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Task Force on the New Comprehensive Diabetes Algorithm

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EXECUTIVE SUMMARY

This new algorithm for the comprehensive management of persons with type 2 diabetes mellitus (T2DM) has been developed to provide clinicians with a practical guide that considers the whole patient, the spectrum of risks and complications for the patient, and evidence-based approaches to treatment. In addition to advocating for glycemic control so as to reduce microvascular complications, this document focuses on obesity and prediabetes as the underlying risk factors for diabetes and associated macrovascular complications. It is now clear that the progressive beta-cell defect that drives the deterioration of metabolic control over time begins early and may be present before the diagnosis of diabetes (1).

This document is organized into discrete sections that address the following topics: obesity, prediabetes, management of hyperglycemia through lifestyle modifications, pharmacotherapy and insulin, management of hypertension, management of hyperlipidemia, and other risk-reduction strategies.

Obesity

Obesity is a disease with genetic, environmental, and behavioral determinants that confers increased morbidity and mortality (2). 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 T2DM, given the known therapeutic effects of weight loss to lower glycemia, improve the lipid profile, and reduce blood pressure.

The American Association of Clinical Endocrinologists (AACE) Obesity Treatment Algorithm emphasizes a complications-centric model as opposed to a body mass index (BMI)-centric approach for the treatment of overweight or obese patients. (See Comprehensive Diabetes Management Algorithm-Complications-Centric Model for Care of the Overweight/Obese Patient). The patients who will benefit the most from medical and surgical intervention have obesity-related comorbidities that can be classified into two general categories: insulin resistance/cardiometabolic disease and mechanical consequences of excess body weight (3). 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 (4,5). 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 to determine if targets for improvement have been reached; if not, weight loss therapy should be changed or intensified. Therapeutic lifestyle changes (TLC) can be recommended for all overweight/obese patients, and more intensive options can be prescribed for patients with comorbidities. For example, weight-loss medications can be used in combination with lifestyle modification for all patients with a BMI ≥ 27 kg/m² and comorbidities. In 2012, the

U.S. Food and Drug Administration approved 2 drugs, lorcaserin and phentermine/topiramate extended-release (ER), as adjuncts to lifestyle modification in overweight/ obese patients. In clinical trials, both drugs were associated with placebo-subtracted weight loss (lorcaserin, 3.6%; phentermine/topiramate ER, 9.7%) after 1 year of treatment. Both drugs improved blood pressure, triglycerides, and insulin sensitivity, prevented progression to diabetes during the trial period, and improved glycemic control and lipids in patients with T2DM (6–11). Bariatric surgery should be considered for patients with a BMI ≥ 35 kg/m² and comorbidities, especially if therapeutic goals have not been reached using other modalities.

Prediabetes

Prediabetes reflects failing pancreatic compensation to 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 Diabetes Management Algorithm-Prediabetes Algorithm). Any one of these factors is associated with a 5-fold increase in future T2DM risk (12).

The primary goal of prediabetes management is weight loss. Whether achieved through TLC, pharmacotherapy, surgery, or some combination thereof, weight loss reduces insulin resistance and can effectively prevent progression to diabetes as well as improve lipids and blood pressure. However, weight loss may not directly address the pathogenesis of declining beta-cell function. When indicated, bariatric surgery can also be highly effective in preventing progression to diabetes (12).

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 confer a cardiovascular risk benefit (13,14). 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 (15,16). Glucagon-like peptide 1 (GLP-1) receptor agonists may be equally effective, but data on these drugs are inadequate, particularly regarding safety (17). Therefore, TZDs and GLP-1 receptor agonists are reserved for patients at the greatest risk of developing future diabetes and those failing more conventional therapies.

As with diabetes, prediabetes increases the risk for cardiovascular disease (CVD). Patients with prediabetes should be offered TLC and pharmacotherapy to achieve lipid and blood pressure targets that will reduce CVD risk.

Pharmacotherapy

In patients with T2DM, achieving the glucose target and hemoglobin A1C (A1C) goal requires a nuanced approach that balances age, comorbidities, and hypoglycemia risk (18). The AACE supports an A1C goal of $\leq 6.5\%$ for most patients and a goal of $>6.5\%$ if the lower target cannot be achieved without adverse outcomes. (See Comprehensive Diabetes Management Algorithm-Goals for Glycemic Control). In one large clinical trial, intensive glucose-lowering therapy (A1C target of $<6.0\%$ in patients with baseline A1C $>8.5\%$) was

associated with increased mortality in older and middle-aged patients with longstanding diabetes who were at high risk for or had established CVD. In contrast, a clinical trial with a higher A1C target for intensively treated patients (1.5% lower than the standard treatment group) showed no between-group differences in CVD endpoints, cardiovascular death, or overall death (19,20). Therefore, selection of glucose-lowering agents should consider a patient's therapeutic goal, age or other factors that impose limitations on treatment, and 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.

For patients with recent-onset T2DM or mild hyperglycemia (A1C <7.5%), TLC with monotherapy is recommended. (See Comprehensive Diabetes Management Algorithm-Glycemic Control Algorithm). Metformin has a low risk of hypoglycemia, can promote modest weight loss, produces durable antihyperglycemic effects, and has robust cardiovascular safety; however, it cannot be used in patients with advanced renal impairment (21–23). 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. Acceptable alternatives to metformin include GLP-1 agonists, dipeptidyl-peptidase-4 (DPP-4) inhibitors, and alpha-glucosidase inhibitors (AGIs). TZDs, sulfonylureas (SFUs), and glinides may also be used, but these agents should be used with caution owing to the potential for weight gain, hypoglycemia, or other risks.

Patients who present with an A1C >7.5% or who do not reach their target A1C with metformin should be started on a second agent (24). (See Comprehensive Diabetes Management Algorithm-Glycemic Control Algorithm). In metformin-intolerant patients, 2 drugs with complementary mechanisms of action from other classes should be considered.

- GLP-1 agonists have robust A1C-lowering properties, promote weight loss (25), and are available in several formulations. (See Comprehensive Diabetes Management Algorithm-Profiles of Antidiabetic Medications). The risk of hypoglycemia with GLP-1 agonists is low (26), and they reduce fluctuations in both fasting and postprandial glucose levels.
- DPP-4 inhibitors have modest A1C-lowering properties, are weight-neutral, and they are available in combination tablets with metformin. The risk of hypoglycemia with DPP-4 inhibitors is low (26–28). Most of the DPP-4 inhibitors are excreted by the kidneys except for linagliptin; therefore, dose restrictions may be advisable for some patients.
- AGIs have modest A1C-lowering effects and low risk for hypoglycemia (29). Clinical trials have shown CVD benefit in patients with impaired glucose tolerance and diabetes (14,30). Side effects (e.g., bloating, flatulence, diarrhea) have limited their use in the United States.
- The TZD pioglitazone has relatively potent A1C-lowering properties, a low risk of hypoglycemia, possible CVD benefit (31), and durable glycemic effects (22). Side effects that have limited its use include increased bone fracture risk, elevated risk

for chronic edema or heart failure, and a possible association with bladder cancer (32).

- The insulin-secretagogue SFUs have relatively potent A1C-lowering effects but lack durability and are associated with modest weight gain and hypoglycemia. SFUs have the highest risk of serious hypoglycemia of any noninsulin therapy (22,24). By comparison, the secretagogue glinides have reduced A1C-lowering effects and hypoglycemia risk (33).
- Colesevelam, which is a bile acid sequestrant (BAS), lowers glucose modestly, does not cause hypoglycemia, and decreases low-density lipoprotein cholesterol (LDL-C). Gastrointestinal intolerance limits its use, and it can increase triglyceride levels (34).
- The dopamine receptor agonist bromocriptine mesylate has slight glucose-lowering properties (35) 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 (36).
- The sodium-glucose cotransporter-2 inhibitor canagliflozin has been tested as a monotherapy and in combination with metformin and other agents. In clinical trials, canagliflozin had a modest A1C-lowering effect and promoted weight loss and reduction of systolic blood pressure, but it also slightly increased LDL-C levels. This medication was only recently approved, so there is little experience (as of this writing) with its use (37).

The addition of a third agent may safely enhance treatment efficacy to a modest degree, possibly benefitting patients with A1C <8.0%. (See Comprehensive Diabetes Management Algorithm-Glycemic Control Algorithm). Patients with A1C >9.0% would derive greater benefit from the addition of insulin. Progression of therapy should be accompanied by intensified TLC and anti-obesity treatment.

Certain patient populations are at higher risk for adverse treatment-related outcomes, underscoring the need for individualized therapy. Many antihyperglycemic agents (e.g., metformin, GLP-1 agonists, DPP-4 inhibitors, AGIs, SFUs) have limitations in patients with impaired renal function and may require dose adjustments or special precautions. In general, diabetes therapy does not require modification for mild to moderate liver disease, but the risk of hypoglycemia increases in severe cases.

Insulin

Many factors come into play when deciding at what point to start insulin therapy and what type of insulin to use. (See Comprehensive 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 and general well-being, risk of hypoglycemia, and overall health status. Patients with A1C >8.0%, patients on two or more oral antidiabetic drugs (OADs) or on GLP-1 therapy, and patients with longstanding T2DM are unlikely to reach their target A1C with additional

OADs. In such cases, a single daily dose of basal insulin should be added to the OAD regimen. The dosage should be adjusted at regular and fairly short intervals to achieve the glucose target while avoiding hypoglycemia. Recent studies (38,39) have shown that titration is equally effective, whether it is guided by the healthcare provider or a patient who has been instructed in self-monitoring of blood glucose (SMBG).

Basal insulin analogues 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 equally effective in reducing A1C in clinical trials, insulin analogs caused significantly less hypoglycemia (40–44).

Premixed insulins are popular with patients, but they provide less dosing flexibility and have been associated with a higher frequency of hypoglycemic events compared to basal and basal-bolus regimens (45–47). Nevertheless, there are some patients for whom a simpler regimen is a reasonable compromise.

Patients who fail to achieve glucose control with basal or premixed insulin and those with symptomatic hyperglycemia and A1C levels >10% often achieve better glycemic control with combined basal and mealtime bolus insulin. A full basal-bolus program is most effective and provides greater flexibility for patients with variable mealtimes and meal carbohydrate content (48). A simpler approach is to cover the larger meal with a prandial injection and then add additional mealtime injections 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 (38,39,48).

It is important to avoid hypoglycemia. Approximately 7 to 15% of insulin-treated patients experience at least one annual episode of hypoglycemia (49), and 1 to 2% have severe hypoglycemia (50,51). Several large randomized trials found that T2DM patients with a history of one or more severe hypoglycemic events have an approximately 2- to 4-fold higher death rate (52,53). It has been proposed that hypoglycemia may be a marker for persons at higher risk of death, rather than the proximate cause of death (51). Patients receiving insulin also gain about 1 to 3 kg more weight than those receiving other agents.

Pramlintide is indicated for use with basal-bolus insulin regimens; the incretin therapies have been studied with basal insulin. 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 (54,55). Incretins also increase endogenous insulin secretion, decrease basal and postprandial glucose and, when added to basal insulin therapy, may minimize weight gain and hypoglycemia associated with basal-bolus insulin (8,56–60).

Blood Pressure

Elevated blood pressure in patients with T2DM is associated with an increased risk of cardiovascular events. (See Comprehensive Diabetes Management Algorithm-CVD Risk Factor Modifications Algorithm). AACE recommend a blood pressure target of approximately 130/80 mm Hg based on results of the Action to Control Cardiovascular Risk

in Diabetes Blood Pressure (ACCORD BP) trial (61). The ACCORD BP trial demonstrated no significant differences in primary cardiovascular outcomes or all-cause mortality between standard therapy (which achieved a mean blood pressure of 133/71 mm Hg) and intensive therapy (mean blood pressure 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) (61). A meta-analysis of antihypertensive therapy in patients with T2DM or impaired fasting glucose demonstrated similar findings. Systolic blood pressure ≥ 135 mm Hg was associated with decreased nephropathy and a significant reduction in all-cause mortality compared with systolic blood pressure ≥ 140 mm Hg. Below 130 mm Hg, stroke and nephropathy, but not cardiac events, declined further, but SAEs increased by 40% (62). Given these findings, the mean blood pressure achieved by standard therapy in the ACCORD BP trial (approximately 130/80 mm Hg) appears to be a prudent goal for most patients; those at high risk for stroke may benefit from a lower target, however (62–64).

Therapeutic lifestyle modification can help T2DM patients reach their blood pressure goal:

- Weight loss can improve blood pressure in patients with T2DM. Compared with standard intervention, the results of the Action for HEAlth in Diabetes (Look AHEAD) trial found that significant weight loss is associated with significant reduction in blood pressure, without the need for increased use of antihypertensive medications (65).
- Sodium restriction is recommended for all patients with hypertension. Clinical trials indicate that potassium chloride supplementation is associated with blood pressure reduction in people without diabetes (66). 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 T2DM (67–72).
- Numerous studies have shown that moderate alcohol intake is associated with a lower incidence of heart disease and cardiovascular mortality (73,74).
- The effect of exercise in lowering blood pressure in people without diabetes has been well-established. In hypertensive patients with T2DM however, exercise appears to have a more modest effect (75,76); still, it is reasonable to recommend a regimen of moderately intense physical activity in this population.

Most patients with T2DM and hypertension will require medications to achieve their blood pressure goal. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers (CCBs), and diuretics are favored choices for first-line treatment. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (77) recommends starting with a thiazide diuretic, based on the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT found no differences between chlorthalidone and amlodipine or lisinopril with respect to coronary heart disease (CHD) mortality, nonfatal myocardial infarction (MI), all-cause mortality, or end-stage renal disease, but chlorthalidone was superior in preventing heart

failure (78). However, many other trials support the recommendation that ACEIs/ARBs be considered as first-line treatment (79–82).

Selection of an antihypertensive regimen for patients with T2DM must also consider special circumstances. Patients with heart failure could benefit from beta blockers, those with proteinuria from ACEIs or ARBs, those with prostatism from alpha blockers, and those with coronary artery disease (CAD) from beta blockers or CCBs. In patients with blood pressure >150/100 mm Hg, 2 agents should be given initially because it is unlikely any single agent would be sufficient to achieve the blood pressure target. An ARB/ACEI combination more than doubles the risk of renal failure and hyperkalemia and is therefore not recommended.

Lipids

Compared to nondiabetics, patients with T2DM have a significantly increased risk of CVD (83). To reduce the significant risk of CHD in T2DM patients, early, intensive management of dyslipidemia is warranted. (See Comprehensive Diabetes Management Algorithm-CVD Risk Factor Modifications Algorithm).

The classic major risk factors that modify the LDL-C goal for all individuals include cigarette smoking, hypertension (blood pressure $\geq 140/90$ 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 (84). Recognizing that T2DM carries a high lifetime risk for developing CHD, risk should be stratified as “moderate” (patients <40 years of age; no major risk factors) or “high” (one or more major risk factors). A potential third category of “very high” risk (patients with T2DM and established CVD) could also be considered. Risk stratification in this manner can guide management strategies.

In addition to hyperglycemia, the majority of T2DM patients have a syndrome of “insulin resistance,” which is characterized by a number of CVD risk factors, including hypertension, hypertriglyceridemia, low HDL-C, elevated apolipoprotein (apo) B and small, dense LDL, and a pro-coagulant and proinflammatory milieu. All of these additional factors justify classifying these patients as being at high risk (85,86). The lipid targets recommended by the AACE for patients with T2DM are shown in Table 1.

Many patients with T2DM can achieve lipid profile improvements using TLC (smoking cessation, physical activity, weight management, and healthy eating) (84). However, most patients will require pharmacotherapy to reach their target lipid levels and reduce their cardiovascular risk.

Numerous studies have demonstrated that statins significantly reduce the risk of cardiovascular events and death in patients with T2DM, making these drugs the first-line therapy (87,88). However, considerable residual risk persists even after aggressive statin monotherapy, especially in patients with clinical atherosclerotic disease or CVD risk factors (88–90). Intensification of statin therapy (e.g., through use of higher dose or higher potency agents) can further reduce LDL-C and the risk of cardiovascular events (91), although residual risk will remain (92). 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 (93). Furthermore, side effects (e.g., myositis/myopathy) can limit the use of intensive statin therapy in some patients (94).

- Other lipid-modifying agents must often be utilized in combination with statins when therapeutic levels of LDL-C, non-HDL-C, apo B, or LDL-P have not been reached. Drugs such as ezetimibe, BASs, fibrates, niacin, and fish oil-derived prescription-grade omega-3 fatty acids have lower efficacy for lipid modification and CVD risk reduction compared with statins, but they may have potential additive effects.
- Ezetimibe decreases hepatic cholesterol stores, upregulates LDL receptors, and lowers apo B, non-HDL-C, LDL-C, and triglycerides (95).
- The BAS colesevelam reduces LDL-C and LDL-P and improves glycemic status, but it can increase triglycerides when statins are not utilized (95–98).
- Fibrates are best known for lowering triglycerides, but they also have been shown to have inconsistent primary outcome cardiovascular benefits that may be explained by differences in the targeted trial populations (99–102). The use of fibrates together with statins in the ACCORD study (103) showed no benefit.
- Niacin lowers apo B, LDL-C, and triglycerides, and raises HDL-C. Niacin is the most powerful lipid-modifying agent available for raising HDL-C (104), but it may reduce cardiovascular events through a mechanism other than an increase in HDL-C (105). 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 (106).
- 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 eicosapentaenoic acid (EPA) added to a statin regimen was associated with a 22% reduction in the risk of CHD in patients with impaired fasting glucose or T2DM (107–109).

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

BAS	bile acid sequestrant
BMI	body mass index
CHD	coronary heart disease
CVD	cardiovascular disease
DPP	dipeptidyl-peptidase-4
GLP-1	glucagon-like peptide 1
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
LDL-P	low-density lipoprotein particle
OAD	oral antidiabetic drugs
SFU	sulfonylurea
T2DM	type 2 diabetes mellitus
TLC	therapeutic lifestyle changes
TZD	thiazolidinedione

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Table 1

AACE Lipid Targets for Patients With Type 2 Diabetes

	Moderate-Risk Patients	High-Risk Patients
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; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; TC = total cholesterol.