LDL-C lowering is warranted. Clinical studies have demonstrated that colesevelam provides both lipid-lowering and glycemic benefits in adults with T2D and is FDA approved for both indications.[204]

Bempedoic acid, a prodrug that inhibits ATP citrate lyase and cholesterol synthesis upstream from hydroxymethylglutaryl coenzyme A reductase, appears to be a promising oral agent for those with statin intolerance or where modest additional LDL-C lowering is needed.[205]

Triglyceride Lowering in Diabetes

The initial approach to hypertriglyceridemia in diabetes should focus on potential secondary causes or contributory factors, including glycemic control, that should be addressed with pharmacologic and lifestyle approaches with evidenced-based cardiovascular benefit.[139,191] Modest weight loss, increased physical activity, reduction of sugar-sweetened beverages, processed carbohydrates, and reduction in alcohol use can lead to significant serum triglyceride reduction. Occult hypothyroidism and nephrosis should be excluded, and adjustment of medications that can raise triglycerides such as β-blockers, thiazide diuretics, and others should be considered.

In adults with diabetes and severe hypertriglyceridemia (fasting triglycerides >500 mg/dL), pharmacological and lifestyle therapy is warranted to prevent acute pancreatitis. In addition to the aforementioned lifestyle therapies, first-line pharmacotherapy includes fibrates or high-dose prescription omega-3 fatty acids. If a fibrate is necessary in a patient treated with concomitant statin therapy, fenofibrate is recommended rather than gemfibrozil, given the lower risk of drug interaction and myopathy.[191]

Moderate hypertriglyceridemia (fasting triglycerides 135–499 mg/dL) is considered a risk-enhancing factor,[191] and is often a manifestation of cardiometabolic risk. Moderate hypertriglyceridemia and an abnormal non–HDL-C are commonly encountered as components of diabetic dyslipidemia. In diabetes with moderate hypertriglyceridemia, statins are the recommended first-line pharmacotherapy.[191] The intensity of statin therapy should be based on both the absolute risk of ASCVD and the degree of hypertriglyceridemia because higher-intensity statins are more effective at lowering triglycerides. In patients with diabetes and ASCVD or patients with diabetes at high risk for ASCVD with serum triglycerides of 135 to 500 mg/dL despite maximally tolerated statin, and addressing contributory factors including lifestyle modification prescription icosapent ethyl at a dose of 4 g/d, as well, should be considered given the 30% additional cardiovascular risk reduction in the REDUCE-IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial).[206] Of note, the median baseline LDL-C in this trial was 75 mg/dL, and 29% of the study population had diabetes. Several RCTs have assessed the additional impact on cardiovascular events of fibrates when used in combination with statins; thus far, the data are inconclusive, although post hoc analyses have suggested potential benefit in those with residual modest hypertriglyceridemia.[207]

HDL-Raising Therapies in Diabetes

Overall, HDL-C–raising therapies, other than lifestyle and behavioral approaches, have been disappointing. Mendelian randomization data suggest that HDL-C is likely a marker of ASCVD risk versus a causative factor.[208] Low HDL-C is a common finding in individuals with diabetes and metabolic risk, in addition to dysfunctional HDL-C. Despite significantly increasing HDL-C, cholesterol ester transfer protein inhibitors have not demonstrated a reduction in cardiovascular events.[209] Niacin would not be favored in people with diabetes given the potential adverse effect on glycemic control. RCTs have not demonstrated additional cardiovascular benefit of niacin in combination with statin therapy.[209]

Lipid-Lowering Therapy in Diabetes Summary

Timely and aggressive lipid-lowering therapy is warranted for both primary and secondary prevention in diabetes as a component of comprehensive cardiovascular risk reduction. Lifestyle- and behavioral-focused approaches are recommended for all individuals with diabetes as the cornerstone to addressing dyslipidemia. Statins are the foundation of lipid therapy in diabetes given the consistent and compelling evidence supporting cardiovascular risk reduction. The 2018 Cholesterol Guidelines recommend statins as first-line therapy for both primary and secondary prevention in diabetes. In those with established ASCVD, the highest intensity statin tolerated should be initiated or continued with the aim of reducing LDL-C by at least 50% with a more individualized approach for those >75 years of age. For primary prevention in T2D, at least moderate-intensity statin should be considered based on age, absolute ASCVD risk, or the presence of risk-enhancing factors. Nonstatin therapies including ezetimibe, PCSK9 inhibitors, icosapent ethyl, bile acid resins, and fibrates should be considered after thorough evaluation of risk, LDL-C after optimal statin therapy, and presence of hypertriglyceridemia. An ongoing process of shared decision-making focused on net clinical benefit, patient preference, potential cost concerns, and medication adherence should be a consistent thread of care.[210]

ANTITHROMBOTIC THERAPY

Among the primary factors contributing to the increased cardiovascular risk in diabetes is a generalized prothrombotic state[211,212] that can be attributed to altered coagulation and platelet function and exacerbated in the setting of common comorbid conditions such as CKD (Table 6).[213–231] Although antiplatelet-based secondary

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