AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS' COMPREHENSIVE DIABETES MANAGEMENT ALGORITHM 2013 CONSENSUS STATEMENT

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This document represents the official position of the American Association of Clinical Endocrinologists. 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. Guidelines are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

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Abbreviations:
A1C = hemoglobin A1C; **AACE** = American Association of Clinical Endocrinologists; **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ACCORD BP** = Action to Control Cardiovascular Risk in Diabetes Blood Pressure; **ACEI** = angiotensin-converting enzyme inhibitor; **ACS** = acute coronary syndrome; **AGI** = alpha-glucosidase inhibitor; **ALLHAT** = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **apo** = apolipoprotein; **ARB** = angiotensin II receptor blocker; **ATP** = adenosine triphosphate; **BAS** = bile acid sequestrant; **BMI** = body mass index; **CAD** = coronary artery disease; **CCB** = calcium channel blocker; **CDP** = Coronary Drug Project; **CHD** = coronary heart disease; **CKD** = chronic kidney disease; **CrCl** = creatinine clearance; **CVD** = cardiovascular disease; **DASH** = Dietary Approaches to Stop Hypertension; **DHA** = docosahexaenoic acid; **DPP** = dipeptidyl-peptidase-4; **eGFR** = estimated glomerular filtration rate; **EPA** = eicosapentaenoic acid; **ER** = extended-release; **ESRD** = end-stage renal disease; **FDA** = Food and Drug Administration; **GLP-1** = glucagon-like peptide 1; **HDL-C** = high-density lipoprotein cholesterol; **IDL** = intermediate-density lipoprotein; **ILI** = intensive lifestyle; **JNC** = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; **LDL-C** = low-density lipoprotein cholesterol; **LDL-P** = low-density lipoprotein particle; **MI** = myocardial infarction; **NHLBI** = National Heart, Lung, and Blood Institute; **NMR** = nuclear magnetic resonance; **NPH** = neutral protamine Hagedorn; **OAD** = oral antidiabetic drug; **RAS** = renin-angiotensin system; **RR** = relative risk; **SAE** = serious adverse events; **SFU** = sulfonylurea; **SGLT2** = sodium-glucose cotransporter 2; **SMBG** = self-monitoring of blood glucose; **T2DM** = type 2 diabetes mellitus; **TLC** = therapeutic lifestyle changes; **TZD** = thiazolidinedione; **VLDL** = very low-density lipoprotein

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/m^2 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/m^2 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 ≤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

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