ABSTRACT

Type 2 diabetes mellitus and obesity are associated with increased cardiovascular risk. While lifestyle interventions such as medical nutrition therapy and appropriately prescribed physical activity remain cornerstones of disease prevention and treatment, most patients with type 2 diabetes will eventually require pharmacotherapy for glycemic control. Fortunately, many of these patients are able to achieve desired glycemic targets with the use of currently available antihyperglycemic agents. Both not-for-profit disease-specific organizations and healthcare specialty societies have provided guidance about the appropriate selection of these therapies. Type 2 diabetes treatment guidelines and algorithms have been developed, taking into account a combination of evidence-based information and expert opinions, with various groups offering diverse glucose goals and approaches to hyperglycemia management. Virtually all recognize that type 2 diabetes is a multifaceted disease, necessitating an integrated yet individualized approach to patient care.

KEYWORDS: Algorithm; Hemoglobin A1c; Treatment guidelines; Type 2 diabetes mellitus

FOCAL POINTS OF ANTIHYPERGLYCEMIC TREATMENT GUIDELINES FOR TYPE 2 DIABETES

A number of medical organizations have developed guidelines and algorithms for the treatment of patients with type 2 diabetes. Most recent recommendations are derived from evidence-based information and expert opinion. They include the 2007 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Diabetes Clinical Practice Guidelines,5 the 2007 Texas Diabetes Council Glycemic Control Algorithm,6 the 2008 AACE/ACE Road Map,7 the 2009 AACE/ACE treatment algorithm,8 the 2008 Canadian Diabetes Association (CDA) Clinical Practice Recommendations for T2DM,9 the 2010 American Diabetes Association (ADA) Standards of Medical Care,10 and the 2009 ADA/European Association for the Study of Diabetes (EASD) writing group consensus statement and algorithm on the medical management of hyperglycemia in type 2 diabetes.11
To determine whether glycemic control was improving in patients with diabetes, 3 phases of the National Health and Nutrition Examination Survey (NHANES), conducted between 1999 and 2004, were reviewed for trends in hemoglobin A1c (HbA1c) concentrations. Data showed that mean HbA1c for the entire NHANES population cohort declined from 7.82% in 1999 to 7.18% in 2004, at which time 55.7% of study patients achieved HbA1c <7.0%, the goal recommended for most diabetes patients by the ADA. These findings suggest that the care of patients with diabetes, including those with type 2 diabetes, has improved but further improvement is possible.

The AACE/ACE guidelines that were published in 2007 and the ADA Standards of Medical Care updated in 2010 (Table 1) emphasize the importance of educating patients on the potential short- and long-term complications of type 2 diabetes, teaching self-management skills, psychosocial adjustments, and lifestyle interventions (Figure 1). As even modest weight loss has been shown to reduce insulin resistance, the AACE/ACE and ADA guidelines specifically address medical nutrition therapy and appropriately prescribed physical activity. A healthy nutritional diet is considered an essential component of any comprehensive diabetes program. Diets should be individualized, based on weight, lipid profiles, medications, and lifestyle. Total carbohydrates should represent 45% to 65% of daily energy intake. Fiber intake of up to 50 g/day is encouraged, and fat intake should be limited to 30% of total calories. At least 150 min/wk of physical activity is encouraged.

The ADA Standards of Medical Care recommend weight loss for overweight or obese individuals who have or are at risk for diabetes and indicate that “for weight loss, either low-carbohydrate or low-fat, calorie-restricted diets may be effective in the short-term (up to 1 year).” Patients on low-carbohydrate diets should have their lipid profiles, renal function, and protein intake (in those with nephropathy) monitored and their antihyperglycemic therapy adjusted as needed. Saturated fat intake should be <7% of total calories; intake of trans fat should be minimized. Monitoring carbohydrate intake is essential to achieving glycemic control. Similar to the AACE/ACE guidelines, the ADA recommends ≥150 min/wk of moderate-intensity aerobic physical activity performed at 50% to 70% of maximum heart rate, plus resistance training ≥3 times/wk in the absence of contraindications.

### Reinforcing the Need for Individualized Treatment Goals

Guidelines for treating patients with type 2 diabetes emphasize the need for individualized treatment targets to facilitate attaining and maintaining glycemic goals while minimizing the potential for adverse events. The ADA guidelines consider several factors in goal setting, including the patient’s age, time since diagnosis, presence of comorbidities, and pregnancy status. This is in agreement with the scientific statement by the ADA, the American College of Cardiology (ACC) Foundation, and the American Heart Association (AHA) regarding intensive glycemic control and the prevention of cardiovascular events based on findings from recent large-scale type 2 diabetes trials (Table 2). The ADA/ACC/AHA scientific statement indicates that the data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release and Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial (VADT) do not warrant major adjustment to already established HbA1c targets, but rather emphasize the need for clarification of appropriate goals in certain populations. The scientific statement agreed that HbA1c should be <7.0% in most nonpregnant adults, but also recognized that HbA1c targets should be less stringent in certain individuals, including those prone to hypoglycemia, advanced vascular complications, and/or extensive comorbidities, and those individuals with long-standing diabetes in whom lower HbA1c goals have been difficult to attain despite diabetes self-management education, glucose monitoring that is appropriate for the patient, and the use of

### Table 1 Comparison of treatment targets for the management of patients with type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Target Treatment Goals</th>
<th>AACE/ACE 2007</th>
<th>ADA 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c ≤6.5%</td>
<td>Fasting plasma glucose: &lt;110 mg/dL</td>
<td>&lt;7.0% Preprandial capillary plasma glucose: 70-130 mg/dL</td>
</tr>
<tr>
<td>Fasting glucose*</td>
<td>2-hr postprandial glucose: &lt;140 mg/dL</td>
<td>Peak postprandial capillary plasma glucose: &lt;180 mg/dL</td>
</tr>
<tr>
<td>Postprandial glucose*</td>
<td>&lt;130/80 mm Hg</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>LDL-C &lt;100 mg/dL (&lt;70 mg/dl for patients with diabetes and coronary artery disease)</td>
<td>LDL-C &lt;100 mg/dL</td>
</tr>
<tr>
<td>Cholesterol (lipids)†</td>
<td>HDL-C &gt;40 mg/dl in men, &gt;50 mg/dl in women</td>
<td>HDL-C &gt;40 mg/dl in men, &gt;50 mg/dl in women</td>
</tr>
<tr>
<td></td>
<td>Triglycerides &lt;150 mg/dL</td>
<td>Triglycerides &lt;150 mg/dL</td>
</tr>
</tbody>
</table>

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; ADA = American Diabetes Association; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

*For glucose, 1 mg/dL = 0.0555 mmol/L.
†For cholesterol, 1 mg/dL = 0.0259 mmol/L; for triglycerides, 1 mg/dL = 0.0113 mmol/L.
‡In individuals with overt cardiovascular disease, a lower LDL-C goal of <70 mg/dl (1.8 mmol/L), using a high-dose of a statin, is an option.

Adapted from *Endocr Pract.* and *Diabetes Care.*
multiple glucose-lowering agents in effective dosages including insulin. In contrast, even lower HbA1c goals may be targeted in subjects with a short duration of diabetes, long-life expectancy, no significant CVD, and no significant hypoglycemia or other adverse effects of treatment.16

**Reaching HbA1c Goals with Treatment Algorithms**

To help guide healthcare professionals, the ADA/EASD writing group recently provided an updated consensus algorithm (divided into 2 tiers, consisting of what they term well-validated core therapies and less well-validated therapies) for the management of hyperglycemia in patients with type 2 diabetes (Figure 2).11 The authors noted that type 2 diabetes is a progressive disease that will likely require combinations of antihyperglycemic medications over time.11

The AACE/ACE Road Map and the 2009 AACE/ACE treatment algorithm are also useful diabetes management tools.7,8 These resources stratify recommendations by baseline HbA1c and provide separate algorithms for treatment-naive and previously treated patients. They include all US

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**Table 2** Individualized approach to therapy based on analyses of cardiovascular outcomes studies in diabetes mellitus

<table>
<thead>
<tr>
<th>Target HbA1c Goal</th>
<th>Patient Types*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt;7.0%</td>
<td>General nonpregnant adult population for the delay or prevention of</td>
</tr>
<tr>
<td></td>
<td>- Microvascular disease</td>
</tr>
<tr>
<td></td>
<td>- Macrovascular disease</td>
</tr>
<tr>
<td>Lower than the general goal of HbA1c &lt;7.0% (if possible</td>
<td>Patients with</td>
</tr>
<tr>
<td>without significant hypoglycemia or other treatment-related</td>
<td>- Short duration of diabetes</td>
</tr>
<tr>
<td>adverse events)</td>
<td>- Long-life expectancy</td>
</tr>
<tr>
<td></td>
<td>- No significant cardiovascular disease</td>
</tr>
<tr>
<td>Less stringent than the general goal of HbA1c &lt;7.0%</td>
<td>Patients with</td>
</tr>
<tr>
<td></td>
<td>- History of severe hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>- Limited life expectancy</td>
</tr>
<tr>
<td></td>
<td>- Advanced micro- or macrovascular complications</td>
</tr>
<tr>
<td></td>
<td>- Extensive comorbidities</td>
</tr>
<tr>
<td></td>
<td>- Long-standing diabetes in whom the general goal has been difficult</td>
</tr>
<tr>
<td></td>
<td>- attain despite diabetes self-management education, appropriate glucose</td>
</tr>
<tr>
<td></td>
<td>- monitoring, and effective doses of multiple glucose-lowering agents</td>
</tr>
<tr>
<td></td>
<td>- including insulin</td>
</tr>
</tbody>
</table>

HbA1c = hemoglobin A1c.

*Based on analyses of data from clinical trials in diabetes as presented in a position statement of the American Diabetes Association (ADA), American College of Cardiology (ACC) Foundation, and the American Heart Association (AHA).

Reprinted with permission from *Diabetes Care.*16
Food and Drug Administration (FDA)–approved antihyperglycemic medications and suggest preferred and alternative treatments. In these guidelines, combination therapy can be an initial treatment option for those whose HbA1c is unlikely to be reduced to goal with a single antihyperglycemic agent.7,8

There has recently been a statement by an AACE/ACE consensus panel on type 2 diabetes that issued an algorithm that stratifies recommendations by baseline HbA1c and includes all of the currently available US FDA approved antihyperglycemic therapies. Choices of therapies were prioritized according to efficacy, safety, simplicity, anticipated degree of patient adherence, and cost. However, minimizing risk and severity of hypoglycemia and risk and magnitude of weight gain were also priorities. Both of the AACE/ACE algorithms recommend the option of initial oral combination therapy with classes of medications that have complementary mechanisms of action when monotherapy would be unlikely to achieve glycemic targets.8 In October 2007, the Texas Diabetes Council introduced their current update that set an HbA1c goal of ≤6.0% “if possible without significant hypoglycemia,” with caveats for individualized treatment similar to the AACE/ACE and ADA.6 Dual therapy is mentioned as initial treatment in the Texas algorithm, and physicians are advised to consider monotherapy for their patients when HbA1c concentrations reach <6.5%.

The CDA published their treatment recommendations and algorithm in 2008.9 Similar to the ADA, the CDA suggests an individualized HbA1c goal of ≤7.0%. Physicians may consider lower goals but must balance the potential benefits against the risk of hypoglycemia. The description and recommendations for aerobic exercise (≥150 min/wk) and resistance exercise (3 times per week) are similar to those of the ADA. Helpful additions by the CDA include caveats for patients who need to be careful about initiating physical activity (e.g., those with established CVD, severe autonomic and/or peripheral neuropathy, and preproliferative or proliferative retinopathy) and descriptions of particular categories of exercise. The CDA guidelines provide an overview of the advantages and disadvantages of the various classes of antihyperglycemic agents available at the time of publication, with recommendations as to when certain therapies might be added to baseline treatment.9

In 2007, the American College of Physicians (ACP) published a guidance statement entitled, “Glycemic Control and Type 2 Diabetes Mellitus: the Optimal Hemoglobin A1c Targets.”20 The ACP has launched a fairly comprehensive diabetes initiative with recommendations and resources for healthcare professionals and their patients.21

Unmet Patient Needs with Conventional Antidiabetes Therapies

A number of currently available antihyperglycemic therapies are associated with unmet needs, including the potential for weight gain, increased risk of hypoglycemia, and the inability to optimally control postprandial hyperglycemia.22 Wide glycemic fluctuations may persist despite treatment, and many therapies fail to maintain long-term glycemic control.
The pathophysiologic components of type 2 diabetes include insulin resistance, at least a relative impairment of insulin secretion, inappropriate glucagon secretion, and a decreased incretin effect. Newer treatments for type 2 diabetes, including those that target the incretin system (incretin-based therapies), have improved glycemia while providing weight maintenance or loss. These agents are associated with a low risk for hypoglycemia and edema, reduced fasting and postprandial hyperglycemia, and glycemic fluctuations. If the incretin effects seen in animal studies are reproduced in humans, these therapies may have the potential to better maintain long-term glycemic control.

GUIDELINES AND ALGORITHMS FOR PREDIABETES

Individuals with glucose concentrations above normal but not high enough to be diagnostic for diabetes are said to have prediabetes. Individuals with prediabetes have impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The ADA has defined IFG as a fasting plasma glucose (FPG) level of 100 mg/dL to 125 mg/dL (1 mg/dL = 0.05551 mmol/L), while IGT is defined as a plasma glucose concentration of 140 mg/dL to 199 mg/dL 2 hours after ingestion of 75 g of glucose. These individuals, who often are overweight or obese and have hypertension and/or dyslipidemia, are at increased risk for developing diabetes. Recently, an international expert committee assembled by the ADA, the International Diabetes Federation (IDF), and the EASD recommended the use of the HbA1c assay to diagnose diabetes. The ADA endorsed in principle the use of HbA1c testing as an option to diagnose diabetes and indicated that the ADA will establish a task force to explore the implications of the report, including whether HbA1c can also be used as an option to identify people with prediabetes. With its 2010 Standards of Medical Care, the ADA now supports the use of HbA1c as an option for diagnosing diabetes and prediabetes. An HbA1c of ≥6.5% is diagnostic for diabetes, while an HbA1c of 5.7% to 6.4% identifies patients at risk for diabetes (prediabetes).

The Agency for Healthcare Research and Quality (AHRQ) analyzed data from a number of clinical trials and found that IFG and IGT are robust risk factors for the development of diabetes. Pooled estimates for the unadjusted, annualized relative risk (RR) for diabetes calculated through meta-analysis were 4.70 (P = 0.0003) for IFG, 6.02 (P <0.0001) for IGT, and 12.21 (P = 0.0054) for IFG and IGT combined. The 2010 Standards of Medical Care indicate that an HbA1c cutpoint of 5.7% is less sensitive but more specific than an FPG of 100 mg/dL and has a higher predictive value to identify people at risk for diabetes.

Based on the natural history of IFG and IGT, over a 3- to 5-year period, approximately 25% of individuals will progress to type 2 diabetes, while 50% will remain hyperglycemic and another 25% will revert to a normal glycemic state. Over a longer follow-up period, the majority of individuals with IFG or IGT are likely to eventually develop type 2 diabetes.

Studies have shown that lifestyle measures and/or pharmacotherapy can delay or prevent the progression from prediabetes to overt diabetes. In such studies intensive lifestyle interventions have provided substantial (~60%) reduction in the risk of developing diabetes, along with a modest reduction in CVD risk factors, and a favorable safety profile. No medications are currently approved by the FDA for the treatment of prediabetes. However, several studies have demonstrated the ability of pharmacologic interventions to delay or prevent the progression to type 2 diabetes. The Diabetes Prevention Program Study, metformin reduced the incidence of diabetes by 31% compared with placebo, with a greater benefit seen in younger and more obese subjects. Acarbose therapy compared with placebo was associated with a 25% RR reduction for the development of type 2 diabetes in the Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial. In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial, rosiglitazone reduced type 2 diabetes development compared with placebo by 60%. A trial with orlistat has also demonstrated prevention of the development of type 2 diabetes. In the Actos Now Study for the Prevention of Diabetes (ACT NOW) over a mean follow-up of 2.6 years, pioglitazone decreased the conversion rate of IGT to type 2 diabetes by 81% (P <0.00001) compared with placebo.

The IDF proposed a 3-part plan to prevent the progression to type 2 diabetes from prediabetes by (1) identifying high-risk patients through screening; (2) measuring risk in appropriate patients through the assessment of risk factors, including elevated blood pressure and lipid levels, a family history of diabetes and/or CVD, and increased waist circumference; and then (3) intervening to prevent the development of type 2 diabetes through medical nutrition therapy and appropriately prescribed physical activity. If desired weight loss has not been achieved or glycemic levels have not improved, metformin, 250 to 850 mg bid, could be considered for diabetes prevention, particularly in patients aged <60 years with a body mass index >30 and FPG ≥110 mg/dL, who do not have any contraindications for treatment.

Similarly, the AACE/ACE Prevention Roadmap presents specific lifestyle modifications and identifies pharmacologic agents (including, metformin, orlistat, α-glucosidase inhibitor, and thiazolidinediones (TZDs)) that have been shown in clinical trials to at least delay the progression from prediabetes to diabetes. However, the document indicates that no pharmacologic agents have received FDA approval for the prevention of type 2 diabetes.

A 2007 report of an ADA consensus development conference recommended lifestyle interventions, including weight loss of 5% to 10% and physical activity totaling 30 min/day, as the first treatment steps in preventing or delaying the progression of IFG and/or IGT to type 2 diabetes.
The report also suggested considering lifestyle modification and/or metformin for individuals with IFG and IGT and any of the following characteristics: <60 years of age, body mass index ≥35 kg/m², family history of diabetes in first-degree relatives, elevated triglyceride concentrations, reduced high-density lipoprotein cholesterol concentrations, hypertension and/or HbA₁c >6.0%.

The CDA also suggests weight loss and physical activity to reduce progression from IGT to type 2 diabetes. Life-style modification leading to a weight loss of ≥5% of initial body weight can result in a ~60% reduction in the risk of progression from IGT to type 2 diabetes.⁹

**Keeping Pace with Advances in Research and Therapy**

Currently, there are at least 11 classes of FDA-approved antihyperglycemic agents, including orally administered sulfonylureas, (e.g., glimepiride, glipizide), the biguanide metformin, α-glucosidase inhibitors (e.g., acarbose, miglitol), TZDs (e.g., pioglitazone, rosiglitazone), meglitinides (e.g., nateglinide, repaglinide), dipeptidyl peptidase–4 inhibitors (e.g., sitagliptin, saxagliptin), the bile acid sequestrant colesevlam, a quick-release formulation of bromocriptine mesylate, and parenterally administered insulin and insulin analogs, amylinomimetics, and incretin mimetics (glucagonlike peptide–1 [GLP-1]) receptor agonists.³⁵-³⁷

The increasing number of antihyperglycemic therapies has challenged clinicians.¹¹ Recently published treatment algorithms provide guidance in agent selection by considering such factors as the level of glycemia when initiating treatment, effectiveness in glucose lowering, extraglycemic effects, potential synergies obtained by combining agents, and established safety profiles. The ADA/EASD writing group’s algorithm figure (Figure 2), which is selective in its use of available treatments, noted that the addition of the GLP-1 receptor agonist exenatide or the TZD pioglitazone may be considered as tier 2, step 2 options, especially when hypoglycemia is a concern. The use of the GLP-1 receptor agonist exenatide has the additional advantage of being associated with some degree of weight loss.¹¹ The more recent AACE/ACE algorithm includes virtually all of the available treatments and provides suggestions about the clinical situations in which the use of certain therapeutic agents might be particularly useful.⁸

Dr. Ralph DeFronzo, in his Banting Lecture at the 2008 ADA Scientific Sessions, proposed a “pathophysiologic-based algorithm,” that might be especially applicable to people with diabetes of shorter duration. The algorithm recommended lifestyle modifications plus triple pharmacologic therapy with metformin, a TZD, and exenatide aimed at an HbA₁c goal of <6.0%. DeFronzo provided evidence suggesting this approach might have a greater likelihood of producing durable glycemic control by better preserving β-cell function and mass while having a low risk for hypoglycemia and weight gain.³⁸

**SUMMARY**

Type 2 diabetes and obesity, which are both associated with increased CV risk, have emerged as major public health concerns. Lifestyle-based interventions, including medical nutrition therapy and appropriately prescribed physical activity are the cornerstones of diabetes prevention and treatment. However, many patients who develop type 2 diabetes will require pharmacologic therapy to reach glycemic goals. Most patients with type 2 diabetes should be able to achieve desired glycemic targets by thoughtful application of presently available pharmacologic agents added to lifestyle interventions.

A number of disease-specific organizations and professional societies have developed diverse approaches to hyperglycemic management, which are detailed in published guidelines and/or algorithms. Despite some differences, these guidelines all advocate the use of an individualized treatment approach for patients with type 2 diabetes delivered by a team of knowledgeable healthcare professionals.

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**References**


