or PCSK9 inhibitor	People with ASCVD—consider ezetimibe in addition to the maximum tolerated intensity and dose of statin to reduce ASCVD risk further, even if the lipid target for secondary prevention of ASCVD is met If intolerance to statin, consider alternative or additional lipid-lowering treatments	People with ASCVD—if LDL-C not <70 mg/dL, reasonable to add nonstatins including ezetimibe and PCSK9 inhibitor People without ASCVD—no guidance

(*continued*)

Table 1. Continued

	ADA (2024)	ESC (2023) and ESC/EAS (2019)	NICE (2023)	ACC/AHA (2018, 2020)
Recommendation for type 1 diabetes	Age <40 with 1 or more ASCVD risk factors—consider moderate-intensity statin Age <40 with over 20 years of diabetes—consider moderate-intensity statin	Age >40 Consider statin for primary ASCVD risk reduction Age <40 —consider statin with other risk factors or microvascular complications or ASCVD risk >10%	Do not use QRISK calculator Age over 40 or >10 years of diabetes or other risk factors—offer statin therapy (atorvastatin 20 mg) Age 18-40—consider statin treatment for primary ASCVD prevention including those who have had diabetes <10 years	None specified
Recommendations for high TG	People with ASCVD with LDL-C at target but TG 135-499 mg/dL (2.0-5.6 mmol/L)—icosapent ethyl can be considered	High-dose icosapent ethyl (2 g b.i.d.) may be considered with a statin in patients with hypertriglyceridemia	Icosapent ethyl is recommended for reducing the risk of cardiovascular events in people with elevated TG (>1.7 mmol/L)	Use icosapent ethyl as adjunct to maximum tolerated statin therapy if TG >150 mg/dL and ASCVD Diabetes and 2 or more risk factors[c]

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; b.i.d., twice a day; CV, cardiovascular; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; n/a, not applicable; NICE, National Institute for Health and Care Excellence; non-HDL-C, non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type-9; TG, triglycerides.
[a]High-intensity statin—lowers LDL-C by ≥50%, atorvastatin: 40 to 80 mg and rosuvastatin: 20 to 40 mg.
[b]Moderate-intensity statin (lowers LDL-C by 30-49%) includes atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, pravastatin 40 to 80 mg, lovastatin 40 mg, pitavastatin 1 to 4 mg.
[c]Recommendation is from 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia.

Table 2. Efficacy of lipid-lowering therapies on LDL-C and triglyceride levels

Medication class	% LDL-C lowering	% TG lowering	Cardiovascular benefit
Statins		0-35	Yes
Low intensity	<30		
Moderate intensity	30-49		
High intensity	Up to 60		
Ezetimibe	15 monotherapy Up to 25 (when added to statin)	10-20	Yes (added to statin)
Bempedoic acid	17-28	—	Yes
PCSK9 inhibitors	50-60		
Monoclonal antibodies		5-20	Yes
siRNA			Not known
Fibrates		20-50	
Gemfibrozil	None		Yes (as monotherapy)
Fenofibrate	5-35		No
Omega-3 fatty acids	None	20-50	
Mixed formulation (EPA + DHA)			No
Purified EPA			Yes

Abbreviations: DHA, docosahexanoic acid; EPA, eicosapentanoic acid; LDL-C, low-density lipoprotein-cholesterol; PCSK9, proprotein convertase subtilisin/kexin type-9; siRNA, small-interfering; TG, triglycerides.

sources [low-fat dairy products, low-fat poultry (without the skin), fish/seafood, and nuts] and limiting intake of refined, processed carbohydrates, sugar-sweetened beverages, and red meats. Recommendations should be adjusted to appropriate calorie requirements and personal and cultural food preferences. Dietary interventions such as intermittent fasting and low-carbohydrate, Mediterranean-style, and vegetarian or vegan-style eating patterns can variably reduce LDL-C and TGs and raise HDL-C (38-41). Although aerobic activity does not have any effects on TGs (42), weight loss can lower TGs. An overall healthy eating plan that allows an energy deficit can support glycemic, lipid, and weight goals in adults with T2D (43). Resistance exercise may have beneficial effects on lipid profiles for all adults, but specific effects in diabetes are unclear (44).

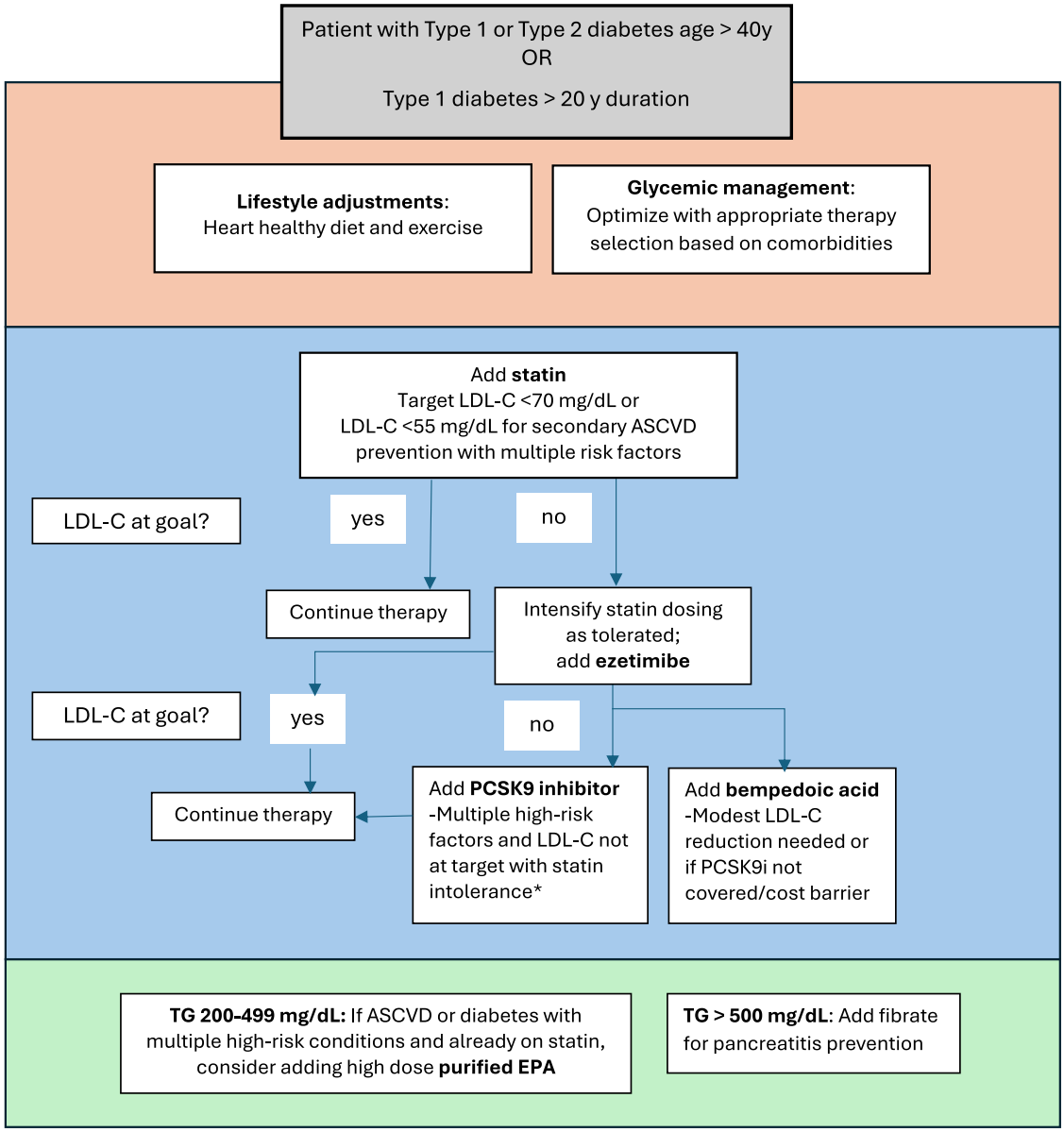

Figure 1. Comprehensive approach to cardiovascular risk reduction in diabetes.

Excessive consumption of alcoholic beverages should be discouraged to prevent TG elevations. Smoking is a risk factor for ASCVD and amplifies this risk in individuals with diabetes (45); increases in cholesterol, LDL-C, and small dense LDL particles can occur. Smoking cession efforts should be strongly encouraged.

Medications for Treatment of Dyslipidemia in Diabetes

Drugs that Target LDL-C to Reduce ASCVD Risk

3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors or statins

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase or statins remain the mainstay of LDL-C reduction in individuals with diabetes. Statins decrease LDL-C by 30% to 60% depending upon the drug, dose, and potency (Table 2).

The efficacy of statin therapy in diabetes has now been well established in multiple primary and secondary prevention studies, involving people with diabetes, and a few landmark trials are highlighted here. The Heart Protection Study, a secondary prevention trial included patients with T1D and T2D, demonstrated a reduction in cardiovascular events with statin use (46). The Collaborative AtoRvastatin Diabetes Study (47) demonstrated the benefit of statins on primary prevention of cardiovascular events in patients with T2D at high risk of developing ASCVD, defined by the presence of hypertension, retinopathy, and micro- or macroalbuminuria. These findings were validated in a large meta-analysis of 18 686 patients with diabetes (the majority with T2D), which reported a 20% reduction in major vascular events and a 9% decrease in all-cause mortality per 39 mg/dL (1 mmol/L) reduction in

LDL-C on statin treatment (48). A subsequent meta-analysis of 170 000 patients across 26 studies found that additional reductions in LDL-C (1-2 mmol/L) with intensive statin regimens resulted in a further reduction in cardiovascular events. These results supported the relationship between LDL-C reductions and proportional risk reductions, which were consistent across trials comparing both intensive, less intensive statin therapy and standard statin regimens compared to control. However, both those with and without diabetes were included in these randomized trials (49).

Statins are overall well tolerated and safe. An increased risk of new-onset diabetes has become apparent in several statin trials (50, 51). In one meta-analysis, statins were associated with a 10% increase in new diagnoses of diabetes in a dose-dependent fashion (52), the risk being higher with use of higher intensity statin dosing and in individuals already at risk of developing diabetes (those with baseline blood glucose levels that were already near the diagnostic threshold for diabetes, increased body weight, and hypertension). A meta-analysis of genetic association studies has shown that exposure to LDL-C-lowering genetic variants in or near HMG-CoA reductase (molecular target of statins), Niemann Pick C1 like protein (molecular target of ezetimibe), and PCSK9 was associated with a higher risk of T2D. These genetic studies suggest that variants associated with lower LDL-C levels are associated with an increased risk of new-onset diabetes rather than drug therapies (53). The benefits of statins in cardiovascular risk reduction far outweigh the risk of developing diabetes, as supported by multiple guidelines that recommend the use of statins in patients with diabetes.

Statin intolerance. Statin-associated symptoms, often referred to as statin intolerance, can significantly reduce adherence to treatment. These symptoms include myalgias, fatigue, memory loss, depression, and sleep disturbances. Statin-associated muscle symptoms (SAMS) specifically involve muscle pain or aching, stiffness, and cramping, all of which are typically symmetric; muscle weakness is also sometimes reported. These symptoms are usually not accompanied by serum creatine kinase elevation (54). SAMS are the most commonly reported adverse events, with prevalence rates ranging from 5% to 25%, and is the leading cause for discontinuation (54). Subjective side effects of statins occur more frequently than objective adverse events and are often attributed to the "nocebo effect." Predisposing factors to SAMS include female sex, low body weight, Asian ethnicity, family history of statin intolerance, and underlying conditions such as untreated hypothyroidism (54). However, current evidence suggests that these reported side effects are unlikely due to the pharmacologic effects of statins. In fact, a large portion of individuals who report statin intolerance are able to tolerate a statin at the same or lower dose when rechallenged. Therefore, in addition to reducing the statin dose, it may be helpful to try a different statin or consider intermittent dosing, including unconventional dosing (every other day), especially with statins that have a longer half-life (eg, rosuvastatin). However, it is important to acknowledge the patient's experience and collaborate with them to address concerns and avoid treatment inertia through shared decision-making. In clinical practice, patients may decline continuing trial statins entirely, at which time nonstatin options such as ezetimibe, bempedoic acid, or PCSK9 inhibitors should be considered. Recognizing and addressing side effects is key to preventing discontinuation of lipid-lowering therapy and ensuring continued cardioprotective benefits. We summarize strategies to overcome statin intolerance in Fig. 2.

Ezetimibe

Ezetimibe lowers LDL-C by 15% to 20% by binding to and inhibiting Niemann Pick C1 like protein at the jejunal brush border, thereby reducing intestinal cholesterol absorption. While it can be used as monotherapy, it is most effective when used in combination with a statin. It is well tolerated without myopathy or increased risk of diabetes.

The cardiovascular benefit of ezetimibe was evaluated in the ImProved Reduction of Outcomes: Vytorin Efficacy International Trial in 18 144 patients after an acute coronary syndrome, including 4933 subjects with T2D treated with statin (55). This study demonstrated a 7% relative risk reduction

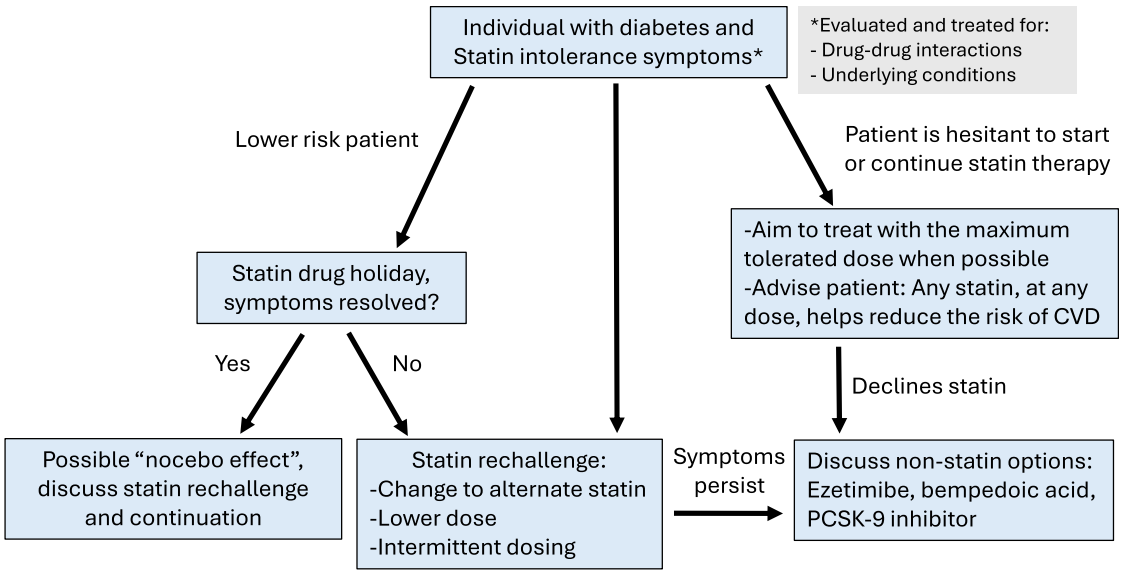

Figure 2. Patient centered approach to statin intolerance or hesitancy.

in major adverse cardiovascular events (MACE) when ezetimibe was added to simvastatin, and a prespecified subgroup analysis demonstrated that this effect was more prominent in patients with diabetes compared to those without diabetes (14% vs 2% relative risk reduction, respectively).

A recent cohort study of 111 954 veterans with cardiovascular disease identified by coronary angiography, including 51% with diabetes, showed that the projected reduction in the 4-year risk of a cardiovascular event was 35% greater with statin and ezetimibe when compared to statin monotherapy (56). Thus, ezetimibe is recommended as an add-on therapy after statins when additional LDL-C lowering is needed (Table 2) (36, 37).

Bempedoic acid

Bempedoic acid inhibits adenosine triphosphate-citrate lyase, an enzyme that is upstream of HMG-CoA reductase, leading to decreased LDL-C levels. Unlike statins, it is a prodrug that is converted into its active form by the liver and thus avoids the skeletal muscle with the potential to avoid myopathy. It lowers LDL-C by 17% to 28% and can be used as monotherapy as well as an adjunct to maximally tolerated statin (Table 2) (57). It is also available in combination with ezetimibe.

In the Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen Outcomes trial, 13 970 patients, including 45% with diabetes, were randomized to bempedoic acid or placebo (58). In these statin-intolerant patients, bempedoic acid decreased LDL-C by 21% and the risk of MACE by 13% when compared to placebo. A prespecified subgroup analysis concluded that patients with diabetes had a significant cardiovascular risk reduction of 17% with bempedoic acid (59). There was no increased risk of new-onset diabetes or worsening glycemic indices with bempedoic acid in those without known diabetes.

An increased risk of gout and cholelithiasis in addition to small increases in liver enzymes, uric acid, and creatinine have been observed in studies (60). An increased number of tendon ruptures in the bempedoic acid group than placebo was observed in early studies but not in the Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial; despite this, a black-box warning for tendon rupture remains. A major barrier to prescribing this drug are high cost and insurance-related barriers including prior authorization and appeals (61).

Agents that inhibit PCSK9

PCSK9 is a protein with a very short half-life that is secreted by hepatocytes. It binds to LDL receptor together with LDL and undergoes endocytosis. The presence of PCSK9 results in degradation of the LDL receptor instead of recycling back to the cell surface. Thus LDL clearance from the circulation is decreased and results in increased LDL-C levels. Evolocumab and alirocumab are monoclonal antibodies targeting PCSK9 while inclisiran is a small-interfering RNA that inhibits intrahepatic PCSK9 production. The monoclonal antibodies are self-administered subcutaneously every 2 weeks or monthly, while inclisiran is administered subcutaneously by a health care professional; the first dose is followed by another dose at 3 months and subsequently every 6 months. These agents lead to significant LDL-C reduction up to 50% to 60% and can be used either as monotherapy or in conjunction with other LDL-C lowering medications (Table 2).

The cardiovascular efficacy of evolocumab and alirocumab were studied in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial (62) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab trial (63), respectively. Both trials demonstrated a decrease in LDL-C and reduced risk of cardiovascular events and included patients with diabetes. In a post hoc analysis of FOURIER, including 11 031 patients with T2D and 16 533 without diabetes, there was no increase in new-onset diabetes or worsening of baseline glycemic metrics (64). Similarly, in a subgroup analysis of Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab trial, 5444 patients with diabetes, 8246 patients with prediabetes, and 5234 with normoglycemia were studied. Alirocumab was associated with approximately twice the absolute reduction in cardiovascular events in patients with diabetes compared to those without diabetes. Like evolocumab, alirocumab did not lead to an increase in the risk of new-onset diabetes (65).

In the open label extension of FOURIER (FOURIER-OLE), 6635 patients were transitioned to receive evolocumab and followed up over a median of 5 years (66). This study found that long-term LDL-C lowering <40 mg/dL was associated with a lower risk of cardiovascular outcomes without an increase in adverse events, including new-onset diabetes. A recent meta-analysis of 12 trials examined over 14 000 patients with diabetes taking PCSK9 inhibitors versus controls. In patients with diabetes, LDL-C was reduced by 48.2%, with a trend toward a stronger effect for evolocumab compared to alirocumab and inclisiran. There was no significant difference in fasting plasma glucose or A1c (67).

A pooled analysis of 7 ORION trials evaluating inclisiran that included over 5544 patients including those with diabetes showed decreased cardiovascular-related safety events validating its safety profile (68). Results of cardiovascular outcomes trials of inclisiran are forthcoming (NCT03705234, NCT05030428).

Combination therapies

Individuals with diabetes are often categorized as high cardiovascular risk and achieving LDL-C goals is often limited by the lack of adequate response to high-intensity statin monotherapy, adherence issues, or intolerance. A recent meta-analysis examined the effects of high-intensity statin monotherapy compared to a combination of low- or moderate-intensity statin plus ezetimibe in patients with acute coronary syndrome, including those with diabetes. The study, which did not include any randomized controlled trials (RCTs), found no statistically significant difference in MACE between using high-intensity statin vs combination therapy (69). The Randomized Comparison of Efficacy and Safety of Lipid-Lowering with Statin Monotherapy [rosuvastatin 20 mg] vs Statin/Ezetimibe [rosuvastatin 10 mg/ezetimibe 10 mg] Combination for High-Risk Cardiovascular Diseases Trial demonstrated decreased medication discontinuation rates and lower occurrence of new-onset diabetes on statin/ezetimibe combination therapy compared to high-dose statin monotherapy (70). This analysis included patients with drug-eluting stent placement and about 44% to 46% of patients with diabetes at baseline.

Bempedoic acid + ezetimibe

Nonstatin combination therapy is also available in the form of bempedoic acid and ezetimibe. This was studied in a trial involving about 300 subjects with dyslipidemia and a high risk of cardiovascular disease (defined as ASCVD or heterozygous familial hypercholesterolemia or having multiple cardiovascular disease risk factors) who were receiving maximally tolerated statin therapy. Subjects were randomized to combination therapy, bempedoic acid monotherapy, ezetimibe monotherapy, or placebo, in addition to their baseline statin therapy. At week 12, the fixed-dose combination therapy lowered LDL-C significantly more than placebo (−36.2% vs 1.8%, respectively), bempedoic acid monotherapy (17.2%), or ezetimibe monotherapy (−23.2%) (71).

Management of HTG in patients with diabetes

Mild to moderate HTG (TG 150-499 mg/dL or 1.7-5.6 mmol/L) is very common and tracks the prevalence of metabolic syndrome, obesity, and T2D and is also seen in statin-treated individuals. The role of HTG in relation to ASCVD, diabetes, and related metabolic conditions is complex. Recent epidemiologic and genetic studies strongly support TGs as a causal risk for ASCVD. On the other hand, a clear-cut benefit of lowering TGs using pharmacological agents is lacking, as discussed next.

Drugs that Lower TGs

Fibrates

The fibrates gemfibrozil and fenofibrate are peroxisome proliferator-activated receptor-α agonists that lower TGs and modestly raise HDL-C and lower LDL-C (Table 2). The evidence for the use of fibrates in patients with diabetes is limited.

Several older studies of fibrates using gemfibrozil monotherapy including the Helsinki Heart study (72) and the Veterans Affairs HDL Intervention Trial (73) have included individuals with diabetes and demonstrated cardiovascular risk reduction. On the contrary, in the Bezafibrate Infarction Prevention study bezafibrate did not significantly reduce the risk of myocardial infarction or sudden death compared to placebo (74). Patients with insulin-dependent diabetes were excluded, and 10% of the patients in both the bezafibrate and placebo groups had diabetes.

Fibrate and statin combination therapy. The Action to Control Cardiovascular Risk in Diabetes, which was designed to assess if the addition of a fibrate to statin would offer cardiovascular benefit, did not establish a benefit of this combination therapy in patients with T2D (75). On post hoc analysis, a possible benefit was observed in patients with TG >200 and HDL-C < 34 mg/dL. The addition of a fibrate slowed the progression of diabetic retinopathy, a finding that was also observed in other studies. Recently, a novel selective peroxisome proliferator-activated receptor α modulator, pemafibrate, was studied in 10 497 individuals with moderate HTG and T2D in the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes Trial (76). The study failed to demonstrate cardiovascular benefit of adding pemafibrate to statin therapy despite lowering TG levels. Although the reasons for these results are uncertain, it has been hypothesized that a low baseline LDL-C in recruited subjects and an observed increase in LDL-C and apo B levels in the pemafibrate group may have contributed to these results (77). Therefore, adding a fibrate to a statin in individuals with diabetes for cardiovascular risk reduction is not recommended. However, fibrates should be considered for pancreatitis prevention in patients with TG > 500 mg/dL. Fenofibrate does not alter statin metabolism and can be used safely in combination with statins (78).

Omega-3 fatty acids

Omega-3 fatty acids, mainly eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), are polyunsaturated fatty acids that lower TGs (Table 2). Historically several RCTs demonstrated minimal cardiovascular benefit of omega-3 fatty acids. In 2018, the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial evaluated the cardioprotective effect of addition of 4 g/daily icosapent ethyl (highly purified EPA) compared to placebo in high-risk patients with mild to moderate HTG on statin therapy (79). Nearly 60% of patients had T2D at baseline. Icosapent ethyl resulted in a 25% risk reduction in cardiovascular risk independent of baseline TG levels, suggesting that other factors such as an anti-inflammatory effect may have contributed. However, a common critique of this trial is the use of mineral oil as placebo, which resulted in an increase in both LDL-C and C-reactive protein thereby potentially increasing the risk of the control group (80).

Subsequently, the Long-Term Outcomes Study to Assess Statin Residual Risk with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridemia study evaluated mixed EPA and DHA formulation (81). Results found no benefit on cardiovascular events, similar to findings seen in other trials of omega-3 fatty acids including the Outcome Reduction with an Initial Glargine Intervention Trial (82), the VITamin D and OmegA-3 TriaL (83), and A Study of Cardiovascular Events iN Diabetes (84).

Thus, there is no evidence of benefit to the addition of mixed fish oil preparations (EPA + DHA) for cardiovascular risk reduction and therefore is not recommended. Over-the-counter omega-3 fish oil supplements should therefore also not be used for ASCVD risk reduction. Current guidelines recommend addition of icosapent ethyl (branded Vascepa in North America, Vazkepa in Europe, Asia) in addition to a statin for residual hypertriglyceridemia in high-risk individuals such as those with known ASCVD or diabetes and additional risk factors (36, 37, 85). Increased bleeding risk due to platelet inhibition and prolonged bleeding time have been observed in all trials of high-dose omega-3 fatty acids. Risk of atrial fibrillation was observed in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial and the Long-Term Outcomes Study to Assess Statin Residual Risk with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridemia in the treatment arms.

Newer lipid therapies in development

Several novel therapies targeting TGs are in progress. Apo C-III, present on the surface of TG rich lipoproteins inhibits activity of LPL and impairs TG clearance from the circulation. Thus Apo C-III inhibition for the treatment of HTG is a promising approach since blocking the effect of apo C-III on LPL activity can promote TG-rich lipoproteins catabolism and lower plasma TGs. Volanesorsen is an antisense oligonucleotide administered

subcutaneously that blocks apo C-III protein synthesis. Volanosorsen has been studied in individuals with genetic LPL deficiency or familial chylomicronemia syndrome (FCS) and trials support efficacy and safety, with decreased incidence of acute pancreatitis and improved quality of life (86, 87). It is approved in Europe (as Waylivra) in individuals with FCS, but did not receive US Food and Drug Administration approval due to the increased risk of thrombocytopenia. Two other agents, olezarsen (AKCEA-APOCIII-LRx), and plozasiran (ARO-APOC3) are in ongoing phase 3 clinical trials for the treatment of severe HTG and FCS as well as mixed hyperlipidemia (88). Similarly, zodasiran, an inhibitor of ANGPTL3, has demonstrated safety and efficacy, and a phase 3 trial is anticipated (89).

Severe hypertriglyceridemia. In some individuals with diabetes, severe hypertriglyceridemia can occur. This condition, called multifactorial chylomicronemia syndrome, develops in individuals with polygenic susceptibility and is exacerbated by suboptimal glycemic control, dietary indiscretions, excessive alcohol consumption, and initiation of certain medications. Risk of acute pancreatitis is increased when TGs are well over 1000 mg/dL. Improving glycemic management is crucial in this situation; fibrate therapy should be initiated to prevent pancreatitis. Fish oil mixtures/compounds often are unhelpful when TGs are markedly elevated.

Effects of Diabetes Medications on Lipids and Cardiovascular Risk

Effects of antihyperglycemic agents on lipids are variable and detailed later (Table 3). The choice of agent for glycemic management should be driven by individual characteristics such as the need to reduce cardiorenal risk and glucose-lowering efficacy rather than effects on lipids. Sulfonylureas, meglitinides, and α-glucosidase inhibitors are not known to alter lipid levels.

Metformin

The effects of metformin on lipids are variable and modest at best. Metformin may decrease serum TG levels with minimal or no changes to LDL-C and HDL-C levels (90). A large meta-analysis of metformin has demonstrated no effects on HDL-C or TGs with a modest lowering of cholesterol (91). The TG effects may be related to the modest weight loss of ~2-3 kg variably seen with metformin initiation (92).

Table 3. Lipid effects of commonly used glucose-lowering agents

Drug	Lipid effect
Metformin	↓ TG
Sulfonylureas	↔
Thiazoledinediones: pioglitazone	↓ TG ↑ HDL-C ↓ LDL-C
DPP4 inhibitors	↓ postprandial TG
SGLT2 inhibitors	↑ LDL-C ↑ HDL-C
GLP-1 receptor agonists	↓ ↓ TG ↓ ↓ ↓ postprandial TG
Insulin	↓ TG

Abbreviations: DPP4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium-glucose cotransporter-2; TG, triglycerides.

Thiazolidinediones

Thiazolidinediones are insulin-sensitizing agents that affect their metabolic effects via activation of peroxisome proliferator-activated receptor alpha-ϒ. Pioglitazone, the only currently available agent in this class, reduces fasting and postprandial TG levels, increases HDL-C, and is neutral on LDL-C levels (93-95), with the presence of larger, more buoyant LDL particles (96). There is substantial evidence that pioglitazone can delay the progress of atherosclerosis (94, 97) and related cardiovascular events. Although the PROactive trial, which randomized 5238 individuals with T2D to pioglitazone and placebo, did not demonstrate a benefit in the primary endpoint, participants with a prior myocardial infarction or stroke had robust reductions in recurrence of cardiovascular disease (93). In the IRIS trial, participants with a recent transient ischemic attack or stroke and insulin resistance who received pioglitazone demonstrated improved insulin sensitivity, plasma TGs, and HDL-C while reducing the risk of myocardial infarction or stroke over 4.8 years (98).

Sodium glucose cotransporter 2 inhibitors

Sodium glucose cotransporter 2 inhibitors can cause modest increases in LDL-C and HDL-C levels. In a meta-analysis of 60 RCTs with over 147 000 patients, treatment with sodium glucose cotransporter 2 inhibitors increased total cholesteroal, LDL-C, and HDL-C and decreased TGs (99). The mechanism for these changes in cholesterol levels is unclear, though alterations in plasma volume may be responsible while TG reductions may result from treatment-associated weight loss. The modest lipid changes are unlikely to have major clinical impact, as the beneficial effects of these agents far outweigh the theoretical risk associated with minimally increased LDL-C levels. Additionally, patients with diabetes should be on an appropriate lipid-lowering regimen as part of guideline-based therapy.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors are weight-neutral agents, have little to no effects on fasting lipids, and have demonstrated cardiovascular safety but not superiority in randomized trials (100, 101). Several dipeptidyl peptidase-4 inhibitors (alogliptin, vildagliptin, and sitagliptin) appear to decrease postprandial lipemia (102).

Glucagon-like peptide 1 receptor agonists

The cardiovascular benefit of several glucagon-like peptide 1 receptor agonists (GLP-1RAs) independent of antihyperglycemic actions have been demonstrated in large RCTs. The effects of GLP-1RAs on lipids have been observed in phase 2 and phase 3 studies and small clinical trials. Liraglutide, dulaglutide, and semaglutide decrease LDL-C levels compared to placebo, even in the presence of statin therapy (103). Several meta-analyses have assessed GLP-1RA-related lipid changes, which show very modest (~4-8 mg/dL) reductions in LDL-C levels (104-106).

With the expansion of GLP-1RAs and development of dual and triple agonists combining GLP-1, glucose-dependent insulinotropic polypeptide and glucagon, similar lipid effects have been observed. Tirzepatide, the dual GLP-1 and glucose-dependent insulinotropic polypeptide agonist, increases HDL-C and decreases LDL-C levels (107, 108). TG levels can decrease by up to 25% from baseline, with greater

reductions seen with higher doses of tirzepatide (109). Significant reductions in TGs and non-HDL-C levels also have been observed in the phase 2 study of retatrutide, a single peptide triagonist (110).

Direct lipid effects of GLP-1RAs. The primary *direct* lipid effect of GLP-1RA therapy is decreased postprandial hypertriglyceridemia in individuals without or with diabetes, with near-complete attenuation observed in several studies (independent of effects of insulin) (103). GLP-1 receptor agonism importantly improves postprandial plasma TGs, independent of effects on body weight. Intestinal chylomicron overproduction is thought to be a main causative factor for postprandial hypertriglyceridemia in the insulin-resistant state. GLP-1 may mediate these changes by decreasing intestinal chylomicron synthesis and possibly by improving clearance. There may be qualitative effects on LDL particle composition including decrease in proatherogenic small dense LDL. HDL-C levels are overall mostly unchanged, but improved HDL function has been reported (102, 111).

Indirect lipid effects of GLP-1RAs. Indirect mechanisms of TG lowering of GLP-1RAs could include increased insulin secretion, weight loss resulting in decreased TG availability, improved insulin sensitivity and restored LPL activity, decreased intestinal motility, signaling via the central nervous system, and other unidentified mechanisms (102). Additionally preclinical studies suggest that GLP-1RAs beneficially modulate endothelial function, immune responses, and inflammatory markers, which can play a role in improved lipid and cardiovascular risk.

Insulin

Insulin therapy decreases plasma TG levels through stimulation of LPL activity and increases HDL-C levels (112). All available insulin analogues and human insulins result in similar effects on lipids (113-115). Subcutaneous insulin therapy does not seem to alter lipoprotein composition (116).

Effects of weight loss surgery

The most commonly performed bariatric procedures are Roux-en-Y gastric bypass and sleeve gastrectomy, both of which improve dyslipidemia in patients with diabetes. HDL-C levels tend to decrease during the first 6 months of rapid postsurgical weight loss (117). Studies have demonstrated equivalent (118) or greater LDL-C reductions in patients undergoing gastric bypass compared to sleeve gastrectomy (119, 120). A recent meta-analysis demonstrated improvement in all lipid profile variables (TG, HDL-C, and LDL-C) for both RYGB and sleeve gastrectomy, consistent with older meta-analyses (121). There are no RCTs of whether metabolic surgery decreases cardiovascular outcomes; a recent meta-analysis of 39 cohort studies suggests that metabolic surgery decreases all-cause and cardiovascular mortality by ~30% to 40% (122).

Other Considerations

Diabetes with kidney disease

There is benefit for use of statins in patients with diabetes and CKD but not in end-stage kidney disease. The 2013 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease offers guidance on lipid management in all patients with CKD (123). Dose adjustments are required for rosuvastatin (maximum dose 10 mg in CKD stage 4-5) but not for atorvastatin. Statins are also indicated in renal transplant recipients, and the dose should be adjusted if cyclosporine is part of the immune suppression regimen. Initiation of statins is not recommended for patients receiving dialysis; however, they can be continued if the patient was already taking them at the time dialysis was started. Statins are recommended in adults under the age of 50 with CKD and risk factors including diabetes and/or ASCVD, as well as for adult kidney transplant recipients. Finally, ezetimibe and PCSK9 inhibitors can be safely used in individuals with CKD.

Early-onset diabetes

While early onset is common in T1D, it is important to note T2D is increasingly diagnosed in people under the age of 40 years (124). Early-onset T2D has a more aggressive cardiometabolic phenotype, with severe insulin resistance, early β-cell failure, and earlier onset of complications, and is associated with higher risk of mortality and vascular disease in several cohorts (125-127). There have been no randomized trials in cohorts with adults aged <40 years with T2D. In the Diabetes Control and Complications Trial in people with T1D, 6.5 years of intensive diabetes management reduced ASCVD events after 18 years of follow-up (128). Long-term studies in adults with diabetes under 40 years of age for outcomes-based ASCVD risk assessment are lacking. Adults between ages 30 and 39 with T2D and those with T1D over 20 years duration can be considered intermediate risk, and statin therapy should be considered, as driven by the presence of additional risks and risk enhancers (129).

Ethnicity, diversity, and sex considerations

Studies worldwide have consistently shown that women have higher cardiometabolic risk burden but are less likely than men to receive guideline directed care and meet treatment targets for glycemia and lipids than are men (130, 131). Women are also underrepresented in randomized clinical trials assessing cardiovascular outcomes of therapies. Similarly, there is underrepresentation of minority ethnic groups in cardiometabolic research despite higher metabolic risk, even at lower BMI. Identifying higher risk groups such as Hispanics and South Asians is important for attaining appropriate treatment targets.

Clinical Scenarios Revisited

Patient 1 is a 45-year-old man with a 14-year history of type 2 diabetes and microalbuminuria presents for a visit. Diabetes is treated with metformin and empagliflozin, and he takes losartan for hypertension. He consumes up to 21 alcoholic beverages a week. His A1C levels range between 6.9% and 7.5%. His BMI is 33 kg/m^2. A recent lipid panel reveals a total cholesterol 206 mg/dL, TGs 362 mg/dL, LDL-C 103 mg/dL, and HDL-C 42 mg/dL. Lp(a) is 10 nmol/L. TSH, creatinine, and eGFR are within normal range. Lipid-lowering therapy is recommended but he is hesitant to start a new medication.

Discussion. This individual with early-onset T2D requires primary ASCVD risk reduction (Fig. 1). Counseling on

lifestyle modifications is crucial, as well as emphasis on the importance of reducing alcohol consumption, as it can raise TG and affect glycemia. According to available guidelines, a moderate-intensity statin should be considered for primary prevention of ASCVD (refer to Tables 1 and 2). Given his statin hesitancy, it is important to explain that any dose of statin is acceptable to reduce cardiovascular risk in individuals with diabetes (Fig. 2). Addressing mental health barriers can also improve adherence. He eventually revealed that his reluctance to add medications was due to distress over the number of medications he needed to take. Ongoing education of the risks associated with diabetes at every clinic visit can help eventually prevent therapy inertia. Optimizing diabetes therapy by considering a GLP-1RA to promote weight loss and lowering TGs should be considered.

Patient 2 is a 39-year-old woman with a 21-year history of type 1 diabetes and no complications who has a lipid panel as follows: total cholesterol 253 mg/dL; TGs 96 mg/dL; HDL-C 64 mg/dL, LDL-C 170 mg/dL. She is on an automated insulin delivery device system and her last A1C was 6.4%. She does not take any medications besides insulin. She does not smoke cigarettes or drink alcoholic beverages. She is married with 2 children and an avid runner. There is a family history of coronary artery disease in her father at age 62 and paternal grandfather at age 58. BMI is 22 kg/m^2 and blood pressure 118/78 mmHg. TSH, creatinine, and eGFR are within normal range. Lipid-lowering therapy for cardiovascular risk reduction is discussed, but she is concerned about side effects.

Discussion. The individual in this vignette has a primary hypercholesterolemia. She has had diabetes for >20 years and has a family history of ASCVD (Fig. 1). Since her baseline LDL-C is elevated, it is important to rule out underlying secondary causes. Hypothyroidism and underlying renal disease have been ruled out based on available information, and she does not take any medications that can lead to elevated LDL-C levels. A review of her lipid panels over the years revealed LDL-C ranging between 170 and 190 mg/dL, which, along with her family history, suggests an underlying genetic etiology. Lp(a) levels should be checked to ensure no additional cardiovascular risk is present. In her case, her Lp(a) levels were elevated at 189 nmol/L (<75). Due to her significantly elevated cardiovascular risk, LDL-C-lowering therapies should be discussed and initiated, with a goal LDL-C of <70 mg/dL for primary prevention. Based on available guidelines (Table 1), due to the long duration of diabetes and the presence of additional genetic risk factors, a high-intensity statin dose would be the best next step. However, as a woman with childbearing potential, therapy should be initiated only after discussion of future desire for pregnancies, since statins are category X in pregnancy. Her husband had undergone a vasectomy. After a detailed discussion of her cardiovascular risk and shared decision-making, she agreed to initiate rosuvastatin 20 mg, which decreased her LDL-C levels to 90 mg/dL. However, she was unable to tolerate a dose escalation to 40 mg, so ezetimibe 10 mg was added and her LDL-C improved to 65 mg/dL.

Conclusions and Overall Approach to Lipid Management in Diabetes

People with diabetes are at high or very high ASCVD risk. Table 4 offers a summary of important clinical aspects of lipid and cardiovascular risk management in people with diabetes. Dyslipidemia is often present in patients with T2D and is characterized by mild to moderate hypertriglyceridemia, low HDL-C, and normal LDL-C levels. This lipid pattern is a major contributor to ASCVD risk. Individuals with T1D who are well managed may not have a lipid abnormality but do have increased cardiovascular risk. Lifestyle adjustments are an important but often forgotten aspect of management of lipid disorders, especially in diabetes. Statins remain the cornerstone for decreasing ASCVD risk in individuals with diabetes. Goal LDL-C should be set based on the need for primary or secondary cardiovascular risk, additional risk factors, and enhancers, and statin therapy should be initiated at appropriate intensity; add-on therapies such as ezetimibe and PCSK9 inhibitors should be initiated without delay when ASCVD risk is high and further LDL-C reduction is warranted. Purified EPA can be considered judiciously for residual moderate hypertriglyceridemia. If TGs are >1000 mg/dL, the risk of pancreatitis is high, and the priority is to lower TG levels using fibrates. Fenofibrate can be safely used with statins. Of the available antihyperglycemic agents, GLP-1RAs can decrease postprandial HTG. Appropriate cardiovascular risk mitigation strategies should be taken in younger and older individuals with diabetes, women, and high-risk groups without clinical inertia.

Table 4. Clinical pearls for lipid lowering in diabetes

- All individuals with diabetes are at higher ASCVD risk.
- Screening lipid profile (fasting or nonfasting) is an important first step; measure lipoprotein(a)—once in patient's lifetime, for further cardiovascular risk stratification.
- Lifestyle adjustments are a key aspect of managing ASCVD risk in diabetes.
- Statins are recommended as a first choice of medication therapy.
- Combination therapy of a lower dose of statin in combination with ezetimibe may result in better adherence in some individuals.
- Add a PCSK9 inhibitor when cardiovascular risk is very high, when LDL-C is above target on maximum tolerated statin dose with or without ezetimibe.
- High-dose prescription purified eicosapentanoic acid (icosapent ethyl) can be considered in addition to statin in individuals with hypertriglyceridemia and increased cardiovascular risk.
- Use of appropriate glucose-lowering agents which decrease ASCVD risk is recommended.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type-9.

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Data Availability

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