CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2019 EXECUTIVE SUMMARY*

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This document represents the official position of the American Association of Clinical Endocrinologists and 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 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; **ACE** = American College of Endocrinology; **ACEI** = angiotensin-converting enzyme inhibitor; **AGI** = alpha-glucosidase inhibitor; **apo B** = apolipoprotein B; **ARB** = angiotensin II receptor blocker; **ASCVD** = atherosclerotic cardiovascular disease; **BAS** = bile acid sequestrant; **BMI** = body mass index; **BP** = blood pressure; **CCB** = calcium channel blocker; **CGM** = continuous glucose monitoring; **CHD** = coronary heart disease; **CKD** = chronic kidney disease; **DKA** = diabetic ketoacidosis; **DPP4** = dipeptidyl peptidase 4; **eGFR** = estimated glomerular filtration rate; **EPA** = eicosapentaenoic acid; **ER** = extended release; **FDA** = Food and Drug Administration; **GLP1** = glucagon-like peptide 1; **HDL-C** = high-density-lipoprotein cholesterol; **HeFH** = heterozygous familial hypercholesterolemia; **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; **PCSK9** = proprotein convertase subtilisin-kexin type 9 serine protease; **RCT** = randomized controlled trial; **SU** = sulfonylurea; **SGLT2** = sodium-glucose cotransporter 2; **SMBG** = self-monitoring of blood glucose; **T2D** = type 2 diabetes; **TZD** = thiazolidinedione

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, his or her spectrum of risks and complications, and evidence-based approaches to treatment. It is now clear that the progressive pancreatic beta-cell defect that drives the deterioration of metabolic control over time begins early and may be present before the diagnosis of T2D (1-3). 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 (BP) and lipid control, the two most important risk factors for atherosclerotic cardiovascular disease (ASCVD).

Since originally drafted in 2013, the algorithm has been updated as new therapies, management approaches, and important clinical data have emerged. The current algorithm includes up-to-date sections on lifestyle therapy and all classes of obesity, antihyperglycemic, lipid-lowering, and antihypertensive medications approved by the U.S. Food and Drug Administration (FDA) through December 2018.

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 (4) and is organized into discrete sections that address the following topics: the founding principles of the algorithm, lifestyle therapy, obesity, prediabetes, management of hypertension and dyslipidemia, and glucose control with noninsulin antihyperglycemic agents and insulin. In the accompanying algorithm, a chart summarizing the attributes of each antihyperglycemic class appears 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.
2. Minimizing the risk of both severe and nonsevere hypoglycemia is a priority. It is a matter of safety, adherence, and cost.
3. Minimizing risk of weight gain is also a priority. This is important for long-term health, in addition to safety, adherence, and cost. Weight loss should be considered in all patients with prediabetes and T2D who also have overweight or obesity. Weight-loss therapy should consist of a specific 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.
4. The hemoglobin A1C (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. Glycemic control targets include fasting and postprandial glucose as determined by self-monitoring of blood glucose (SMBG). In recent years, continuous

glucose monitoring (CGM) has become more available for people with T2D and has added a considerable degree of clarity for the patient's and clinician's understanding of the glycemic pattern.

5. An A1C level of ≤6.5% (48 mmol/mol) 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.
6. 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 initial A1C, duration of T2D, and obesity status. Other considerations 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 or risk reduction in heart, kidney, or liver disease.
7. The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status. Combination therapy is usually required and should involve agents with complementary mechanisms of action.
8. Comorbidities must be managed for comprehensive care, including management of lipid and BP abnormalities with appropriate therapies and treatment of other related conditions.
9. Targets should be achieved as soon as possible. Therapy must be evaluated frequently (e.g., every 3 months) until stable using multiple criteria, including A1C, SMBG records (fasting and postprandial) or CGM tracings, documented and suspected hypoglycemia events, lipid and BP values, adverse events (weight gain, fluid retention, hepatic or renal impairment, or ASCVD), comorbidities, other relevant laboratory data, concomitant drug administration, complications of diabetes, and psychosocial factors affecting patient care. With CGM, initial therapy adjustments can be made much more frequently until stable. Less frequent monitoring is acceptable once targets are achieved.
10. The choice of therapy includes ease of use and affordability. The therapeutic regimen should be as simple as possible to optimize adherence. 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 acquisition cost.
11. Insulin therapy does not preclude an A1C target of ≤6.5% (48 mmol/mol); however, such patients should be on CGM for safety monitoring.
12. This algorithm includes every FDA-approved class of medications for T2D (as of December 2018).

Lifestyle Therapy

The key components of lifestyle therapy include medical nutrition therapy, regular physical activity, sufficient amounts of sleep, behavioral support, and smoking cessation with 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 Lifestyle Therapy algorithm panel.

Lifestyle therapy begins with nutrition counseling and education. All patients should strive to attain and maintain an optimal weight through a primarily plant-based meal plan high in polyunsaturated and monounsaturated fatty acids, with limited intake of saturated fatty acids and avoidance of *trans* fats. Patients with overweight (body mass index [BMI] 25 to 29.9 kg/m^2) or obesity (BMI ≥30 kg/m^2; see Obesity section) 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 studies, lowering caloric intake is the main driver for weight loss (5-8). The clinician, a registered dietitian, or a nutritionist (i.e., a healthcare professional with formal training in the nutritional needs of individuals with diabetes) 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, including information on specific foods, meal planning, grocery shopping, and dining-out strategies. Clinicians should be sensitive to patients' ethnic and cultural backgrounds and their associated food preferences. 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, high fructose-containing, or other or high-glycemic-index foods. Those who require short-acting insulin with meals need to learn how to adjust insulin doses to match carbohydrate intake (e.g., use of carbohydrate counting with glucose monitoring) (4,9). Carbohydrate counting, however, was not shown to be more effective than a simplified bolus insulin dosage algorithm based on premeal and bedtime glucose patterns (10). 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 (5,8,11-18). 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 (19).

After nutrition, physical activity is the main component in weight loss and maintenance programs. Regular physical activity—both aerobic exercise and strength

training—improves glucose control, lipid levels, and BP; decreases the risk of falls and fractures; and improves functional capacity and sense of well-being (20-27). 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 (5). The physical activity regimen should involve ≥150 minutes per week of moderate-intensity activity such as brisk walking (e.g., 15- to 20-minute miles) and strength training. Patients should start any new activity slowly and gradually increase intensity and duration as they become accustomed to the exercise. Structured programs can help patients learn proper technique, establish goals, prevent injury, 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 a physical activity 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 (28).

Adequate rest is important for maintaining energy levels and well-being, and all patients should be advised to sleep on average approximately 7 hours per night. Evidence supports an association of 6 to 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 (29-34). 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 (35). 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 males, the elderly, and persons with obesity (36,37). 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 (4).

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 (38,39). Alcohol 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. A recent meta-analysis of psychosocial interventions provides insight into successful approaches, such as cognitive behavior therapy (40).

Smoking cessation is the final, and perhaps most important, 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 patients unable to stop smoking on their own (4).

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 (41,42). 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. Weight loss should be considered in all patients with overweight or obesity who have 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) (4,41).

The AACE Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity and Treatment Algorithm (43) provide evidence-based recommendations for obesity care, including screening, diagnosis, clinical evaluation and disease staging, therapeutic decision-making, and follow-up. Rather than a BMI-centric approach for the treatment of patients who have overweight or obesity, the AACE has emphasized a complications-centric model (see Comprehensive Type 2 Diabetes Management Algorithm—Complications-Centric Model for Care of the Patient with Overweight/Obesity). This approach incorporates 3 disease stages: Stage 0 (elevated BMI with no obesity complications), Stage 1 (1 or 2 mild to moderate obesity complications), and Stage 3 (>2 mild to moderate obesity complications, or ≥1 severe complication) (43,44). The patients who will benefit most from medical and surgical intervention have obesity-related complications that can be classified into 2 general categories: insulin resistance/cardiometabolic disease and biomechanical consequences of excess body weight (45). 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 (46,47). Once these factors are assessed, clinicians can set therapeutic goals and select appropriate types and intensities of treatment that may 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 A1C 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 ≥27 kg/m^2 having complications and for patients with BMI ≥30 kg/m^2 whether or not complications are present. The FDA has approved 8 drugs as adjuncts to lifestyle therapy in patients with overweight or obesity. Diethylproprion, phendimetrazine, and phentermine may be used for short-term (≤3 months) 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 can improve BP and lipids, prevent progression to diabetes, and improve glycemic control and lipids in patients with T2D (48-65). The cost and side effects of these medications may limit their use. Bariatric surgery should be considered for adult patients with a BMI ≥35 kg/m^2 and comorbidities, especially if therapeutic goals have not been reached using other modalities (4,66). A successful outcome of surgery usually requires a long-term outpatient commitment to follow-up and support.

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 insulin resistance (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 (67).

The primary goal of prediabetes management is weight loss. Whether achieved through lifestyle therapy alone or a combination of lifestyle therapy with pharmacotherapy and/or surgery, weight loss reduces insulin resistance and can effectively prevent progression to diabetes as well as improve plasma lipid profile and BP (49,53,54,56,58,65,68). 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 (67).

No medications (either weight-loss drugs or antihyperglycemic agents) are approved by the FDA solely for the management of prediabetes and/or prevention of T2D. However, antihyperglycemic medications such as metformin and acarbose reduce the risk of future diabetes in patients with prediabetes by 25 to 30%. Both medications are relatively well-tolerated and safe, and they may confer a cardiovascular risk benefit (68-71). In clinical trials, insulin sensitizers (thiazolidinediones [TZDs]) prevented future development of diabetes in 60 to 75% of subjects with prediabetes (72-74). Cardiovascular benefits, such as reduced major adverse cardiovascular events, have been documented in T2D and in patients with prediabetes and a history of stroke (75,76). However, TZDs have been associated with adverse outcomes, including weight gain related to subcutaneous fat increases (despite visceral adiposity reduction), water retention, and heart failure in susceptible patients, such as those with pre-existing ventricular dysfunction. In addition, there is a small increased risk of distal limb bone fractures (72-74).

Glucagon-like peptide 1 (GLP1) 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 majority of subjects with prediabetes (64,65,77,78). However, owing to the lack of long-term safety data on GLP1 receptor agonists and the known adverse effects of TZDs, these agents should be considered only for patients failing more conventional therapies (i.e., lifestyle therapy and/or metformin).

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

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). The 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 (79-81). Among participants in the ACCORD-BP (Action to Control

Cardiovascular Risk in Diabetes Blood Pressure) 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 (82). 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% (79).

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 (6).
- 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 (83). The Dietary Approaches to Stop Hypertension (DASH) meal plan, which is low in sodium and high in dietary potassium, can be recommended for all patients with T2D without renal insufficiency (84-89).
- Numerous studies have shown that moderate alcohol intake is associated with a lower incidence of heart disease and cardiovascular mortality (90,91).
- The effect of physical activity in lowering BP in people without diabetes has been well-established. In hypertensive patients with T2D, however, physical activity appears to have a more modest effect (28,92); nevertheless, 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 (93-97). The selection of medications should be based on factors such as the presence of albuminuria, ASCVD, 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 (94,98-100). Patients with heart failure could benefit from beta blockers, those with prostatism from alpha blockers, and those with coronary artery disease 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 (101,102). A CCB or other agent may be used based on the clinical characteristics of the patient.

Lipids

Compared to those without diabetes, patients with T2D have a significantly increased risk of ASCVD (103). Whereas blood glucose control is fundamental to prevention of microvascular complications, controlling atherogenic cholesterol particle concentrations is fundamental to prevention of macrovascular 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 low-density-lipoprotein cholesterol (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 males or ≥55 years for females (104). 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 one or more additional risk factors). In addition to hyperglycemia, most T2D patients have a syndrome of insulin resistance, which is characterized by several ASCVD risk factors, including hypertension, hypertriglyceridemia, low HDL-C, elevated apolipoprotein (apo) B and small dense LDL, and a procoagulant and pro-inflammatory milieu. Patients with T2D and a prior ASCVD event (i.e., recognized "clinical ASCVD") or chronic kidney disease (CKD) 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; as such, the 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 (105-121) (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, the 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 (105). 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 apo B (70 mg/dL) result in better outcomes in patients with diabetes after acute coronary syndromes (106). LDL particle (LDL-P) number 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 goal levels. Suggested targets have been proposed as <1,200 for high risk and <1,000 for very high-risk patients. Data for LDL-P in patients now described as extreme risk are not established (122,123).

Some patients with T2D can achieve lipid profile improvements using lifestyle therapy (smoking cessation, physical activity, weight management, and healthy eating) (104). 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 contra-indicated; current evidence supports a moderate- to high-intensity statin (124-127). Numerous randomized controlled trials (RCTs) 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 (107,124,126-129). However, considerable residual risk persists even after aggressive statin monotherapy in primary prevention patients with multiple

Table 1
AACE Lipid Targets for Patients With T2D or T2D Risk Factors (121)

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 one or more risk factor(s) – HeFH	<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

Abbreviations: AACE = American Association of Clinical Endocrinologists; ACS = acute coronary syndrome; Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CKD = chronic kidney disease; DM = diabetes mellitus; HeFH = heterozygous familial hypercholesterolemia; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; NR = not recommended; T2D = type 2 diabetes.

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

[b]Framingham risk scoring is applied to determine 10-year risk.

[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).

cardiovascular risk factors and in secondary prevention patients with stable clinical ASCVD or acute coronary syndrome (108,127,130). 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 (131), some residual risk will remain (132). Data from several studies have shown that even when LDL-C reaches an optimal level (20th percentile), non–HDL-C, apo B, and LDL-P levels can remain suboptimal (133). Furthermore, statin intolerance (usually muscle-related adverse effects) can limit the use of intensive statin therapy in some patients (134).

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 (135). In IMPROVE-IT, the relative risk of ASCVD was reduced by 6.4% (P = .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 prespecified diabetes subgroup, which comprised 27% of the study population and in which the relative risk of ASCVD was reduced by 14.4% (P = .023) (106).
- Monoclonal antibody inhibitors of proprotein convertase subtilisin-kexin type 9 serine protease (PCSK9), a protein that regulates the recycling of LDL receptors, are approved by the FDA for primary prevention in patients with hetero- and homozygous familial hypercholesterolemia (HeFH and HoFH, respectively) 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 (136-142). In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study, evolocumab significantly reduced the risk of myocardial infarction, stroke, and coronary revascularization (143), and similar effects were seen with alirocumab in ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab Study) (144). In post hoc 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 (138,145). 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% (146).
- The highly selective bile acid sequestrant (BAS) colesevelam increases hepatic bile acid production by increasing elimination of bile acids, 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 (147-149). Additionally, colesevelam may worsen hypertriglyceridemia (150).
- 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). 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 (151) and low HDL-C (152). 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 (153). Subgroup analyses and meta-analyses of major fibrate trials, however, have shown a relative risk reduction for ASCVD events of 26 to 35% among patients with moderate dyslipidemia (triglycerides >200 mg/dL and HDL-C <40 mg/dL) (153-158).
- 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 currently available (159), although it may reduce cardiovascular events through a mechanism other than an increase in HDL-C (160). 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 ASCVD protection during the 3- and 4-year trial periods, respectively (161,162); 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 cardiovascular 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 (163). 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 (164). As a result, it is particularly important to closely monitor glycemia in individuals with diabetes or prediabetes who are 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 coronary artery disease through various mechanisms of action other than lowering of LDL-C. In a large clinical trial, highly purified, prescription-grade, moderate-dose (1.8 g) 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 (165) and a 22% reduction in CHD in patients with impaired fasting glucose or T2D (166). Among those with triglycerides >150 mg/dL and HDL-C <40 mg/dL, EPA treatment reduced the risk of coronary events by 53% (167). Other studies of lower doses (1 g) of omega-3 fatty acids (combined EPA and docosahexaenoic acid) in patients with baseline triglycerides <200 mg/dL have not demonstrated cardiovascular benefits (168,169). Recently, the REDUCE-IT (Reduction of Cardiovascular Events with EPA-Intervention Trial) study of icosapent ethyl, an EPA-only prescription-grade omega-3 fatty acid given at a dose of 4 g/day, demonstrated a 25% reduction in risk of major adverse cardiovascular events among patients with LDL-C levels below 100 mg/dL and triglyceride levels between 150 and 499 mg/dL (170). Studies evaluating other high dose (4 g) 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, BAS, fibrates, and niacin have lesser LDL-C–lowering effects (7 to 20%) and ASCVD reduction (121). 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 HeFH, HoFH, or clinical ASCVD as an adjunct to a lipid-management meal plan 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 United States.

If triglyceride levels are severely elevated (>500 mg/dL), begin treatment with a very-low-fat meal plan 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. Blood glucose control is also essential for triglyceride reduction. 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 (171,172).

T2D Pharmacotherapy

In patients with T2D, achieving the glucose and A1C targets requires a nuanced approach that balances age, comorbidities, hypoglycemia risk, and many other factors described above (4). The AACE supports an A1C goal of ≤6.5% (48 mmol/mol) for most patients or >6.5% if the lower target cannot be achieved without adverse outcomes. Significant reductions in the risk or progression of nephropathy were seen in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study, which targeted an A1C <6.5% in the intensive therapy group versus standard approaches. In ADVANCE, the starting A1C was 7.5% (58 mmol/mol), and rates of hypoglycemia were higher in the intensive therapy group (173). In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, intensive glycemic control significantly reduced the risk and/or progression of retinopathy, nephropathy, and neuropathy (174,175). However, in ACCORD, which involved older and middle-aged patients with long-standing T2D who were at high risk for or had established ASCVD and a baseline A1C >8.5% (69 mmol/mol), patients randomized to intensive glucose-lowering therapy (A1C target of <6.0% [42 mmol/mol]) had increased mortality (176). The excess mortality occurred only in patients whose A1C remained >7% (53 mmol/mol) despite intensive therapy, and this critical distinction is sometimes forgotten when the risk and benefits of intensive therapy are discussed. In the standard therapy group (A1C target 7 to 8% [53 to 64 mmol/mol]), mortality followed a U-shaped curve with increasing death rates at both low (<7%) and high (>8%) A1C levels (177). ACCORD showed that cardiovascular autonomic neuropathy may be another useful predictor of cardiovascular risk (178). A combination of cardiovascular autonomic neuropathy and symptoms of peripheral neuropathy increase the odds ratio to 4.55 for ASCVD and mortality (179). In the Veterans Affairs Diabetes Trial (VADT), which had a higher A1C target for intensively treated patients (1.5% lower than the standard treatment group), there were no between-group differences in ASCVD endpoints, cardiovascular

death, or overall death during the 5.6-year study period (176,180). 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 ($P<.04$; 8.6 fewer cardiovascular events per 1,000 person-years), while mortality risk remained the same between treatment groups (181).

Severe hypoglycemia occurs more frequently with intensive glycemic control in RCTs where insulin and/or sulfonylureas (SUs) are utilized (173,176,180,182,183). 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 (183).

Taken together, this evidence supports individualization of glycemic goals (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm) (4). In adults with recent T2D onset and no clinically significant ASCVD, an A1C ≤6.5% (48 mmol/mol), if achieved without substantial hypoglycemia or other unacceptable consequences, may reduce the lifetime risk of micro- and macrovascular complications. A broader A1C range may be suitable for older patients and those at risk for hypoglycemia. A less stringent A1C >6.5% 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 Glycemic 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 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 1,000 to 2,000 mg/day. Its effects are quite durable compared to SUs, and it also has robust cardiovascular safety relative to SUs (184-186). The FDA recently changed the package label for metformin use in CKD patients, lifting the previous contra-indication in males with serum creatinine >1.5 mg/dL and females with serum creatinine >1.4 mg/dL (187,188). 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 <45 mL/min/1.73 m^2. Reduction in total daily dose is prudent in patients with eGFR between 30 and 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 (189,190). In up to 16% of users, metformin is responsible for vitamin B12 malabsorption and/or deficiency (191,192), a causal factor in the development of anemia and peripheral neuropathy (193). In patients taking metformin who develop neuropathy, B12 should be monitored and supplements given to affected patients, if needed (194).
- GLP1 receptor agonists have robust A1C-lowering properties, are usually associated with weight loss and lipid and BP reductions (195,196), and are available in several formulations. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, liraglutide significantly reduced the risk of nephropathy and of death from certain cardiovascular causes (197). Liraglutide recently received FDA approval to reduce the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in adults with T2D and established cardiovascular disease (198). Data from the SUSTAIN-6 trial with semaglutide and preliminary findings from the REWIND trial with dulaglutide suggest other GLP1-RAs may also have cardiovascular disease benefits (199,200). GLP1-RAs of lizard origin have been proven to be safe in cardiovascular disease, but they have not been shown to confer cardiovascular benefits (201,202). The risk of hypoglycemia with GLP1 receptor agonists is low (203), and they reduce fluctuations in both fasting and postprandial glucose levels by stimulating glucose-dependent insulin secretion and suppressing glucagon secretion. GLP1 receptor agonists should not be used in patients with a 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 dose adjustment is required for liraglutide, semaglutide, and dulaglutide in CKD, although renal function should be monitored in patients reporting severe adverse gastrointestinal reactions (204). No studies have confirmed that incretin agents cause pancreatitis (205); however, GLP1 receptor agonists should be used cautiously, if at all,

in patients with a history of pancreatitis and discontinued if pancreatitis develops. Some GLP1 receptor agonists may retard gastric emptying, especially with initial use. Therefore, use in patients with gastroparesis or severe gastro-esophageal reflux disease requires careful monitoring and dose adjustment.

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors have a glucosuric effect that results in decreased A1C, weight, and systolic BP. Empagliflozin was associated with significantly lower rates of all-cause and cardiovascular death and lower risk of hospitalization for heart failure in the EMPA-REG OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) (206). Treatment with canagliflozin significantly reduced the risk of the combined cardiovascular outcomes of cardiovascular death, myocardial infarction, and nonfatal stroke, as well as hospitalization for heart failure, but increased the risk of amputation in CANVAS (Canagliflozin Cardiovascular Assessment Study) (207). Both empagliflozin and canagliflozin reduced secondary renal endpoints (206,207). In DECLARE-TIMI (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction), dapagliflozin reduced a composite of cardiovascular death and heart failure hospitalizations but did not significantly lower the combined risk of cardiovascular death and nonfatal myocardial infarction and stroke (208). Heart failure–related endpoints appear to account for most of the observed benefits in the published studies; a cardiovascular outcomes study of ertugliflozin is ongoing. Empagliflozin has an FDA-approved indication to reduce cardiac mortality in adults with T2D and established ASCVD (209). SGLT2 inhibitors are associated with increased risk of mycotic genital infections and slightly increased LDL-C levels, and because of their mechanism of action, they have limited efficacy in patients with an eGFR <45 mL/min/1.73 m^2. Dehydration due to increased diuresis may lead to initial renal impairment, hypotension, syncope, and falls (210-213). There are ongoing investigations into postmarketing reports of SGLT2 inhibitor–associated diabetic ketoacidosis (DKA), which has been reported to occur in type 1 diabetes (T1D) and T2D patients with less than expected hyperglycemia (euglycemic DKA) (211,214). In a recent review of 2,500 cases of SGLT2 inhibitor–associated DKA, 5% of patients with T1D treated with SGLT2 inhibitors developed DKA and 10% developed ketosis (214). In T2D, the incidence rate ranged from 0.16 to 0.76 events per 1,000 patient-years (215,216). After a thorough review of the evidence during an October 2015 meeting, an AACE/ACE Scientific and Clinical Review expert consensus group recommended stopping SGLT2 inhibitors 24 to 48 hours prior to scheduled surgeries and anticipated metabolically stressful activities (e.g., extreme sports) and that patients taking SGLT2 inhibitors with insulin should avoid very-low-carbohydrate meal plans and excess alcohol intake (217).
- Dipeptidyl peptidase 4 (DPP4) inhibitors exert antihyperglycemic effects by inhibiting DPP4 and thereby enhancing levels of GLP1 and other incretin hormones. This action stimulates glucose-dependent insulin synthesis and secretion and suppresses glucagon secretion. DPP4 inhibitors have modest A1C-lowering properties; are weight-neutral; and are available in combination tablets with metformin, SGLT2 inhibitors, and a TZD. The risk of hypoglycemia with DPP4 inhibitors is low (218,219). The DPP4 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 (and stopped if pancreatitis occurs), although a causative association has not been established (205). DPP4 inhibitors have been shown to have neutral effects on cardiovascular outcomes (220-222). A possible slight increased risk of heart failure with saxagliptin and alogliptin was found in the respective cardiovascular outcome trials (223,224), and a warning is included in the product labels for these agents.
- 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 effects (75,185,225). Pioglitazone may confer ASCVD benefits (75,76,226), while rosiglitazone has a neutral effect on ASCVD risk (227,228). Side effects that have limited TZD use include weight gain, increased bone fracture risk in postmenopausal females and elderly males, and elevated risk for chronic edema or heart failure (229-233). These side effects may be mitigated by using a moderate dose (e.g., ≤30 mg) of pioglitazone, or in the case of fluid retention, by combining the TZD with an SGLT2 inhibitor. A possible association with bladder cancer has largely been refuted (234).
- In general, alpha-glucosidase inhibitors (AGIs) have modest A1C-lowering effects and low risk for hypoglycemia (235). Clinical trials suggested ASCVD benefit in patients with impaired glucose tolerance and diabetes (69,236). Side effects (e.g., bloating, flatulence, diarrhea) have limited their use in the United States; slow titration of premeal doses may mitigate the side effects and facilitate tolerance. These agents should be used with caution in patients with CKD.
- The insulin-secretagogue SUs have relatively potent A1C-lowering effects but lack durability and are associated with weight gain and hypoglycemia (185,237). SUs 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 (186,238). The secretagogue glinides have somewhat lower A1C-lowering effects and a shorter half-life and thus carry a lower risk of prolonged hypoglycemia relative to SUs.

- Colesevelam, a 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, but this is somewhat preventable by concomitant statin use (239).
- The quick-release sympatholytic dopamine receptor agonist bromocriptine mesylate has modest glucose-lowering properties (240) and does not cause hypoglycemia. It can cause nausea and orthostasis, which may be mitigated by limiting use to less than maximal recommended doses and should not be used in patients taking antipsychotic drugs. Bromocriptine mesylate may be associated with reduced cardiovascular event rates (241,242).

For patients with recent-onset T2D or mild hyperglycemia (A1C <7.5% [58 mmol/mol]), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm). GLP1 receptor agonists and SGLT2 inhibitors with proven ASCVD and/or CKD benefits may be preferred in patients with those complications. Other acceptable alternatives to metformin as initial therapy include DPP4 inhibitors and TZDs. AGIs, SUs, and glinides may also be appropriate as monotherapy for select patients.

In patients who do not reach their glycemic target on metformin monotherapy, metformin should be continued in combination with other agents, including insulin. Patients who present with an A1C >7.5% (whether newly diagnosed or not) and who are not already taking any antihyperglycemic agents should be started initially on metformin plus another agent in addition to lifestyle therapy (237) (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. Fixed-dose (single-pill) combinations of oral agents including metformin and/or SGLT2 inhibitors, DPP4 inhibitors, TZDs, and SUs are available for the treatment of T2D. Fixed-ratio combinations of GLP1 receptor agonists and basal insulin are also available.

The addition of a third agent may be needed to enhance treatment efficacy (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm), although any 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% (75 mmol/mol) who are symptomatic (presenting with polyuria, polydipsia, or polyphagia) would likely derive greatest benefit from the addition of insulin, but if presenting without significant symptoms these patients may initiate therapy with maximum doses of two or three other medications. Therapy intensification should include intensified lifestyle therapy and anti-obesity treatment (when indicated), not just antihyperglycemic medication. Therapy de-intensification is also possible when control targets are met.

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, GLP1 receptor agonists, SGLT2 inhibitors, DPP4 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, GLP1 receptor agonists, SGLT2 inhibitors, some DPP4 inhibitors, AGIs, and SUs) 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 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 antihyperglycemic agent. However, many factors should be considered 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, risk of hypoglycemia, and overall health status, as well as cost considerations. Patients taking two oral antihyperglycemic agents who have an A1C >8.0% (64 mmol/mol) and/or long-standing T2D are less likely to reach their target A1C with a third oral antihyperglycemic agent. Although adding a GLP1 receptor agonist as the third agent may successfully lower glycemia, eventually many patients will still require insulin (243,244). When insulin becomes necessary, a single daily dose of basal insulin should be

added to the regimen. The dosage should be adjusted at regular and initially fairly short intervals, measured in days, to achieve the targeted glycemic goal while avoiding hypoglycemia. Studies (245-247) have shown that titration is equally effective whether it is guided by the healthcare professional or a patient who has been instructed in SMBG or CGM.

Basal insulin analogs are preferred over neutral protamine Hagedorn (NPH) insulin because a single basal analog dose provides a relatively flat serum insulin concentration for 24 hours or longer. Although basal insulin analogs and NPH have been shown to be equally effective in reducing A1C in clinical trials, insulin analogs caused significantly less hypoglycemia (245,246,248-250), especially newer ultra-long-acting analogs that demonstrate minimal variability (251). Accordingly, glargine U100 and detemir would be preferred to NPH.

The newest basal insulin formulations—glargine U300 and degludec U100 and U200—have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U100 and detemir (251,252). Degludec may have more stable day-to-day variability than glargine U300 (253), but methodology is complicated. RCTs have reported equivalent glycemic control and lower rates of severe or confirmed hypoglycemia, particularly nocturnal hypoglycemia, with these newest basal insulins compared to glargine U100 and detemir insulin (251,254-259). Cardiovascular outcomes were equivalent in the DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) trial comparing insulin degludec to insulin glargine U100 (251).

Premixed insulins provide less dosing flexibility and have been associated with a higher frequency of hypoglycemic events compared to basal and basal-bolus regimens (260-262). Nevertheless, there are some patients for whom a simpler regimen using these agents is a reasonable compromise, in which case premixed analog insulin may be preferred over premixed human due to lower rates of hypoglycemia.

Patients whose basal insulin regimens (which may already include metformin) fail to provide glucose control may benefit from the addition of a GLP1 receptor agonist, SGLT2 inhibitor, or DPP4 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 SGLT2 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 (243,263-268). The combination of basal insulin with a GLP1 receptor agonist may offer greater efficacy than the oral agents; fixed-ratio combinations of GLP1 receptor agonists and basal insulins are available. Depending on patient response, basal insulin dose may need to be reduced to avoid hypoglycemia.

Patients whose glycemia remains uncontrolled while receiving basal insulin in combination with oral agents or GLP1 receptor agonists may require mealtime insulin to cover postprandial hyperglycemia. Rapid-acting injectable insulin analogs (lispro, glulisine, aspart, or fast-acting aspart) 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 (269,270). However, for those who find the more costly analog insulins unaffordable, human regular insulin or premixed human insulin for T2D are less expensive options (271). 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 (272). 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 meal coverage later, as needed. Several RCTs 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 (273-275). 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 (275).

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 SUs with insulin, but when they are used together, the risks of both weight gain and hypoglycemia increase (276,277).

It is important to avoid hypoglycemia. Approximately 7 to 15% of insulin-treated patients in the UKPDS (United Kingdom Prospective Diabetes Study) experienced at least one annual episode of hypoglycemia (278), and based on other studies, 1 to 2% of patients with T2D have severe hypoglycemia (279,280). In a study using CGM, 49% of patients experienced at least one blood glucose <70 mg/dL over a 5-day study period and 10% experienced a blood glucose <50 mg/dL (281). Several large RCTs found that T2D patients with a history of one or more severe hypoglycemic events have an approximately 2- to 4-fold higher death rate (183,282). Severe hypoglycemia may precipitate fatal ventricular arrhythmia through an effect on baroreflex sensitivity (283), or hypoglycemia may be a marker for persons at higher risk of death, rather than the proximate cause of death (280). SMBG or CGM is necessary in all patients taking insulin, with increased frequency of monitoring recommended for patients taking meal-time insulin. One possible safety measure for prevention of hypoglycemia is the use of CGM that provides real-time glucose data

with or without alarms for hyper- and hypoglycemic excursions and events (284).

Patients receiving insulin also gain about 1 to 3 kg more weight than those receiving other agents.

Role of CGM

While A1C has been established as a biomarker for overall glycemic exposure and correlates with long-term diabetic complications, it is not very useful for making specific recommendations for choice of antihyperglycemic medications in individual patients with T2D. The extent to which A1C reflects glycemia varies by ethnicity and by multiple comorbidities. A1C is also not very helpful to patients for understanding their diabetes, the impact of lifestyle on glycemic control, or their response to interventions. Patients may also be reluctant to advance therapies if they do not really understand their glycemic pattern or are unable to perform SMBG at an adequate frequency. CGM helps patients achieve that understanding, which may help with adherence.

Significant advances have been made in accuracy and availability of CGM devices. As the use of these devices has expanded, both by clinicians and patients, their role in decision-making and management of diabetes has been evolving. While few controlled studies on CGM use in T2D have been published, a current consensus is that use of professional CGM (i.e., the device owned by the clinician's practice) should be considered in patients who have not reached their glycemic target after 3 months of the initial antihyperglycemic therapy and for those who require therapy that is associated with risks of hypoglycemia (i.e., SU, glinide, or insulin) (285,286). The frequency of use would depend on the stability of therapies.

Use of personal CGM devices (i.e., those owned by the patient), on the other hand, should be considered for those patients who are on intensive insulin therapy (3 to 4 injections/day or on insulin pump), for those with history of hypoglycemia unawareness, or those with recurrent hypoglycemia) (285,286). While these devices could be used intermittently in those who appear stable on their therapy, most patients will need to use this technology on a continual basis.

As experience with CGM in T2D grows, we anticipate more frequent use of both professional and personal devices, which may increasingly replace SMBG.

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2019

 DOI 10.4158/CS-2018-0535

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COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

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PRINCIPLES OF THE AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle modification underlies all therapy (e.g., weight control, physical activity, sleep, etc.)
2.	Avoid hypoglycemia
3.	Avoid weight gain
4.	Individualize all glycemic targets (A1C, FPG, PPG)
5.	Optimal A1C is ≤6.5%, or as close to normal as is safe and achievable
6.	Therapy choices are affected by initial A1C, duration of diabetes, and obesity status
7.	Choice of therapy reflects cardiac, cerebrovascular, and renal status
8.	Comorbidities must be managed for comprehensive care
9.	Get to goal as soon as possible—adjust at ≤3 months until at goal
10.	Choice of therapy includes ease of use and affordability
11.	A1C ≤6.5% for those on any insulin regimen as long as CGM is being used

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LIFESTYLE THERAPY

RISK STRATIFICATION FOR DIABETES COMPLICATIONS

INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

Nutrition	• Maintain optimal weight • Calorie restriction (if BMI is increased) • Plant-based diet; high polyunsaturated and monounsaturated fatty acids	+ • Avoid *trans* fatty acids; limit saturated fatty acids	+ • Structured counseling • Meal replacement
Physical Activity	• 150 min/week moderate exertion (e.g., walking, stair climbing) • Strength training • Increase as tolerated	+ • Structured program • Wearable technologies	+ • Medical evaluation/ clearance • Medical supervision
Sleep	• About 7 hours per night • Basic sleep hygiene	+ • Screen OSA • Home sleep study	+ • Referral to sleep lab
Behavioral Support	• Community engagement • Alcohol moderation	+ • Discuss mood with HCP	+ • Formal behavioral therapy
Smoking Cessation	• No tobacco products	+ • Nicotine replacement therapy	+ • Referral to structured program

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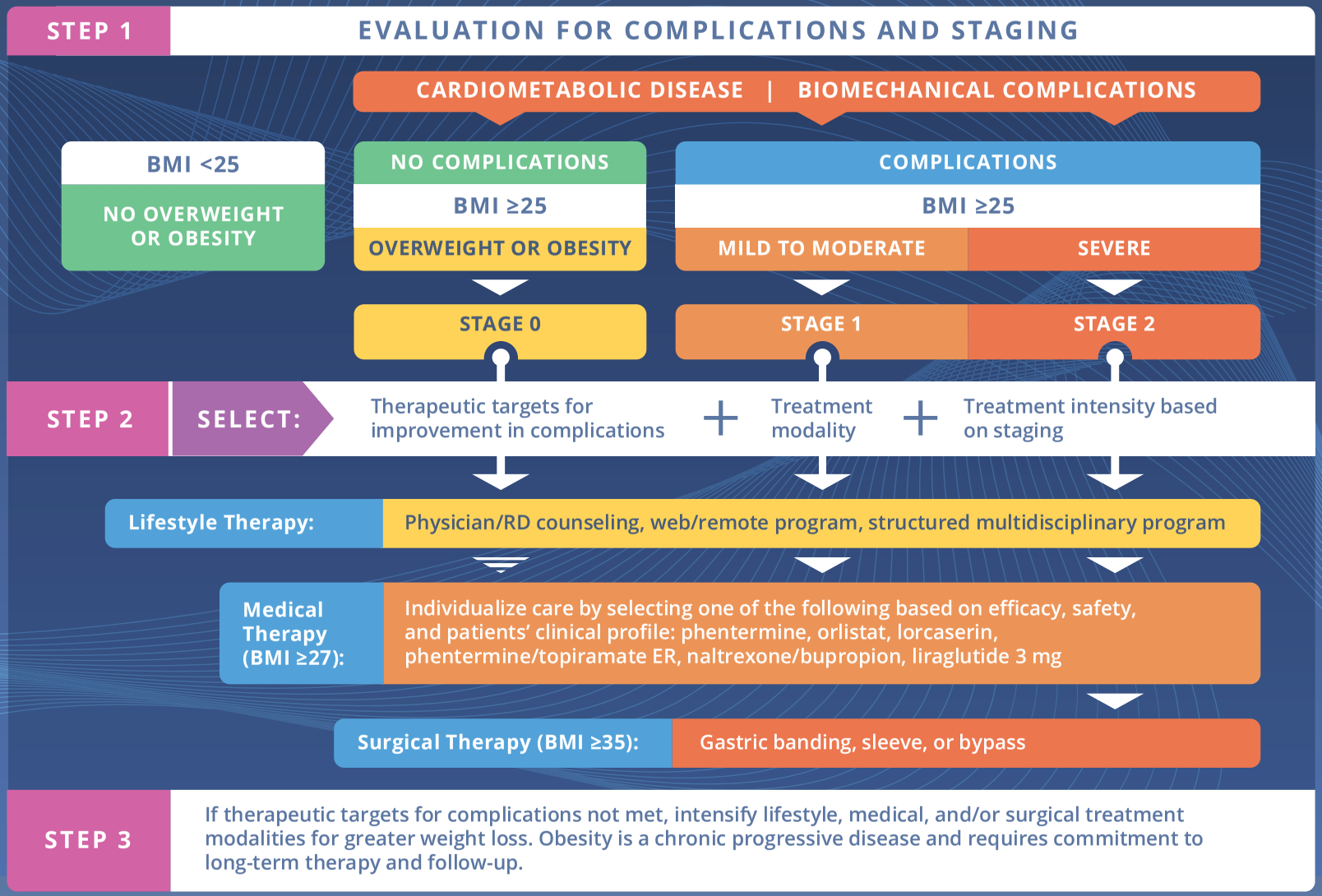
COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE PATIENT WITH OVERWEIGHT/OBESITY



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PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

WEIGHT LOSS THERAPIES

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO GLYCEMIC CONTROL ALGORITHM

TREAT HYPERGLYCEMIA
FPG >100 | 2-hour PG >140

- **1 PRE-DM CRITERION**
  - Intensify Weight Loss Therapies
  - Low-risk Medications: Metformin, Acarbose
  - Consider with Caution: TZD, GLP-1RA
- **MULTIPLE PRE-DM CRITERIA**

If glycemia not normalized

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

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ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG >500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

- Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies
- Repeat lipid panel; assess adequacy, tolerance of therapy
- Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:
- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

If not at desirable levels: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

To lower LDL-C:	Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG:	Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P:	Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:**	Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

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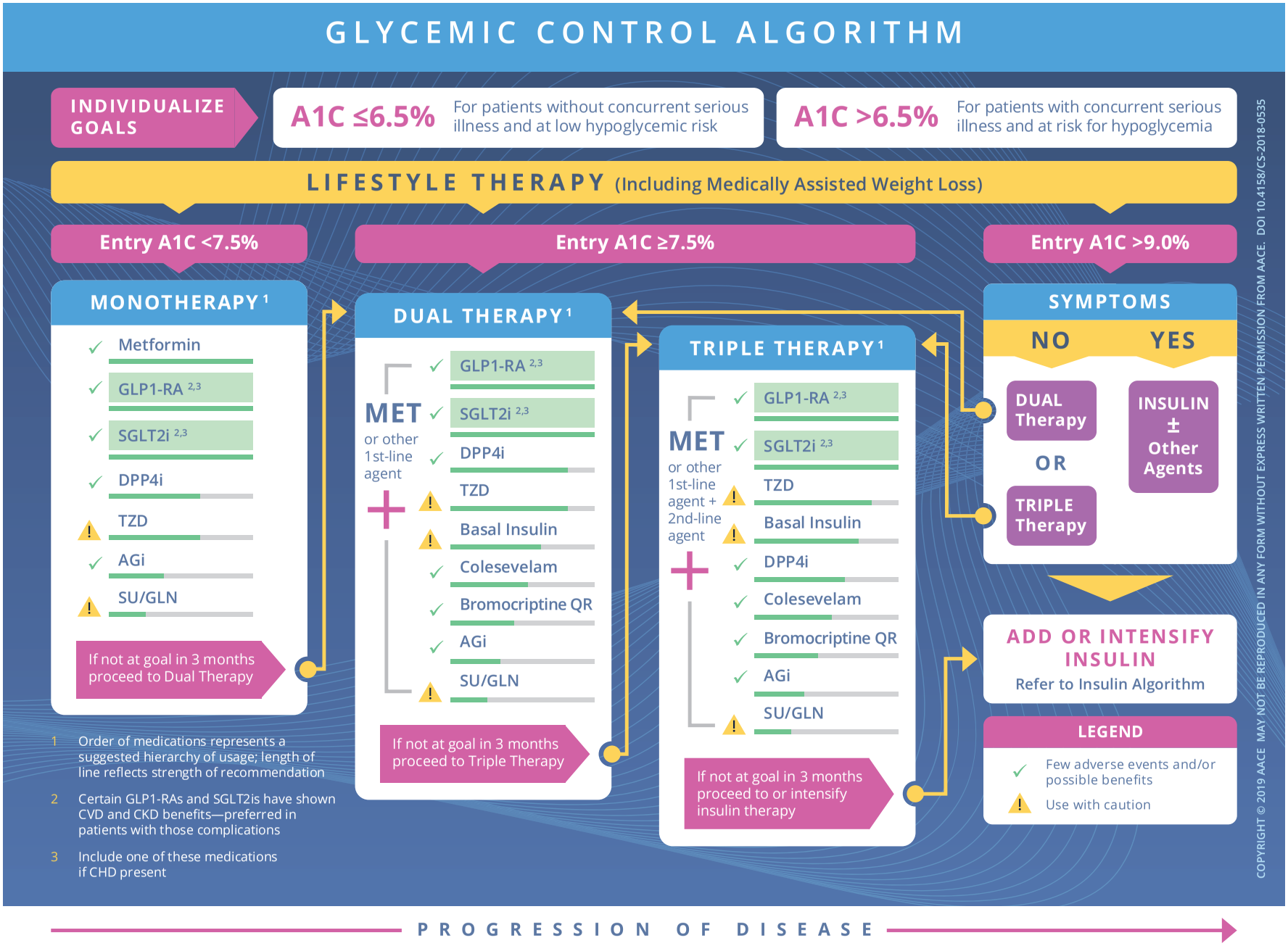
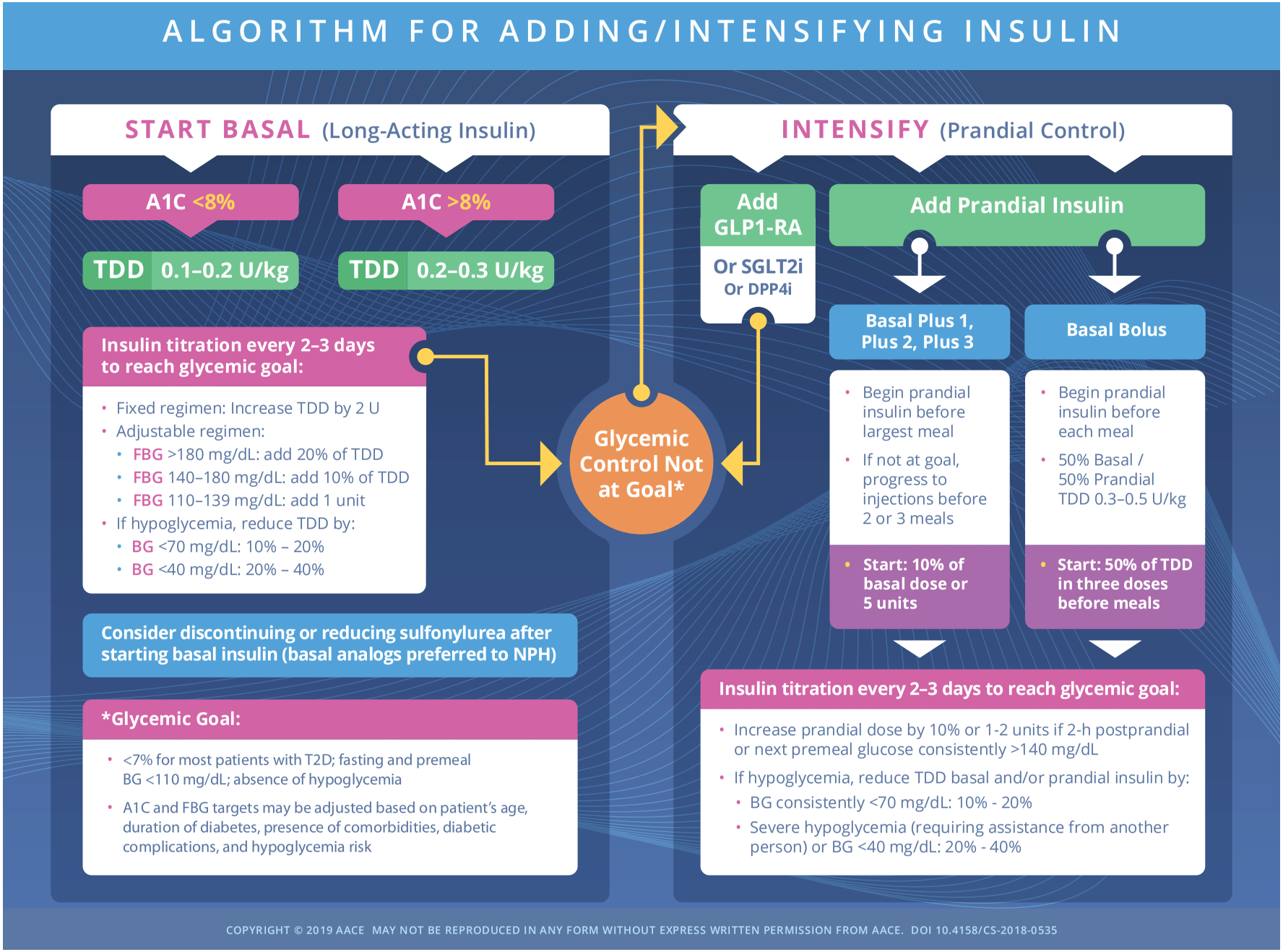


ALGORITHM FOR ADDING/INTENSIFYING INSULIN



PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m^2	Exenatide Not Indicated CrCl <30 Possible Benefit of Liraglutide	Not Indicated for eGFR <45 mL/min/1.73 m^2 Genital Mycotic Infections Possible CKD Benefit	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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Correction

Correction to Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2019 Executive Summary

In the January 2019 issue of *Endocrine Practice*, the authors of the Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2019 Executive Summary (*Endocr Pract*. 2019;25:69-100. doi.org/10.4158/CS-2018-0535) have requested to make the following corrections to the text:

On page 79, the results of the DECLARE-TIMI trial were incorrectly reported to include a reduction in all-cause mortality. The text reads:
"In DECLARE-TIMI (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction), dapagliflozin reduced all-cause mortality and a composite of cardiovascular death and heart failure hospitalizations but did not significantly lower the combined risk of cardiovascular death and nonfatal myocardial infarction and stroke (208)."

The manuscript has been corrected to read:
"In DECLARE-TIMI (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction), dapagliflozin reduced a composite of cardiovascular death and heart failure hospitalizations but did not significantly lower the combined risk of cardiovascular death and nonfatal myocardial infarction and stroke (208)."

Further in the same paragraph, the sentence referring to bone fractures and SGLT2 inhibitors has been removed, as more recent data do not support this association:

"The incidence of bone fractures in patients taking canagliflozin and dapagliflozin was increased in clinical trials (212)."

On page 100, the "Profiles of Antidiabetic Medications" algorithm figure has been changed with the following to reflect more recent evidence:

- the third SGLT2i cell of the Renal/GU row now reads: "Possible CKD Benefit"
- the SGLT2i cell of the Bone row now reads "Neutral."
- Footnotes 4 and 5 were erroneous and have been removed.

The manuscript has been corrected to include these changes and the revised version has replaced the original version online at https://journals.aace.com/doi/abs/10.4158/CS-2018-0535.