CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2016 EXECUTIVE SUMMARY*

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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; **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; **CHD** = coronary heart disease; **CKD** = chronic kidney disease; **CVD** = cardiovascular disease; **DKA** = diabetic ketoacidosis; **DPP-4** = dipeptidyl peptidase 4; **EPA** = eicosapentaenoic acid; **FDA** = Food and Drug Administration; **GLP-1** = glucagon-like peptide 1; **HDL-C** = high-density-lipoprotein cholesterol; **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

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 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 (BP) 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 2016 edition includes a new section on lifestyle therapy as well as discussion of all classes of obesity, antihyperglycemic, lipid-lowering, and antihypertensive medications approved by the U.S. Food and Drug Administration (FDA) through December 2015.

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. **(Endocr Pract. 2016;22:84-113)**

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. 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. An A1C level of ≤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.
3. Glycemic control targets include fasting and postprandial glucose as determined by self-monitoring of blood glucose (SMBG).
4. 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.
5. Minimizing risk of both severe and nonsevere hypoglycemia is a priority. It is a matter of safety, adherence, and cost.
6. Minimizing risk of weight gain is also a priority. It too is a matter of safety, adherence, and cost.
7. The initial acquisition cost of medications is only a part of the total cost of care, which includes monitoring requirements and risks of hypoglyce-

mia and weight gain. Safety and efficacy should be given higher priority than medication cost.

8. 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.
9. Combination therapy is usually required and should involve agents with complementary mechanisms of action.
10. Comprehensive management includes lipid and BP therapies and treatment of related comorbidities.
11. 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 BP 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.
12. The therapeutic regimen should be as simple as possible to optimize adherence.
13. This algorithm includes every FDA-approved class of medications for T2D (as of December 2015).

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] of 25 to 29.9 kg/m^2) or obese (BMI ≥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 studies, lowering caloric intake is the main driver for weight loss (3-6). The clinician or a registered dietitian (or nutritionist) 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 versus 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 (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 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- to 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. 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).

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 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 (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). 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 to a sleep specialist for evaluation and treatment (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). 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. Structured programs should be recommended for patients unable to stop smoking on their own (2).

Obesity

Obesity is a disease with genetic, environmental, and behavioral determinants that confers increased 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, and decrease mechanical strain on the lower extremities (hips and knees) (2,38).

The AACE Obesity Treatment Algorithm emphasizes a complications-centric model as opposed to a BMI-centric approach for the treatment of patients who have obesity or are overweight (see Comprehensive Type 2 Diabetes Management Algorithm—Complications-Centric Model for Care of the Overweight/Obese Patient). The patients who will benefit most from medical and surgical intervention have obesity-related comorbidities that can be classified into 2 general categories: insulin resistance/cardiometabolic disease and biomechanical consequences of excess body weight (40). Clinicians should evaluate and stage patients for each category. The presence and severity of complications, regardless of patient BMI, should guide treatment planning and evaluation (41,42). 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. Patients should be periodically reassessed (ideally every 3 months) 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 comorbidities. For example, weight-loss medications can be used in combination with lifestyle therapy for all patients with a BMI ≥27 kg/m^2 and comorbidities. As of 2015, the FDA has approved 8 drugs as adjuncts to lifestyle therapy in patients with overweight or obesity. Diethylproprion, phendimetrazine, and phentermine are approved for short-term (a few weeks) use, whereas orlistat, phentermine/topiramate extended release (ER), lorcaserin, naltrexone/bupropion, and liraglutide 3 mg may be used 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 (43-60). 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 (2,61).

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 (62).

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 (44,48,49,51,53,60,63). 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 (62).

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 (63-66). In clinical trials, thiazolidinediones (TZDs) prevented future development of diabetes in 60 to 75% of subjects with prediabetes, but this class of drugs has been associated with a number of adverse outcomes (67-69). 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 (59,60,70,71). 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 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 (72). 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 (73,74). 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 (75). The excess mortality occurred only in patients whose A1C remained >7% despite intensive therapy, whereas 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 (76). 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 treatment group), there were no between-group differences in CVD endpoints, cardiovascular death, or overall death during the 5.6-year study period (75,77). 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), whereas mortality risk remained the same between treatment groups (78). Severe hypoglycemia occurs more frequently with intensive glycemic control (72,75,77,79). 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 (80). Cardiovascular autonomic neuropathy may be another useful predictor of cardiovascular risk, and a combination of cardiovascular autonomic neuropathy (81) and symptoms of peripheral neuropathy increase the odds ratio to 4.55 for CVD and mortality (82).

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 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 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 2,000 to 2,500 mg/day. Its effects are quite durable compared to sulfonylureas (SFUs), and it also has robust cardiovascular safety relative to SFUs (83-85). Owing to risk of lactic acido-

sis, the U.S. prescribing information states that metformin is contraindicated if serum creatinine is >1.5 mg/dL in men or >1.4 mg/dL in women, or if creatinine clearance is "abnormal" (86). However, the risk for lactic acidosis in patients on metformin is extremely low (87), and the FDA guidelines prevent many individuals from benefiting from metformin. Newer chronic kidney disease (CKD) guidelines reflect this concern, and some authorities recommend stopping metformin at an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (88,89). AACE recommends metformin not be used in patients with stage 3B, 4, or 5 CKD (2). In up to 16% of users, metformin is responsible for vitamin B12 malabsorption and/or deficiency (90,91), a causal factor in the development of anemia and peripheral neuropathy (92). Vitamin B12 levels should be monitored in all patients taking metformin, and vitamin B12 supplements should be given to affected patients.

- GLP-1 receptor agonists have robust A1C-lowering properties, are usually associated with weight loss and BP reductions (93), and are available in several formulations. The risk of hypoglycemia with GLP-1 receptor agonists is low (94), 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 (95); 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.
- 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 (96). Heart failure–related endpoints appeared to account for most of the observed benefits in this study. 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 eGFR <45 mL/min/1.73 m^2. Dehydration due to increased diuresis may lead to hypotension (97-99). The incidence of bone fractures in patients taking canagliflozin and dapagliflozin was increased in clinical trials (99). Investigations into postmarketing reports of SGLT-2 inhibitor–associated diabetic ketoacidosis (DKA), which has been reported to occur in type 1 diabetes and T2D patients with less than expected hyperglycemia (euglycemic DKA) (98), 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 (100).
- 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 (101,102). 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 (95).
- 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 (84,103,104). Pioglitazone may confer CVD benefits (103,105), whereas rosiglitazone has a neutral effect on CVD risk (106,107). 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 (108-111). A possible association with bladder cancer has largely been refuted (112). 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 (113). Clinical trials have shown CVD benefit in patients with impaired glucose tolerance and diabetes (64,114). 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 (84,115). 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 (85,116). The secretagogue glinides have somewhat lower A1C-lowering effects, have a shorter half-life, and carry a lower risk of hypoglycemia risk than SFUs.

- Colesevelam, which is 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 (117).
- The quick-release dopamine receptor agonist bromocriptine mesylate has slight glucose-lowering properties (118) 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 (119,120).

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 (115) (see Comprehensive Type 2 Diabetes Management Algorithm—Glycemic Control Algorithm). In metformin-intolerant patients, 2 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 2 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 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 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 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 2 oral antihyperglycemic agents who have an A1C >8.0% and/or long-standing T2D are unlikely 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 (121,122). 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 (123,124) 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 (123-127).

Premixed insulins provide less dosing flexibility and have been associated with a higher frequency of hypoglycemic events compared to basal and basal-bolus regimens (128-130). 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, and the incretins also increase endogenous insulin secretion in response to meals, reducing postprandial hyperglycemia (121,131-136). Depending on patient response, basal insulin dose may need to be reduced to avoid hypoglycemia.

Patients whose glycemia remains uncontrolled while receiving basal insulin and those with symptomatic hyperglycemia may require combined basal and mealtime bolus insulin. 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 (137). 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 (138-140). A full basal-bolus program is the most effective insulin regimen and provides greater flexibility for patients with variable mealtimes and meal carbohydrate content (140).

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 (141,142).

It is important to avoid hypoglycemia. Approximately 7 to 15% of insulin-treated patients experience at least one annual episode of hypoglycemia (143), and 1 to 2% have severe hypoglycemia (144,145). 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 (82,146). It has been proposed that hypoglycemia may be a marker for persons at higher risk of death, rather than the proximate cause of death (145). Patients receiving insulin also gain about 1 to 3 kg more weight than those receiving other agents.

BP

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, whereas 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 (147-149). 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) (150). 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% (147).

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).
- 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 (151). 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 (152-157).
- Numerous studies have shown that moderate alcohol intake is associated with a lower incidence of heart disease and cardiovascular mortality (158,159).
- 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 (25,160); 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 (161-165). 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 (162,166-168). 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, 2 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 (169,170).

Lipids

Compared to those without diabetes, patients with T2D have a significantly increased risk of ASCVD (171). 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 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 (172). Recognizing that T2D carries a high lifetime risk for developing ASCVD, risk should be stratified for primary prevention as "high" (patients <40 years of age; ≤1 major risk factor) or "very high" (≥2 major risk factors). Patients with T2D and a prior ASCVD event (i.e., recognized "clinical ASCVD") are also stratified as "very high" or "extreme" risk in this setting for secondary or recurrent events prevention. Risk stratification in this manner can guide management strategies.

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. The presence of these factors justifies classifying these patients as being at either high or very high risk (173,174); as such, AACE recommends LDL-C targets of <100 mg/dL or <70 mg/dL and non-HDL-C targets of <130 mg/dL or <100 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 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 (175). 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 is better in patients after acute coronary syndromes (176).

Many patients with T2D can achieve lipid profile improvements using lifestyle therapy (smoking cessation, physical activity, weight management, and healthy eating) (172). 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 (177-180). 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 (177,179-183). 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) (180,184,185). 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 (186), some residual risk will remain (187). 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 (188). Furthermore, statin intolerance (usually muscle-related adverse effects) can limit the use of intensive statin therapy in some patients (189).

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

Table 1
AACE Lipid Targets for Patients With Type 2 Diabetes

	High-risk patients (T2D but no other major risk and/or age <40 years)	Very-high-risk patients (T2D plus ≥1 major ASCVD risk[a] or established ASCVD)
LDL-C (mg/dL)	<100	<70
Non-HDL-C (mg/dL)	<130	<100
Triglycerides (mg/dL)	<150	<150
TC/HDL-C	<3.5	<3.0
Apo B (mg/dL)	<90	<80
LDL-P (nmol/L)	<1,200	<1,000

Abbreviations: AACE = American Association of Clinical Endocrinologists; Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; LDL-P = low-density-lipoprotein particle; TC = total cholesterol; T2D = type 2 diabetes.
[a] Hypertension, family history of ASCVD, low HDL-C, smoking.

cholesterol stores, upregulates LDL receptors, and lowers apo B, non-HDL-C, LDL-C, and triglycerides (190). 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) (176).

- Monoclonal antibody inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) serine protease, 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 (191-197). 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 (192,193). 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% (198).
- The highly selective BAS colesevelam, by increasing elimination of bile acids, increases hepatic bile acid production, thereby decreasing hepatic cholesterol stores. This leads to an upregulation of LDL receptors and reduces LDL-C, non-HDL-C, apo B, and LDL-P and improves glycemic status. There is a small compensatory increase in de novo cholesterol biosynthesis, which can be suppressed by the addition of statin therapies (199-201).
- 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 (202) and low HDL-C (203). 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 (204). Subgroup analyses and meta-analyses, 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) (204-209).
- 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 (210). It may reduce cardiovascular events through a mechanism other than an increase in HDL-C (211). 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 (212,213); 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 (214). 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 (215).

- 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 (216) and a 22% reduction in CHD in patients with impaired fasting glucose or T2D (217). Among those with triglycerides >150 mg/dL and HDL-C <40 mg/dL, EPA treatment reduced the risk of coronary events by 53% (218). Other studies of lower doses (1 gram) of omega-3 fatty acids (combined EPA and docosahexaenoic acid) in patients with baseline triglycerides <200 mg/dL have not demonstrated cardiovascular benefits (219,220). 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 (221). 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 that require additional cholesterol lowering.

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. Although 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 (222,223).

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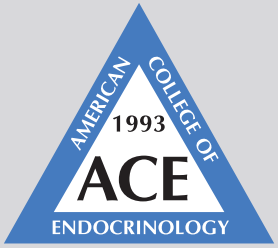

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2016

TASK FORCE

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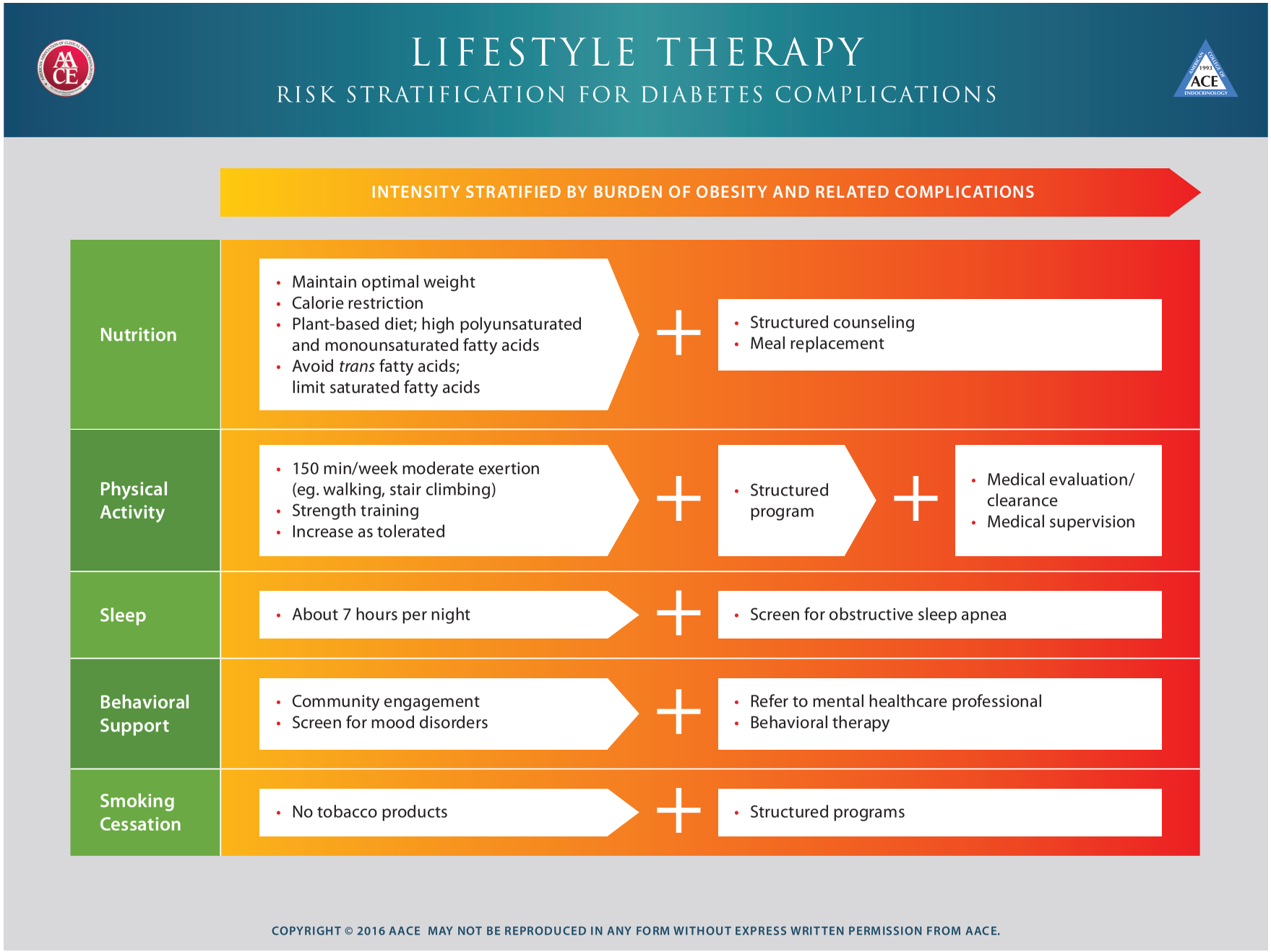
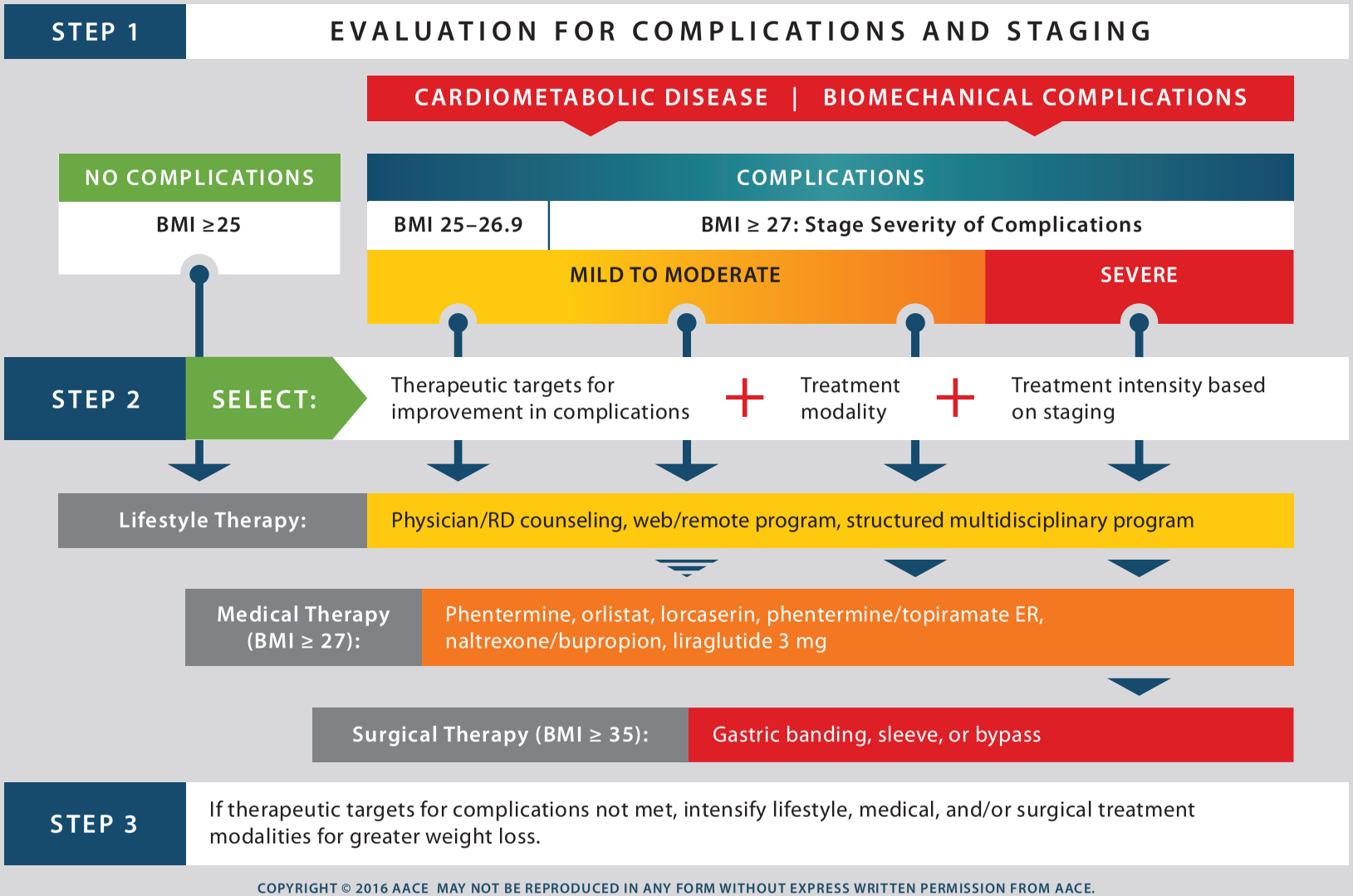
Comprehensive Type 2 Diabetes Algorithm



COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE OVERWEIGHT/OBESE PATIENT



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

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

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO HYPERGLYCEMIA ALGORITHM

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

Intensify Weight Loss Therapies

Low-risk Medications
- Metformin
- Acarbose

Consider with Caution
- TZD
- GLP-1 RA

If glycemia not normalized

LEGEND

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

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

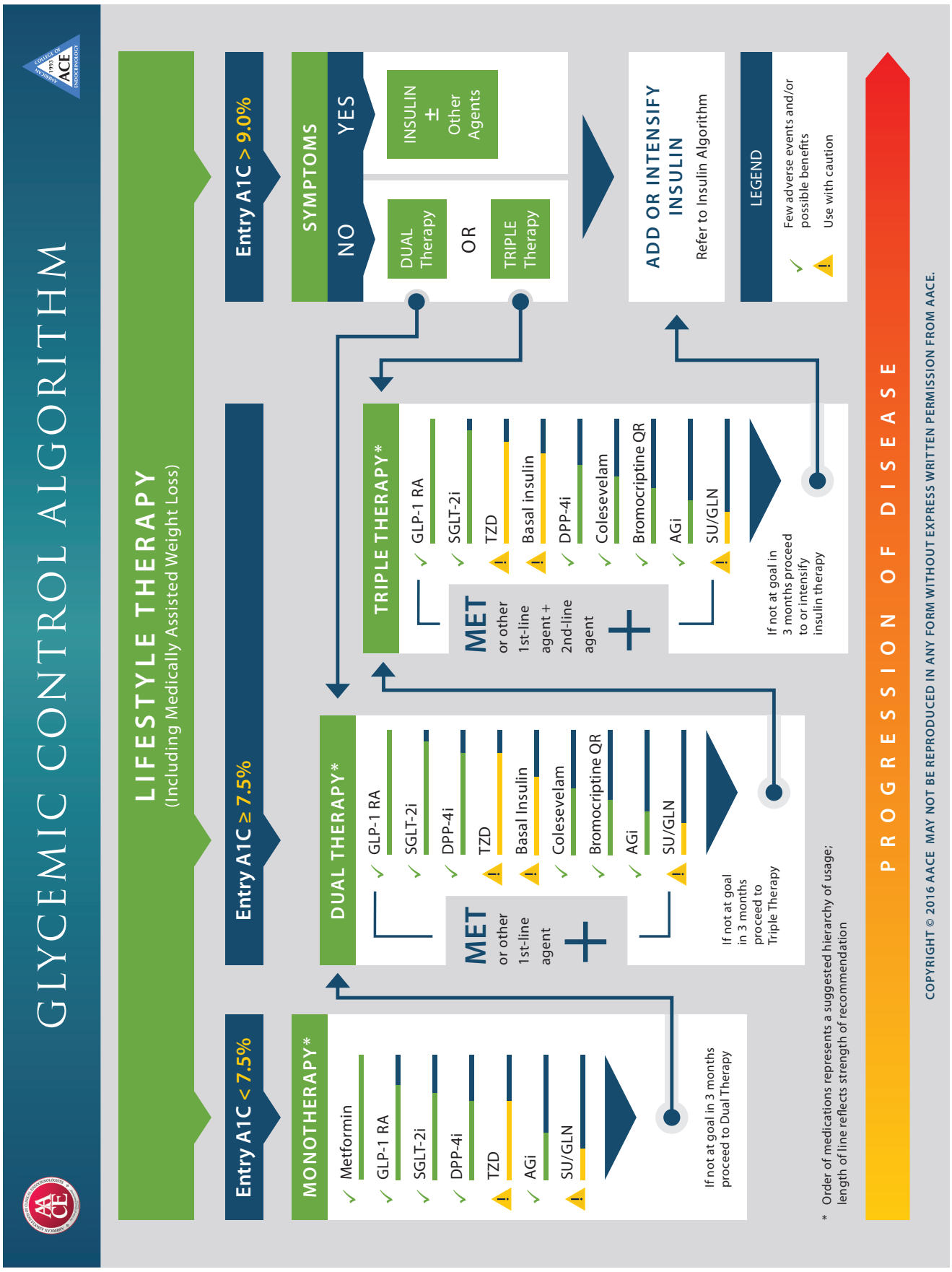
A1C ≤ 6.5%

For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%

For patients with concurrent serious illness and at risk for hypoglycemia

108 T2D Algorithm, Executive Summary, *Endocr Pract.* 2016;22(No. 1)


GLYCEMIC CONTROL ALGORITHM
LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)
Entry A1C < 7.5%
MONOTHERAPY*
Metformin
GLP-1 RA
SGLT-2i
DPP-4i
TZD
AGi
SU/GLN
If not at goal in 3 months proceed to Dual Therapy
Entry A1C ≥ 7.5%
DUAL THERAPY*
GLP-1 RA
SGLT-2i
DPP-4i
TZD
Basal Insulin
Colesevelam
Bromocriptine QR
AGi
SU/GLN
MET or other 1st-line agent
If not at goal in 3 months proceed to Triple Therapy
TRIPLE THERAPY*
GLP-1 RA
SGLT-2i
TZD
Basal insulin
DPP-4i
Colesevelam
Bromocriptine QR
AGi
SU/GLN
MET or other 1st-line agent + 2nd-line agent
If not at goal in 3 months proceed to or intensify insulin therapy
Entry A1C > 9.0%
SYMPTOMS
NO
YES
DUAL Therapy
OR
TRIPLE Therapy
INSULIN ± Other Agents
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm
LEGEND
Few adverse events and/or possible benefits
Use with caution
* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
PROGRESSION OF DISEASE
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ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%

TDD 0.1–0.2 U/kg

A1C > 8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals

- Start: 10% of basal dose or 5 units

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

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: DM but no other major risk and/or age <40	VERY HIGH: DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking) or ASCVD*
	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70
Non-HDL-C (mg/dL)	<130	<100
TG (mg/dL)	<150	<150
TC/HDL-C	<3.5	<3.0
Apo B (mg/dL)	<90	<80
LDL-P (nmol/L)	<1200	<1000

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

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	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 CKD Stage 3B,4,5	Exenatide Not Indicated CrCl < 30	Not Effective with eGFR < 45 / Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	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	Neutral	Possible Benefit	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
CARDIAC ASCVD	Benefit					Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

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

1.	Lifestyle therapy, including medically supervised weight loss, is key to managing type 2 diabetes.
2.	The A1C target must be individualized.
3.	Glycemic control targets include fasting and postprandial glucoses.
4.	The choice of therapies must be individualized on basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.
5.	Minimizing risk of hypoglycemia is a priority.
6.	Minimizing risk of weight gain is a priority.
7.	Initial acquisition cost of medications is only a part of the total cost of care which includes monitoring requirements, risk of hypoglycemia, weight gain, safety, etc.
8.	This algorithm stratifies choice of therapies based on initial A1C.
9.	Combination therapy is usually required and should involve agents with complementary actions.
10.	Comprehensive management includes lipid and blood pressure therapies and related comorbidities.
11.	Therapy must be evaluated frequently until stable (e.g., every 3 months) and then less often.
12.	The therapeutic regimen should be as simple as possible to optimize adherence.
13.	This algorithm includes every FDA-approved class of medications for diabetes.