

For Clinicians

When Patients Do Not Meet Glycemic Goals



Landmark clinical trials have established the benefits of tight glycemic control to reduce diabetes-related macrovascular and microvascular complications.¹ The American Diabetes Association (ADA) recommends a glycosylated hemoglobin (A1C) goal of <7% for most patients with type 2 diabetes mellitus (T2DM); an even tighter glycemic goal (6% to 6.5%) may be appropriate for patients with a short duration of disease, long life expectancy, and no evidence of significant cardiovascular disease (CVD), if this goal can be achieved without significant hypoglycemia or adverse effects.^{2,3} A higher target is indicated in patients at increased risk for hypoglycemia and with other comorbidities.

However, maintaining glycemic control is challenging for many patients with T2DM, and many fail to meet recommended targets.^{3,4} This challenge reflects the progressive nature of T2DM, as insulin resistance increases and pancreatic beta-cell function declines.⁵ Lifestyle interventions that promote healthy eating, increased physical activity, and weight loss are the cornerstone of diabetes management.³ The United Kingdom Prospective Diabetes Study demonstrated the significant and long-term benefits of tight glycemic control to reduce the risk for diabetic complications and mortality, findings that support a treat-to-target approach rather than waiting for treatment failure.^{6,7} Current treatment position statements proposed by the ADA and European Association for the

Study of Diabetes (EASD) in 2012, and by the American Association of Clinical Endocrinologists and the American College of Endocrinology (AAACE/ACE) in 2009 provide clinicians a road map for timely revisions in antidiabetic treatment regimens to achieve glycemic targets.^{3,8} Both algorithms promote therapeutic lifestyle changes as a basis for T2DM management and recommend metformin as first-line pharmacologic therapy.^{3,8}

FEATURES OF THE ADA/EASD TREATMENT ALGORITHM

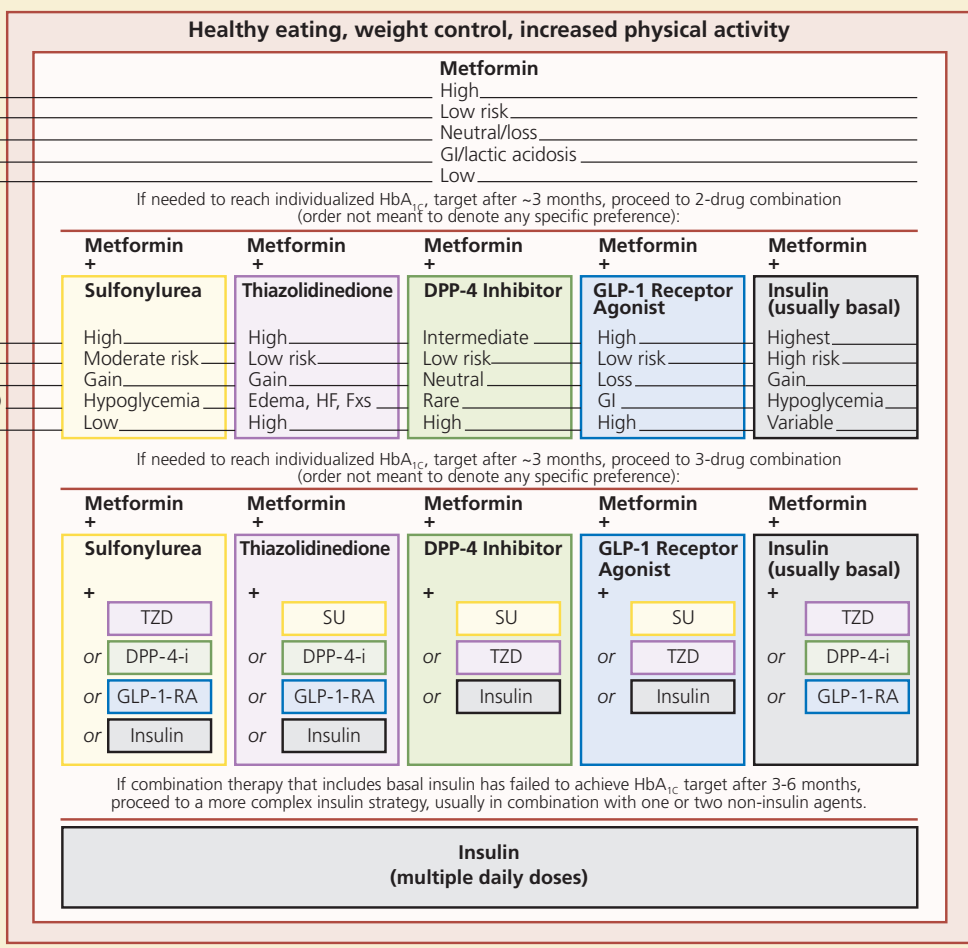
The ADA/EASD guidelines for medical management of T2DM emphasize a patient-centered approach to glycemic control with individualized treatment goals, with consideration of comorbidities and cultural preferences.³ Drug treatment strategies are proposed based on the efficacy, risk for hypoglycemia, impact on body weight, possible side effects, and cost within each class of antidiabetic agents (**Figure 1**).^{3,9} If glycemic control is not achieved after approximately 3 months of metformin treatment, the addition of another antidiabetic agent with a different mechanism of action—a sulfonylurea (SU), thiazolidinedione (TZD), glucagon-like peptide-1 (GLP-1) agonist, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or basal insulin—is recommended.³ Failure to reach the glycemic target on a 2-drug regimen warrants the addition of a third agent from these drug classes with yet another mechanism of action.³ Finally, treat-

Initial drug monotherapy
 Efficacy (↓HbA_{1c})
 Hypoglycemia
 Weight
 Side effects
 Costs

Two-drug combinations
 Efficacy (↓HbA_{1c})
 Hypoglycemia
 Weight
 Major side effect(s)
 Costs

Three-drug combinations

More complex insulin strategies



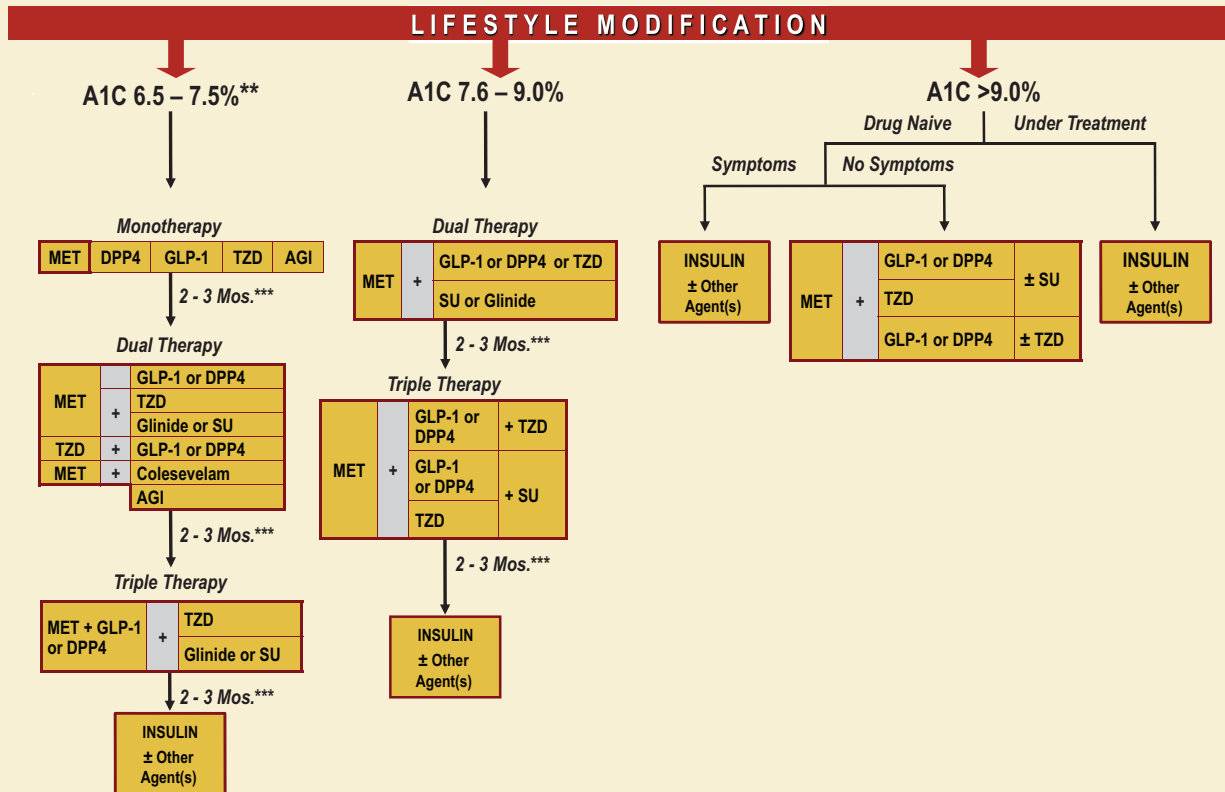
Fxs=fractures; GI=gastrointestinal; HF=heart failure; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; HbA_{1c}=glycosylated hemoglobin; DPP-4-i=dipeptidyl peptidase-4 inhibitor; GLP-1-RA=glucagon-like peptide-1 receptor agonist; TZD=thiazolidinedione; SU=sulfonyleurea. Used with permission from Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379. Figure 2.

FIGURE 1. ADA/EASD 2012 Treatment Algorithm for the Management of Type 2 Diabetes

ment with multiple daily doses of insulin may be appropriate if combination therapy that includes basal insulin has not been effective.³

Like the ADA/EASD treatment algorithm, the AACE/ACE algorithm recommends lifestyle modification for all patients with diabetes but bases its strategies for drug therapy on A1C level (Figure 2).⁸ Monotherapy with metformin, an SU, a DPP-4 inhibitor,

a GLP-1 agonist, a TZD, or an alpha-glucosidase inhibitor is recommended as initial treatment for patients with an A1C of 6.5% to 7.5%.⁸ If the glycemic target is not achieved after 2 to 3 months, up to 2 additional drugs with different mechanisms of glucose-lowering action can be added at 2- to 3-month intervals before initiating insulin therapy, with or without oral or noninsulin injectable



AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; MET = metformin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione; SU = sulfonylurea; AGI = alpha-glucosidase inhibitor.

Adapted from Rodbard HW, Jellinger PS, Davidson JA, et al. *Endocr Pract.* 2009;15:540-559.

FIGURE 2. AACE/ACE Treatment Algorithm for the Management of Type 2 Diabetes Mellitus

agents.⁸ For patients with an A1C between 7.5% and 9%, the AACE/ACE algorithm recommends a metformin-based 2-drug

regimen as initial therapy and the addition of a third, then initiating insulin therapy, if glycemic targets are not met.⁸

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