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AACE/ACE Consensus Statement

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – 2017 EXECUTIVE SUMMARY

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This document represents the position of the American Association of Clinical Endocrinologists and the American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position and consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

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Abbreviations:

A1C = hemoglobin A1C; **AACE** = American Association of Clinical Endocrinologists; **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ACCORD BP** = Action to Control Cardiovascular Risk in Diabetes Blood Pressure; **ACEI** = angiotensin-converting enzyme inhibitor; **ADVANCE** = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; **AGI** = alpha-glucosidase inhibitor; **apo B** = apolipoprotein B; **ASCVD** = atherosclerotic cardiovascular disease; **BAS** = bile acid sequestrant; **BMI** = body mass index; **BP** = blood pressure; **CHD** = coronary heart disease; **CKD** = chronic kidney disease; **CVD** = cardiovascular disease; **DASH** = Dietary Approaches to Stop Hypertension; **DPP-4** = dipeptidyl peptidase 4; **eGFR** = estimated glomerular filtration rate; **FDA** = Food and Drug Administration; **GLP-1** = glucagon-like peptide 1; **HDL-C** = high-density lipoprotein cholesterol; **IMPROVE-IT** = Improved Reduction of Outcomes: Vytorin Efficacy International Trial; **LDL-C** = low-density lipoprotein cholesterol; **LDL-P** = low-density lipoprotein particle; **Look AHEAD** = Look Action for Health in Diabetes; **NPH** = neutral protamine Hagedorn; **OSA** = obstructive sleep apnea; **SFU** = sulfonylurea; **SGLT-2** = sodium glucose cotransporter-2; **SMBG** = self-monitoring of blood glucose; **T2D** = type 2 diabetes; **TZD** = thiazolidinedione; **VADT** = Veterans Affairs Diabetes Trial.

EXECUTIVE SUMMARY

This algorithm for the comprehensive management of persons with type 2 diabetes (T2D) was developed to provide clinicians with a practical guide that considers the whole patient, their spectrum of risks and complications, and evidence-based approaches to treatment. It is now clear that the progressive

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pancreatic beta-cell defect that drives the deterioration of metabolic control over time begins early and may be present before the diagnosis of diabetes (1). In addition to advocating glycemic control to reduce microvascular complications, this document highlights obesity and prediabetes as underlying risk factors for the development of T2D and associated macrovascular complications. In addition, the algorithm provides recommendations for blood pressure and lipid control, the two most important risk factors for cardiovascular disease (CVD).

Since originally drafted in 2013, the algorithm has been updated as new therapies, management approaches, and important clinical data have emerged. The 2017 edition includes an updated section on lifestyle therapy as well as discussion of all classes of obesity, antihyperglycemic, lipid-lowering, and antihypertensive medications approved by the US Food and Drug Administration (FDA) through December 2016.

This algorithm supplements the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2015 Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2) and is organized into discrete sections that address the following topics: the founding principles of the algorithm, lifestyle therapy, obesity, prediabetes, glucose control with noninsulin antihyperglycemic agents and insulin, management of hypertension, and management of dyslipidemia. In the accompanying algorithm, a chart summarizing the attributes of each antihyperglycemic class and the principles of the algorithm appear at the end.

Principles

The founding principles of the Comprehensive Type 2 Diabetes Management Algorithm are as follows (see Comprehensive Type 2 Diabetes Management Algorithm—Principles):

1. Lifestyle optimization is essential for all patients with diabetes. Lifestyle optimization is multifaceted, ongoing, and should engage the entire diabetes team. However, such efforts should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it.

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2. Weight loss should be considered in all patients with prediabetes and T2D who also have overweight or obesity. Weight loss therapy should consist of lifestyle prescription that includes a reduced-calorie healthy meal-plan, physical activity, and behavioral interventions. Weight loss medications approved for the chronic management of obesity should also be considered if needed to obtain the degree of weight loss required to achieve therapeutic goals in prediabetes and T2D. Obesity is a chronic disease, and a long-term commitment to therapy is necessary.
3. The A1C target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. An A1C level of $\leq 6.5\%$ is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
4. Glycemic control targets include fasting and postprandial glucose as determined by self-monitoring of blood glucose (SMBG).
5. The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes that affect this choice include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other adverse effects, tolerability, ease of use, likely adherence, cost, and safety in heart, kidney, or liver disease.
6. Minimizing risk of both severe and nonsevere hypoglycemia is a priority. It is a matter of safety, adherence, and cost.
7. Minimizing risk of weight gain is also a priority. It too is a matter of safety, adherence, and cost.
8. The initial acquisition cost of medications is only a part of the total cost of care, which includes monitoring requirements and risks of hypoglycemia and weight gain. Safety and efficacy should be given higher priority than medication cost.
9. This algorithm stratifies choice of therapies based on initial A1C level. It provides guidance as to what therapies to initiate and add, but respects individual circumstances that could lead to different choices.

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10. Combination therapy is usually required and should involve agents with complementary mechanisms of action.
11. Comprehensive management includes lipid and blood pressure therapies and treatment of related comorbidities.
12. Therapy must be evaluated frequently (e.g., every 3 months) until stable using multiple criteria, including A1C, SMBG records (fasting and postprandial), documented and suspected hypoglycemia events, lipid and blood pressure values, adverse events (weight gain, fluid retention, hepatic or renal impairment, or CVD), comorbidities, other relevant laboratory data, concomitant drug administration, diabetic complications, and psychosocial factors affecting patient care. Less frequent monitoring is acceptable once targets are achieved.
13. The therapeutic regimen should be as simple as possible to optimize adherence.
14. This algorithm includes every FDA-approved class of medications for T2D (as of December 2016).

Lifestyle Therapy

The key components of lifestyle therapy include medical nutrition therapy, regular physical activity, sufficient amounts of sleep, behavioral support, and smoking cessation and avoidance of all tobacco products (see Comprehensive Type 2 Diabetes Management Algorithm—Lifestyle Therapy). In the algorithm, recommendations appearing on the left apply to all patients. Patients with increasing burden of obesity or related comorbidities may also require the additional interventions listed in the middle and right side of the figure.

Lifestyle therapy begins with nutrition counseling and education. All patients should strive to attain and maintain an optimal weight through a primarily plant-based diet high in polyunsaturated and monounsaturated fatty acids, with limited intake of saturated fatty acids and avoidance of *trans* fats. Patients who are overweight (body mass index [BMI] 25-29.9 kg/m^2) or obese (BMI $\geq$30 kg/m^2) should also restrict their caloric intake with the goal of reducing body weight by at least 5 to 10%. As shown in the Look AHEAD (Action for Health in Diabetes) and Diabetes Prevention Program (DPP) studies, lowering caloric intake is the main driver for weight loss (3-6). The clinician, a registered dietitian, or a nutritionist

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should discuss recommendations in plain language at the initial visit and periodically during follow-up office visits. Discussion should focus on foods that promote health vs those that promote metabolic disease or complications and should include information on specific foods, meal planning, grocery shopping, and dining-out strategies. In addition, education on medical nutrition therapy for patients with diabetes should also address the need for consistency in day-to-day carbohydrate intake, limiting sucrose-containing or high-glycemic index foods, and adjusting insulin doses to match carbohydrate intake (e.g., use of carbohydrate counting with glucose monitoring) (2,7). Structured counseling (e.g., weekly or monthly sessions with a specific weight-loss curriculum) and meal replacement programs have been shown to be more effective than standard in-office counseling (3,6,8-15). Additional nutrition recommendations can be found in the 2013 *Clinical Practice Guidelines for Healthy Eating for the Prevention and Treatment of Metabolic and Endocrine Diseases in Adults* from AACE/ACE and The Obesity Society (TOS) (16).

After nutrition, physical activity is the main component in weight loss and maintenance programs. Regular physical exercise—both aerobic exercise and strength training—improves glucose control, lipid levels, and blood pressure (BP); decreases the risk of falls and fractures; and improves functional capacity and sense of well-being (17-24). In Look AHEAD, which had a weekly goal of ≥175 minutes per week of moderately intense activity, minutes of physical activity were significantly associated with weight loss, suggesting that those who were more active lost more weight (3). The physical activity regimen should involve at least 150 minutes per week of moderate-intensity exercise such as brisk walking (e.g., 15-20 minute mile) and strength training; patients should start any new activity slowly and increase intensity and duration gradually as they become accustomed to the exercise. Structured programs can help patients learn proper technique, establish goals, and stay motivated. Wearable technologies, such as pedometers or accelerometers, can provide valuable information to motivate as well as guide healthy amounts of physical activity. Patients with diabetes and/or severe obesity or complications should be evaluated for contraindications and/or limitations to increased physical activity, and an exercise prescription should be developed for each patient according to both goals and limitations. More detail on the benefits and risks of physical activity and the practical aspects of implementing a training program in people with T2D can be found in a joint position statement from the American College of Sports Medicine and American Diabetes Association (25).

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Adequate rest is important for maintaining energy levels and well-being, and all patients should be advised to sleep approximately 7 hours per night. Evidence supports an association of 6-9 hours of sleep per night with a reduction in cardiometabolic risk factors, whereas sleep deprivation aggravates insulin resistance, hypertension, hyperglycemia, and dyslipidemia and increases inflammatory cytokines (26-31). Daytime drowsiness—a frequent symptom of sleep disorders such as sleep apnea—is associated with increased risk of accidents, errors in judgment, and diminished performance (32). Basic sleep hygiene recommendations should be provided to all patients with diabetes. The most common type of sleep apnea, obstructive sleep apnea (OSA), is caused by physical obstruction of the airway during sleep. The resulting lack of oxygen causes the patient to awaken and snore, snort, and grunt throughout the night. The awakenings may happen hundreds of times per night, often without the patient's awareness. OSA is more common in men, the elderly, and persons with obesity (33,34). Individuals with suspected OSA should be referred for a home study in lower risk settings or to a sleep specialist for formal evaluation and treatment in higher risk settings (2).

Behavioral support for lifestyle therapy includes the structured weight loss and physical activity programs mentioned above as well as support from family and friends. Patients should be encouraged to join community groups dedicated to a healthy lifestyle for emotional support and motivation. In addition, obesity and diabetes are associated with high rates of anxiety and depression, which can adversely affect outcomes (35,36). Alcohol moderation and substance abuse counseling should be provided where appropriate. Healthcare professionals should assess patients' mood and psychological well-being and refer patients with mood disorders to mental healthcare professionals. Cognitive behavioral therapy may be beneficial. A recent meta-analysis of psychosocial interventions provides insight into successful approaches (37).

Smoking cessation is the final component of lifestyle therapy and involves avoidance of all tobacco products. Nicotine replacement therapy should be considered in patients having difficulty with smoking cessation. Structured programs should be recommended for more recalcitrant patients unable to stop smoking on their own (2).

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Obesity

Obesity is a progressive chronic disease with genetic, environmental, and behavioral determinants that result in excess adiposity associated with an increase in morbidity and mortality (38,39). An evidence-based approach to the treatment of obesity incorporates lifestyle, medical, and surgical options, balances risks and benefits, and emphasizes medical outcomes that address the complications of obesity rather than cosmetic goals. Weight loss should be considered in all overweight and obese patients with prediabetes or T2D, given the known therapeutic effects of weight loss to lower glycemia, improve the lipid profile, reduce BP, prevent or delay the progression to T2D in patients with prediabetes, and decrease mechanical strain on the lower extremities (hips and knees) (2,38).

The AACE Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity and Treatment Algorithm (40, 41) provide evidence-based recommendations for obesity care including screening, diagnosis, clinical evaluation and disease staging, therapeutic decision-making, and follow-up. AACE has emphasized a complications-centric model as opposed to a BMI-centric approach for the treatment of patients who have obesity or are overweight (42). The patients who will benefit most from medical and surgical intervention have obesity-related complications that can be classified into two general categories: insulin resistance/cardiometabolic disease and biomechanical consequences of excess body weight (43). Clinicians should evaluate patients for the risk, presence, and severity of complications, regardless of BMI, and these factors should guide treatment planning and further evaluation (44,45). Once these factors are assessed, clinicians can set therapeutic goals and select appropriate types and intensities of treatment that will help patients achieve their weight-loss goals linked to the prevention or amelioration of weight-related complications. The primary clinical goal of weight loss therapy is to prevent progression to T2D in patients with prediabetes and to achieve the target for HbA1c in patients with T2D, in addition to improvements in lipids and BP. Patients should be periodically reassessed to determine if targets for improvement have been reached; if not, weight loss therapy should be changed or intensified. Lifestyle therapy can be recommended for all patients with overweight or obesity, and more intensive options can be prescribed for patients with complications. For example, weight-loss medications can be used to intensify therapy in combination with lifestyle therapy for all patients with a BMI $\geq$27 kg/m^2 having complications and for patients with BMI $\geq$30 kg/m^2 whether or not complications are present. As of 2016, the FDA has

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approved 8 drugs as adjuncts to lifestyle therapy in patients with overweight or obesity. Diethyproprion, phendimetrazine, and phentermine may be used for short-term (3 months or less) use, whereas orlistat, phentermine/topiramate extended release (ER), lorcaserin, naltrexone ER/bupropion ER, and liraglutide 3 mg have been approved for long-term weight reduction therapy. In clinical trials, the 5 drugs approved for long-term use were associated with statistically significant weight loss (placebo-adjusted decreases ranged from 2.9% with orlistat to 9.7% with phentermine/topiramate ER) after 1 year of treatment. These agents improve BP and lipids, prevent progression to diabetes during trial periods, and improve glycemic control and lipids in patients with T2D (46-63). Bariatric surgery should be considered for adult patients with a BMI $\geq$35 kg/m^2 and comorbidities, especially if therapeutic goals have not been reached using other modalities (2,64).

Prediabetes

Prediabetes reflects failing pancreatic islet beta-cell compensation for an underlying state of insulin resistance, most commonly caused by excess body weight or obesity. Current criteria for the diagnosis of prediabetes include impaired glucose tolerance, impaired fasting glucose, or metabolic syndrome (see Comprehensive Type 2 Diabetes Management Algorithm—Prediabetes Algorithm). Any one of these factors is associated with a 5-fold increase in future T2D risk (65).

The primary goal of prediabetes management is weight loss. Whether achieved through lifestyle therapy, pharmacotherapy, surgery, or some combination thereof, weight loss reduces insulin resistance and can effectively prevent progression to diabetes as well as improve plasma lipid profile and BP (47,51,52,54,57,63,66). However, weight loss may not directly address the pathogenesis of declining beta-cell function. When indicated, bariatric surgery can be highly effective in preventing progression from prediabetes to T2D (65).

No medications (either weight loss drugs or antihyperglycemic agents) are approved by the FDA solely for the management of prediabetes and/or the prevention of T2D. However, antihyperglycemic medications such as metformin and acarbose reduce the risk of future diabetes in prediabetic patients by 25 to 30%. Both medications are relatively well-tolerated and safe, and they may confer a cardiovascular risk benefit (66-69). In clinical trials, thiazolidinediones (TZDs) prevented future development of diabetes in 60 to 75%

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of subjects with prediabetes, but this class of drugs has been associated with a number of adverse outcomes (70-72). Glucagon-like peptide 1 (GLP-1) receptor agonists may be equally effective, as demonstrated by the profound effect of liraglutide 3 mg in safely preventing diabetes and restoring normoglycemia in the vast majority of subjects with prediabetes (62,63,73,74). However, owing to the lack of long-term safety data on the GLP-1 receptor agonists and the known adverse effects of the TZDs, these agents should be considered only for patients at the greatest risk of developing future diabetes and those failing more conventional therapies.

As with diabetes, prediabetes increases the risk for atherosclerotic cardiovascular disease (ASCVD). Patients with prediabetes should be offered lifestyle therapy and pharmacotherapy to achieve lipid and BP targets that will reduce ASCVD risk.

T2D Pharmacotherapy

In patients with T2D, achieving the glucose target and hemoglobin A1C (A1C) goal requires a nuanced approach that balances age, comorbidities, and hypoglycemia risk (2). The AACE supports an A1C goal of ≤6.5% for most patients and a goal of >6.5% (up to 8%; see below) if the lower target cannot be achieved without adverse outcomes (see Comprehensive Type 2 Diabetes Management Algorithm—Goals for Glycemic Control). Significant reductions in the risk or progression of nephropathy were seen in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, which targeted an A1C <6.5% in the intensive therapy group versus standard approaches (75). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive glycemic control significantly reduced the risk and/or progression of retinopathy, nephropathy, and neuropathy (76,77). However, in ACCORD, which involved older and middle-aged patients with longstanding T2D who were at high risk for or had established CVD and a baseline A1C >8.5%, patients randomized to intensive glucose-lowering therapy (A1C target of <6.0%) had increased mortality (78). The excess mortality occurred only in patients whose A1C remained >7% despite intensive therapy, while in the standard therapy group (A1C target 7 to 8%), mortality followed a U-shaped curve with increasing death rates at both low (<7%) and high (>8%) A1C levels (79). In contrast, in the Veterans Affairs Diabetes Trial (VADT), which had a higher A1C target for intensively treated patients (1.5% lower than the standard

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treatment group), there were no between-group differences in CVD endpoints, cardiovascular death, or overall death during the 5.6-year study period (78,80). Cardiovascular autonomic neuropathy may be another useful predictor of cardiovascular risk. Moreover, a combination of cardiovascular autonomic neuropathy (81) and symptoms of peripheral neuropathy increase the odds ratio to 4.55 for CVD and mortality (82). After approximately 10 years, however, VADT patients participating in an observational follow-up study were 17% less likely to have a major cardiovascular event if they received intensive therapy during the trial (P <0.04; 8.6 fewer cardiovascular events per 1000 person-years), while mortality risk remained the same between treatment groups (83). Severe hypoglycemia occurs more frequently with intensive glycemic control (75,78,80,84). In ACCORD, severe hypoglycemia may have accounted for a substantial portion of excess mortality among patients receiving intensive therapy, although the hazard ratio for hypoglycemia-associated deaths was higher in the standard treatment group (85).

Taken together, this evidence supports individualization of glycemic goals (2). In adults with recent onset of T2D and no clinically significant CVD, an A1C between 6.0 and 6.5%, if achieved without substantial hypoglycemia or other unacceptable consequences, may reduce lifetime risk of microvascular and macrovascular complications. A broader A1C range may be suitable for older patients and those at risk for hypoglycemia. A less stringent A1C of 7.0 to 8.0% is appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing T2D in which the A1C goal has been difficult to attain despite intensive efforts, so long as the patient remains free of polydipsia, polyuria, polyphagia, or other hyperglycemia-associated symptoms. Therefore, selection of glucose-lowering agents should consider a patient's therapeutic goal, age, and other factors that impose limitations on treatment, as well as the attributes and adverse effects of each regimen. Regardless of the treatment selected, patients must be followed regularly and closely to ensure that glycemic goals are met and maintained.

The order of agents in each column of the Glucose Control Algorithm suggests a hierarchy of recommended usage, and the length of each line reflects the strength of the expert consensus recommendation (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm). Each medication's properties should be considered when selecting a therapy for individual

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patients (see Comprehensive Type 2 Diabetes Management Algorithm—Profiles of Antidiabetic Medications), and healthcare professionals should consult the FDA prescribing information for each agent.

- Metformin has a low risk of hypoglycemia, can promote modest weight loss, and has good antihyperglycemic efficacy at doses of 2000-2500 mg/day. Its effects are quite durable compared to sulfonylureas (SFUs), and it also has robust cardiovascular safety relative to SFUs (86-88). The FDA recently changed the package label for metformin use in chronic kidney disease (CKD) patients lifting the previous contraindication in men with serum creatinine > 1.5 mg/dL and women with serum creatinine > 1.4 mg/dL (89,90). Newer CKD guidelines are based on estimated glomerular filtration rate (eGFR), not on serum creatinine. Metformin can be used in patients with stable eGFR > 30 mL/min/1.73 m^2; however, it should not be started in patients with an eGFR below 45 mL/min/1.73 m^2, Reduction in total daily dose is prudent in patients with eGFR between 30-45 mL/min/1.73 m^2, and due to risk of lactic acidosis, it should not be used in patients with eGFR < 30 mL/min/1.73 m^2 (91,92). In up to 16% of users, metformin is responsible for vitamin B12 malabsorption and/or deficiency (93,94), a causal factor in the development of anemia and peripheral neuropathy (95). In patients taking metformin who develop neuropathy, B12 should be monitored and supplements given to affected patients, if needed (96).
- GLP-1 receptor agonists have robust A1C-lowering properties, are usually associated with weight loss and blood pressure reductions (97), and are available in several formulations. The risk of hypoglycemia with GLP-1 receptor agonists is low (98), and they reduce fluctuations in both fasting and postprandial glucose levels. GLP-1 receptor agonists should not be used in patients with personal or family history of medullary thyroid carcinoma or those with multiple endocrine neoplasia syndrome type 2. Exenatide should not be used if creatinine clearance is <30 mL/min. No studies have confirmed that incretin agents cause pancreatitis (99); however, GLP-1 receptor agonists should be used cautiously—if at all—in patients with a history of pancreatitis and discontinued if acute pancreatitis develops. Some GLP-1 receptor agonists may retard gastric emptying, especially with initial use. Therefore, use in patients with gastroparesis or severe gastroesophageal reflux disease requires careful monitoring and dose adjustment.

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- Sodium glucose cotransporter 2 (SGLT-2) inhibitors have a glucosuric effect that results in decreased A1C, weight, and systolic BP. In the only SGLT-2 inhibitor cardiovascular outcomes trial reported to date, empagliflozin was associated with significantly lower rates of all-cause and cardiovascular death and lower risk of hospitalization for heart failure (100). Heart failure–related endpoints appeared to account for most of the observed benefits in this study. Empagliflozin has recently received FDA approval for indication of reduction in cardiac mortality (101). SGLT-2 inhibitors are associated with increased risk of mycotic genital infections and slightly increased low-density lipoprotein cholesterol (LDL-C) levels, and because of their mechanism of action, they have limited efficacy in patients with an estimated glomerular filtration rate <45 mL/min/1.73 m^2. Dehydration due to increased diuresis may lead to hypotension (102-104). The incidence of bone fractures in patients taking canagliflozin and dapagliflozin was increased in clinical trials (104). Investigations into postmarketing reports of SGLT-2 inhibitor–associated diabetic ketoacidosis (DKA), which has been reported to occur in T1D and T2D patients with less than expected hyperglycemia (euglycemic DKA) (103), are ongoing. After a thorough review of the evidence during an October 2015 meeting, an AACE/ACE Scientific and Clinical Review expert consensus group found that the incidence of DKA is infrequent and recommended no changes in SGLT-2 inhibitor labeling (105).
- Dipeptidyl peptidase 4 (DPP-4) inhibitors exert antihyperglycemic effects by inhibiting DPP-4 and thereby enhancing levels of GLP-1 and other incretin hormones. This action stimulates glucose-dependent insulin synthesis and secretion and suppresses glucagon secretion. DPP-4 inhibitors have modest A1C-lowering properties, are weight-neutral, and are available in combination tablets with metformin, an SGLT-2 inhibitor, and a TZD. The risk of hypoglycemia with DPP-4 inhibitors is low (106,107). The DPP-4 inhibitors, except linagliptin, are excreted by the kidneys; therefore, dose adjustments are advisable for patients with renal dysfunction. These agents should be used with caution in patients with a history of pancreatitis, although a causative association has not been established (99).
- The TZDs, the only antihyperglycemic agents to directly reduce insulin resistance, have relatively potent A1C-lowering properties, a low risk of hypoglycemia, and durable glycemic

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effects (86,108,109). Pioglitazone may confer CVD benefits (108,110), while rosiglitazone has a neutral effect on CVD risk (111,112). Side effects that have limited TZD use include weight gain, increased bone fracture risk in postmenopausal women and elderly men, and elevated risk for chronic edema or heart failure (113-116). A possible association with bladder cancer has largely been refuted (117). Side effects may be mitigated by using a moderate dose (e.g., ≤30 mg) of pioglitazone.

- In general, alpha glucosidase inhibitors (AGIs) have modest A1C-lowering effects and low risk for hypoglycemia (118). Clinical trials have shown CVD benefit in patients with impaired glucose tolerance and diabetes (67,119). Side effects (e.g., bloating, flatulence, diarrhea) have limited their use in the United States. These agents should be used with caution in patients with CKD.
- The insulin-secretagogue SFUs have relatively potent A1C-lowering effects but lack durability and are associated with weight gain and hypoglycemia (87,120). SFUs have the highest risk of serious hypoglycemia of any noninsulin therapy, and analyses of large datasets have raised concerns regarding the cardiovascular safety of this class when the comparator is metformin, which may itself have cardioprotective properties (88,121). The secretagogue glinides have somewhat lower A1C-lowering effects, a shorter half-life, and carry a lower risk of hypoglycemia risk than SFUs.
- Colesevelam, a bile acid sequestrant (BAS), lowers glucose modestly, does not cause hypoglycemia, and decreases LDL-C. A perceived modest efficacy for both A1C and LDL-C lowering as well as gastrointestinal intolerance (constipation and dyspepsia), which occurs in 10% of users, may contribute to limited use. In addition, colesevelam can increase triglyceride levels in individuals with pre-existing triglyceride elevations (122).
- The quick-release dopamine receptor agonist bromocriptine mesylate has slight glucose-lowering properties (123) and does not cause hypoglycemia. It can cause nausea and orthostasis and should not be used in patients taking antipsychotic drugs. Bromocriptine mesylate may be associated with reduced cardiovascular event rates (124,125).

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For patients with recent-onset T2D or mild hyperglycemia (A1C <7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm). Acceptable alternatives to metformin as initial therapy include GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and TZDs. AGIs, SFUs, and glinides may also be appropriate as monotherapy for select patients.

Metformin should be continued as background therapy and used in combination with other agents, including insulin, in patients who do not reach their glycemic target on monotherapy. Patients who present with an A1C >7.5% should be started on metformin plus another agent in addition to lifestyle therapy (120) (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm). In metformin-intolerant patients, two drugs with complementary mechanisms of action from other classes should be considered.

The addition of a third agent may safely enhance treatment efficacy (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm), although any given third-line agent is likely to have somewhat less efficacy than when the same medication is used as first- or second-line therapy. Patients with A1C >9.0% who are symptomatic would derive greater benefit from the addition of insulin, but if presenting without significant symptoms these patients may initiate therapy with maximum doses of two other medications. Doses may then be decreased to maintain control as the glucose falls. Therapy intensification should include intensified lifestyle therapy and anti-obesity treatment (where indicated).

Certain patient populations are at higher risk for adverse treatment-related outcomes, underscoring the need for individualized therapy. Although several antihyperglycemic drug classes carry a low risk of hypoglycemia (e.g., metformin, GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and TZDs), significant hypoglycemia can still occur when these agents are used in combination with an insulin secretagogue or exogenous insulin. When such combinations are used, one should consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. Many antihyperglycemic agents (e.g., metformin, GLP-1 receptor agonists, SGLT-2 inhibitors, some DPP-4 inhibitors, AGIs, SFUs) have limitations in patients with impaired renal function and may require dose adjustments or special precautions (see Comprehensive Type 2 Diabetes Management Algorithm—Profiles of Antidiabetic

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Medications). In general, diabetes therapy does not require modification for mild to moderate liver disease, but the risk of hypoglycemia increases in severe cases.

Insulin

Insulin is the most potent glucose-lowering agent. However, many factors come into play when deciding to start insulin therapy and choosing the initial insulin formulation (see Comprehensive Type 2 Diabetes Management Algorithm—Algorithm for Adding/Intensifying Insulin). These decisions, made in collaboration with the patient, depend greatly on each patient's motivation, cardiovascular and end-organ complications, age, general well-being, risk of hypoglycemia, and overall health status, as well as cost considerations. Patients taking two oral antihyperglycemic agents who have an A1C >8.0% and/or long-standing T2D are less likely to reach their target A1C with a third oral antihyperglycemic agent. Although adding a GLP-1 receptor agonist as the third agent may successfully lower glycemia, eventually many patients will still require insulin (126,127). In such cases, a single daily dose of basal insulin should be added to the regimen. The dosage should be adjusted at regular and fairly short intervals to achieve the glucose target while avoiding hypoglycemia. Recent studies (128,129) have shown that titration is equally effective whether it is guided by the healthcare professional or a patient who has been instructed in SMBG.

Basal insulin analogs are preferred over neutral protamine Hagedorn (NPH) insulin because a single basal dose provides a relatively flat serum insulin concentration for up to 24 hours. Although insulin analogs and NPH have been shown to be equally effective in reducing A1C in clinical trials, insulin analogs caused significantly less hypoglycemia (128-132).

Newer basal insulin formulations – glargine U300 and degludec U100 and U200 – have more prolonged and stable pharmacokinetic (PK) and pharmacodynamics (PD) characteristics than glargine U100 and detemir (133). Randomized clinical studies have reported equivalent glycemic control and lower rate of severe or confirmed hypoglycemia, particularly nocturnal hypoglycemia compared to glargine U100 and detemir insulin (134-139). To date, there are no head-to-head trials comparing glargine U300 and degludec.

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Premixed insulins provide less dosing flexibility and have been associated with a higher frequency of hypoglycemic events compared to basal and basal-bolus regimens (140-142). Nevertheless, there are some patients for whom a simpler regimen using these agents is a reasonable compromise.

Patients whose basal insulin regimens fail to provide glucose control may benefit from the addition of a GLP-1 receptor agonist, SGLT-2 inhibitor, or DPP-4 inhibitor (if not already taking one of these agents; see Comprehensive Type 2 Diabetes Management Algorithm—Algorithm for Adding/Intensifying Insulin). When added to insulin therapy, the incretins and SGLT-2 inhibitors enhance glucose reductions and may minimize weight gain without increasing the risk of hypoglycemia. The incretins also increase endogenous insulin secretion in response to meals, reducing postprandial hyperglycemia (126,143-148). Depending on patient response, basal insulin dose may need to be reduced to avoid hypoglycemia.

Patients whose glycemia remains uncontrolled while receiving basal insulin alone or in combination with oral agents may require mealtime insulin to cover postprandial hyperglycemia. Rapid-acting analogs (lispro, aspart, or glulisine) or inhaled insulin are preferred over regular human insulin because the former have a more rapid onset and offset of action and are associated with less hypoglycemia (149). Prandial insulin should be considered when the total daily dose of basal insulin is greater than 0.5 U/kg. Beyond this dose, the risk of hypoglycemia increases markedly without significant benefit in reducing A1C (150). The simplest approach is to cover the largest meal with a prandial injection of a rapid-acting insulin analog or inhaled insulin and then add additional mealtime insulin later, if needed. Several randomized controlled trials have shown that the stepwise addition of prandial insulin to basal insulin is safe and effective in achieving target A1C with a low rate of hypoglycemia (151-153). A full basal-bolus program is the most effective insulin regimen and provides greater flexibility for patients with variable mealtimes and meal carbohydrate content, although this type of program has been associated with weight gain (153).

Pramlintide is indicated for use with basal-bolus insulin regimens. Pioglitazone is indicated for use with insulin at doses of 15 and 30 mg, but this approach may aggravate weight gain. There are no specific approvals for the use of SFUs with insulin, but when they are used together, the risks of both weight gain and hypoglycemia increase (154,155).

It is important to avoid hypoglycemia. Approximately 7 to 15% of insulin-treated patients experience at least one annual episode of hypoglycemia (156), and 1 to 2% have severe hypoglycemia (157,158).

doi: 10.4158/EP161682.CS

Several large randomized trials found that T2D patients with a history of one or more severe hypoglycemic events have an approximately 2- to 4-fold higher death rate (85,159). It has been proposed that hypoglycemia may be a marker for persons at higher risk of death, rather than the proximate cause of death (158). Patients receiving insulin also gain about 1 to 3 kg more weight than those receiving other agents.

Blood Pressure

Elevated BP in patients with T2D is associated with an increased risk of cardiovascular events (see Comprehensive Type 2 Diabetes Management Algorithm—ASCVD Risk Factor Modifications Algorithm). AACE recommends that BP control be individualized, but that a target of <130/80 mm Hg is appropriate for most patients. Less stringent goals may be considered for frail patients with complicated comorbidities or those who have adverse medication effects, while a more intensive goal (e.g., <120/80 mm Hg) should be considered for some patients if this target can be reached safely without adverse effects from medication. Lower BP targets have been shown to be beneficial for patients at high risk for stroke (160-162). Among participants in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial, there were no significant differences in primary cardiovascular outcomes or all-cause mortality between standard therapy (which achieved a mean BP of 133/71 mm Hg) and intensive therapy (mean BP of 119/64 mm Hg). Intensive therapy did produce a comparatively significant reduction in stroke and microalbuminuria, but these reductions came at the cost of requiring more antihypertensive medications and produced a significantly higher number of serious adverse events (SAEs). In particular, a greater likelihood of decline in renal function was observed in the intensive arm of ACCORD-BP (163). A meta-analysis of antihypertensive therapy in patients with T2D or impaired fasting glucose demonstrated similar findings. Systolic BP ≤135 mm Hg was associated with decreased nephropathy and a significant reduction in all-cause mortality compared with systolic BP ≤140 mm Hg. Below 130 mm Hg, stroke and nephropathy, but not cardiac events, declined further, but SAEs increased by 40% (160).

Lifestyle therapy can help T2D patients reach their BP goal:

- Weight loss can improve BP in patients with T2D. Compared with standard intervention, the results of the Look AHEAD trial found that significant weight loss is associated with significant reduction in BP, without the need for increased use of antihypertensive medications (4).

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- Sodium restriction is recommended for all patients with hypertension. Clinical trials indicate that potassium chloride supplementation is associated with BP reduction in people without diabetes (164). The Dietary Approaches to Stop Hypertension (DASH) diet, which is low in sodium and high in dietary potassium, can be recommended for all patients with T2D without renal insufficiency (165-170).
- Numerous studies have shown that moderate alcohol intake is associated with a lower incidence of heart disease and cardiovascular mortality (171,172).
- The effect of exercise in lowering BP in people without diabetes has been well-established. In hypertensive patients with T2D, however, exercise appears to have a more modest effect (25,173); still, it is reasonable to recommend a regimen of moderately intense physical activity in this population.

Most patients with T2D and hypertension will require medications to achieve their BP goal. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers (CCBs), and thiazide diuretics are favored choices for first-line treatment (174-178). The selection of medications should be based on factors such as the presence of albuminuria, CVD, heart failure, or post-myocardial infarction status as well as patient race/ethnicity, possible metabolic side effects, pill burden, and cost. Because ACEIs and ARBs can slow progression of nephropathy and retinopathy, they are preferred for patients with T2D (175,179-181). Patients with heart failure could benefit from beta blockers, those with prostatism from alpha blockers, and those with coronary artery disease (CAD) from beta blockers or CCBs. In patients with BP >150/100 mm Hg, two agents should be given initially because it is unlikely any single agent would be sufficient to achieve the BP target. An ARB/ACEI combination more than doubles the risk of renal failure and hyperkalemia and is therefore not recommended (182,183).

Lipids

Compared to those without diabetes, patients with T2D have a significantly increased risk of ASCVD (184). Whereas blood glucose control is fundamental to prevention of microvascular complications, controlling atherogenic cholesterol particle concentrations is fundamental to prevention of macrovascular

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disease (i.e., ASCVD). To reduce the significant risk of ASCVD, including coronary heart disease (CHD), in T2D patients, early intensive management of dyslipidemia is warranted (see Comprehensive Type 2 Diabetes Management Algorithm—ASCVD Risk Factor Modifications Algorithm).

The classic major risk factors that modify the LDL-C goal for all individuals include cigarette smoking, hypertension (BP ≥140/90 mm Hg or use of antihypertensive medications), high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, family history of CHD, and age ≥45 years for men or ≥55 years for women (185). Recognizing that T2D carries a high lifetime risk for developing ASCVD, risk should be stratified for primary prevention as "*high*" (diabetes with no other risk factors) or "*very high*" (diabetes plus 1 or more additional risk factors). In addition to hyperglycemia, the majority of T2D patients have a syndrome of "insulin resistance," which is characterized by a number of ASCVD risk factors, including hypertension; hypertriglyceridemia; low HDL-C; elevated apolipoprotein (apo) B and small dense LDL; and a procoagulant and proinflammatory milieu. Patients with T2D and a prior ASCVD event (i.e., recognized "clinical ASCVD") or chronic kidney disease stage 3 or 4 are classified as "*extreme*" risk, in this setting for secondary or recurrent events prevention. Risk stratification in this manner can guide management strategies.

Patients with diabetes, therefore, can be classified as high risk, very high risk, or extreme risk (186,187); as such AACE recommends LDL-C targets of <100 mg/dL, <70 mg/dL, and <55 mg/dL, non-HDL-C targets of <130 mg/dL, <100 mg/dL, and <80 mg/dL, and apo B targets of <90 mg/dL, <80 mg/dL, and 70 mg/dL, respectively, with additional lipid targets shown in Table 1 (see also Comprehensive Type 2 Diabetes Management Algorithm—ASCVD Risk Factor Modifications Algorithm). The atherogenic cholesterol goals appear identical for very high risk primary prevention and for very high risk secondary (or recurrent events) prevention. However, AACE does not define how low the goal should be and now recognizes that even more intensive therapy, aimed at lipid levels far lower than an LDL-C <70 mg/dL or non-HDL-C <100 mg/dL, might be warranted for the secondary prevention group. A meta-analysis of 8 major statin trials demonstrated that those individuals achieving an LDL-C <50 mg/dL, a non-HDL-C <75 mg/dL, and apo B <50 mg/dL have the lowest ASCVD events (188). Furthermore, the primary outcome and subanalyses of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), a study involving 18,144 patients, provided evidence that lower LDL-C (53 mg/dL) and apoB (70

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mg/dL) results in better outcomes in patients with diabetes after acute coronary syndromes (189). LDL particle number (LDL-P) can also be useful as a target for treatment in patients with diabetes. However, in the absence of robust prospective clinical trial evidence, there is a lack of uniform agreement as to the target levels. Suggested targets have been proposed as <1200 for high risk and <1000 for very high risk patients. Data for LDL-P in patients now described as extreme risk is not established (190, 191).

Some patients with T2D can achieve lipid profile improvements using lifestyle therapy (smoking cessation, physical activity, weight management, and healthy eating) (185). However, most patients will require pharmacotherapy to reach their target lipid levels and reduce their cardiovascular risk.

A statin should be used as first-line cholesterol-lowering drug therapy, unless contraindicated; current evidence supports a moderate- to high-intensity statin (192-195). Numerous randomized clinical trials and meta-analyses conducted in primary and secondary prevention populations have demonstrated that statins significantly reduce the risk of cardiovascular events and death in patients with T2D (192,194-198). However, considerable residual risk persists even after aggressive statin monotherapy in primary prevention patients with multiple cardiovascular risk factors and in secondary prevention patients with stable clinical ASCVD or acute coronary syndrome (ACS) (195,199,200). Although intensification of statin therapy (e.g., through use of higher dose or higher potency agents) can further reduce atherogenic cholesterol particles (primarily LDL-C) and the risk of ASCVD events (201), some residual risk will remain (202). Data from several studies have shown that even when LDL-C reaches an optimal level (20th percentile), non-HDL-C, apo B, and low-density lipoprotein particle (LDL-P) number can remain suboptimal (203). Furthermore, statin intolerance (usually muscle-related adverse effects) can limit the use of intensive statin therapy in some patients (204).

Other lipid-modifying agents should be utilized in combination with maximally tolerated statins when therapeutic levels of LDL-C, non-HDL-C, apo B, or LDL-P have not been reached:

- Ezetimibe inhibits intestinal absorption of cholesterol, reduces chylomicron production, decreases hepatic cholesterol stores, upregulates LDL receptors, and lowers apo B, non-HDL-C, LDL-C, and triglycerides (205). In IMPROVE-IT, the relative risk of ASCVD was reduced by 6.4% (P=0.016) in patients taking simvastatin plus ezetimibe for 7 years (mean LDL-C: 54 mg/dL) compared to simvastatin alone (LDL-C: 70 mg/dL). The ezetimibe benefit was almost exclusively noted in the

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prespecified diabetes subgroup, which comprised 27% of the study population and in which the relative risk of ASCVD was reduced by 14.4% (*P*=0.023) (189).

- Monoclonal antibody inhibitors of proprotein convertase subtilisin–kexin type 9 serine protease (PCSK9), a protein that regulates the recycling of LDL receptors, have recently been approved by the FDA for primary prevention in patients with hetero- and homozygous familial hypercholesterolemia or as secondary prevention in patients with clinical ASCVD who require additional LDL-C–lowering therapy. This class of drugs meets a large unmet need for more aggressive lipid-lowering therapy beyond statins in an attempt to further reduce residual ASCVD risk in many persons with clinical ASCVD and diabetes. When added to maximal statin therapy, these once- or twice-monthly injectable agents reduce LDL-C by approximately 50%, raise HDL-C, and have favorable effects on other lipids (206-212). In posthoc cardiovascular safety analyses of alirocumab and evolocumab added to statins with or without other lipid-lowering therapies, mean LDL-C levels of 48 mg/dL were associated with statistically significant relative risk reductions of 48 to 53% in major ASCVD events (207,208). Furthermore, a subgroup analysis of patients with diabetes taking alirocumab demonstrated that a 59% LDL-C reduction was associated with an ASCVD event relative risk reduction trend of 42% (213).
- The highly selective BAS colesevelam, increases hepatic bile acid production by increasing elimination of bile acids, and thereby decreasing hepatic cholesterol stores. This leads to an upregulation of LDL receptors, a reduction in LDL-C, non-HDL-C, apo B, and LDL-P, and improved glycemic status. There is a small compensatory increase in de novo cholesterol biosynthesis, which can be suppressed by the addition of statin therapies (214-216). Additionally, BAS colesevelam may worsen hypertriglyceridemia (217).
- Fibrates have only small effects on lowering atherogenic cholesterol (5%) and are used mainly for lowering triglycerides. By lowering triglycerides, fibrates unmask residual atherogenic cholesterol in triglyceride-rich remnants (i.e., very low density lipoprotein cholesterol [VLDL-C]). In progressively higher triglyceride settings, as triglycerides decrease, LDL-C increases, thus exposing the need for additional lipid therapies. As monotherapy, fibrates have demonstrated significantly favorable outcomes in populations with high non-HDL-C (218) and low HDL-C

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(219). The addition of fenofibrate to statins in the ACCORD study showed no benefit in the overall cohort in which mean baseline triglycerides and HDL-C were within normal limits (220). Subgroup analyses and meta-analyses of major fibrate trials, however, have shown a relative risk reduction for CVD events of 26 to 35% among patients with moderate dyslipidemia (triglycerides >200 mg/dL and HDL-C <40 mg/dL) (220-225).

- Niacin lowers apo B, LDL-C, and triglycerides in a dose-dependent fashion and is the most powerful lipid-modifying agent for raising HDL-C on the market (226), although it may reduce cardiovascular events through a mechanism other than an increase in HDL-C (227). Two trials designed to test the HDL-C–raising hypothesis (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes [AIM-HIGH] and Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE]) failed to show CVD protection during the 3- and 4-year trial periods, respectively (228,229); by design, between-group differences in LDL-C were nominal at 5 mg/dL and 10 mg/dL, respectively. Previous trials with niacin that showed CVD benefits utilized higher doses of niacin, which were associated with much greater between-group differences in LDL-C, suggesting niacin benefits may result solely from its LDL-C–lowering properties (230). Although niacin may increase blood glucose, its beneficial effects appear to be greatest among patients with the highest baseline glucose levels and those with metabolic syndrome (231). As a result, it is particularly important to closely monitor glycemia in diabetic and pre-diabetic person not receiving glucose-lowering treatment and taking niacin.
- Dietary intake of fish and omega-3 fish oil is associated with reductions in the risks of total mortality, sudden death, and CAD through various mechanisms of action other than lowering of LDL-C. In a large clinical trial, highly purified, prescription-grade, moderate-dose (1.8 grams) eicosapentaenoic acid (EPA) added to a statin regimen was associated with a significant 19% reduction in risk of any major coronary event among Japanese patients with elevated total cholesterol (232) and a 22% reduction in CHD in patients with impaired fasting glucose or T2D (233). Among those with triglycerides >150 mg/dL and HDL-C <40 mg/dL, EPA treatment reduced the risk of coronary events by 53% (234). Other studies of lower doses (1 gram) of

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omega-3 fatty acids (combined EPA and docosahexaenoic acid [DHA]) in patients with baseline triglycerides <200 mg/dL have not demonstrated cardiovascular benefits (235,236). Studies evaluating high dose (4 grams) prescription-grade omega-3 fatty acids in the setting of triglyceride levels >200 mg/dL are ongoing.

Relative to statin efficacy (30 to >50% LDL-C lowering), drugs such as ezetimibe, BASs, fibrates, and niacin have lesser LDL-C–lowering effects (7 to 20%) and ASCVD reduction (237). However, these agents can significantly lower LDL-C when utilized in various combinations, either in statin-intolerant patients or as add-on to maximally tolerated statins. Triglyceride-lowering agents such as prescription-grade omega-3 fatty acids, fibrates, and niacin are important agents that expose the atherogenic cholesterol within triglyceride-rich remnants, which require additional cholesterol lowering. PCSK9 inhibitors are currently indicated for adult patients with heterozygous familial hypercholesterolemia (HeFH or HoFH) or clinical ASCVD as an adjunct to diet and maximally tolerated statin therapy, who require additional LDL-C lowering. Patients with diabetes and characteristics consistent with ASCVD risk equivalents are not currently candidates in the US.

If triglyceride levels are severely elevated (>500 mg/dL), begin treatment with a very low-fat diet and reduced intake of simple carbohydrates and initiate combinations of a fibrate, prescription-grade omega-3-fatty acid, and/or niacin to reduce triglyceride levels and to prevent pancreatitis. While no large clinical trials have been designed to test this objective, observational data and retrospective analyses support long-term dietary and lipid management of hypertriglyceridemia for prophylaxis against or treatment of acute pancreatitis (238,239).

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Table 1

AACE Lipid Targets for Patients with Type 2 Diabetes (188, 189, 197, 200, 240-251)

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme Risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very High Risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease – Diabetes or CKD 3/4 with 1 or more risk factor(s) – Heterozygous familial hypercholesterolemia	<70	<100	<80
High Risk	≥2 risk factors and 10-year risk >10% **or** CHD risk equivalent[c], including diabetes or CKD 3, 4 with no other risk factors	<100	<130	<90
Moderate Risk	≥2 risk factors and 10-year risk <10%	<130	<160	NR
Low Risk	≤1 risk factor	<160	<190	NR

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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-ethnic Study of Atherosclerosis; NR, not recommended; UKPDS, United Kingdom Prospective Diabetes Study.

[a] Major independent risk factors are high low-density lipoprotein cholesterol, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low high-density lipoprotein cholesterol (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3,4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high high-density lipoprotein cholesterol.

[b] Framingham risk scoring is applied to determine 10-year risk (10 [EL 4]).

[c] Coronary artery disease risk equivalents include diabetes and clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease).

NR=Not Recommended

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