Individualizing Treatment of Hyperglycemia in Type 2 Diabetes
Maryam T. Fazel, PharmD, BCPS, BCACP, CDE, and Merri L. Pendergrass, MD, PhD

ABSTRACT
• **Objective:** To summarize key issues relevant to managing hyperglycemia in patients with type 2 diabetes mellitus (T2DM) and review a strategy for initiating and intensifying therapy.
• **Methods:** Review of the literature.
• **Results:** The 6 most widely used pharmacologic treatment options for hyperglycemia in T2DM are metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and insulin. Recent guidelines stress the importance of an individualized, patient-centered approach to managing hyperglycemia in T2DM, although sufficient guidance for nonspecialists on how to individualize treatment is often lacking. For patients with no contraindications, metformin should be recommended concurrent with lifestyle intervention at the time of diabetes diagnosis. Due to the progressive nature of T2DM, glycemic control on metformin monotherapy is likely to deteriorate over time, and there is no consensus as to what the second-line agent should be. A second agent should be selected based on glycemic goal and potential advantages and disadvantages of each agent for any given patient. If the patient progresses to the point where dual therapy does not provide adequate control, either a third non-insulin agent or insulin can be added.
• **Conclusion:** Although research is increasingly focusing on what the ideal number and sequence of drugs should be when managing T2DM, investigating all possible combinations in diverse patient populations is not feasible. Physicians therefore must continue to rely on clinical judgment to determine how to apply trial data to the treatment of individual patients.

Key words: type 2 diabetes; patient-centered care; antihyperglycemic drugs; insulin; therapeutic decision-making.

Diabetes mellitus affects approximately 29.1 million people, or 9.3% of the U.S. population [1,2]. The high prevalence of diabetes and its associated multiple complications, including cardiovascular disease (CVD), blindness, renal failure, lower extremity amputations, and premature death, lead to a tremendous overall burden of disease. The financial cost is staggering as well, with more than 1 in 5 health care dollars spent on treating diabetes or its complications [3]. The goal of diabetes treatment is to prevent acute complications and reduce the risk of long-term complications. Interventions that have been shown to improve diabetes outcomes include medications for glycemic control and treatment of cardiovascular risk factors, nutrition and physical activity counseling, smoking cessation, immunizations, psychosocial care, and ongoing surveillance and early treatment for eye, kidney, and foot problems [4].

Glycemic management in type 2 diabetes mellitus (T2DM), the focus of this review, is growing increasingly complex and has been the subject of numerous extensive reviews [5,6] and published guidelines [4,7]. In the context of an increasing array of available pharmacologic options, there are mounting uncertainties regarding the benefits of intensive glycemic control as well as increasing concerns about potential adverse treatment effects, hypoglycemia in particular. While previous guidelines encouraged specific approaches for most patients, more recent guidelines stress the importance of a patient-centered approach with shared decision-making [4]. Less prescriptive guidelines are more appropriate, given the current state of science, but they also may be viewed as providing insufficient guidance to some providers. It can be overwhelming for a non-specialist to try to match the nuances of antihyperglycemic medications to the nuances of each patient’s preferences and medical characteristics.
This article examines key issues faced by primary care providers when managing hyperglycemia in patients with T2DM and outlines a stepwise approach to determining the optimal antihyperglycemic agent(s) (Table 1). Focusing on the most widely used agents today, we discuss current evidence and recommendations around glycemic goal setting and the potential risks and benefits of various pharmacologic treatment options with emphasis on hypoglycemia risk, effects on weight, and cardiovascular outcomes.

**Confirm Diagnosis of T2DM**
It can be difficult to distinguish between type 1 diabetes mellitus and T2DM in some individuals due to overlapping characteristics. However, correctly classifying a patient’s diabetes at the outset is essential, as the classification helps determine the best treatment regimen and is rarely reconsidered [4,8]. Considerable evidence suggests that misclassification of diabetes occurs frequently [9,10], resulting in patients receiving inappropriate treatment. Clinical characteristics suggestive of T2DM include older age and features of insulin resistance such as obesity, hyper-tension, hypertriglyceridemia, and low high-density lipoprotein cholesterol. When these features are not present, an alternate diagnosis should be entertained.

**Establish Glycemic Goal**
Research over the past decade has led to a growing appreciation of the enormous complexity of hyperglycemia management. During the 1990s, landmark trials such as the Diabetes Control and Complications Trial (DCCT) [11] and UK Prospective Diabetes Study (UKPDS) [12] demonstrated that improving glucose control could reduce the incidence of microvascular complications [11,12], prompting a lower-is-better philosophy regarding glucose targets. Despite limited evidence to support such thinking, this viewpoint was adopted by the developers of many guidelines. During the following decade more research was devoted to determining whether aggressively lowering a patient’s glucose could also improve macrovascular outcomes. Table 2 summarizes microvascular and macrovascular effects of intensive glycemic control seen in major trials [11–23]. After several major trials [20,22] found only mild cardiovascular benefits and even suggested harm [18], experts and policy makers began to reconsider the value of tightly controlling glucose levels [24]. Since then, other studies have demonstrated that the potential benefits and risks of glucose control are strongly related to individual patient factors, such as age and duration of diabetes, and associated comorbidities, such as CVD and impaired renal function [6].

A one-size-fits-all glycemic goal is no longer recommended. Personalization is necessary, balancing the potential benefits and risks of treatments required to achieve that goal. Whereas an A1C of < 7% is an appropriate target for some individuals with diabetes, glycemic targets may be more or less stringent based on patient features including life expectancy, duration of diabetes, and associated comorbidities, such as CVD and impaired renal function [6].

A particular group in which less stringent goals should be considered is older patients, especially those with complex or poor health status [4,25]. The risk of intensive glycemic control may exceed the benefits in these patients, as they are at higher risk of hypoglycemia and polypharmacy [26]. A goal A1C of 7% to 7.5% is now recommended for healthy older adults, and less stringent A1C goals of 7.5% to 8% and 8% to 8.5% should be considered based on the presence and severity of multiple coexisting chronic illnesses, decreased self-care ability, or cognitive impairment [4,25]. Unfortunately, overtreatment is frequently seen in this group. In a recent study of patients over age 65 years, about 40% of those with complex or poor health status had tight glycemic control with A1C below 6.5% [26]. An analysis of U.S. Veterans Affairs administration data showed that only 27% of 12,917 patients older than 65 with very low A1C (< 6%)
and about 21% of those with A1C of 6% to 6.5% underwent treatment deintensification [27].

**Initiate Treatment with Metformin**
There is strong consensus that metformin is the preferred drug for monotherapy due to its long proven safety record, low cost, weight-reduction benefit, and potential cardiovascular advantages [4,16]. As long as there are no contraindications, metformin should be recommended concurrent with lifestyle intervention at the time of diabetes diagnosis. The recommendation is based on the fact that adherence to diet, weight reduction, and regular exercise is not sustained in most patients, and most patients ultimately will require treatment. Since metformin is usually well-tolerated, does not cause hypoglycemia, has a favorable effect on body weight, and is relatively inexpensive, potential benefits of early initiation of medication appear to outweigh potential risks.

The U.S. Food and Drug Administration (FDA) recently relaxed prescribing policies to extend the use of this important medication to patients who have mild-moderate, but stable, chronic kidney disease (CKD) [28]. Metformin is recommended as first-line therapy and should be used unless it is contraindicated (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) [4,7,29].

**Add Additional Agent(s) as Needed to Achieve Goal**
Other than metformin, evidence is limited for the optimal use of the burgeoning array of available agents, especially in dual or triple combinations [6,30]. Research is now starting to focus more on what the ideal number and sequence of drugs should be. The Glycemic Reduction Approach in Diabetes (GRADE) study, which will compare long-term benefits and risks of the 4 most widely used antihyperglycemic medications in combination with metformin, is now underway [31,32]. The 4 classes being studied are sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and a basal, long-acting insulin. From a practical standpoint, investigating all possible combinations in diverse patient populations is not feasible. Physicians therefore must continue to rely on clinical judgment to determine how to apply trial data to the treatment of individual patients.

Eleven classes of non-insulin medications are currently approved for treating hyperglycemia in T2DM [4].

### Table 2. Summary of Microvascular and Macrovascular Effects of Intensive Glycemic Control

<table>
<thead>
<tr>
<th>Trial</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Trial</td>
<td>Long-term Follow-up</td>
<td>Initial Trial</td>
</tr>
<tr>
<td></td>
<td>DCCT/EDIC (2005–2014) [13,14]</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>T2DM, recent diagnosis</td>
<td>UKPDS-33,34 (1998) [12,15]</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>UKPDS-80 (2008) [16]</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>T2DM, high CVD risk</td>
<td>ACCORD (2008) [18]</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>ACCORD (2011) [19]</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>ADVANCE (2008) [20]</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>ADVANCE-ON (2016) [21]</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>VADT (2009) [22]</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>VADT (2015) [23]</td>
<td>↓</td>
<td>↔</td>
</tr>
</tbody>
</table>

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ADVANCE-ON = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation posttrial Observational Study; CVD = cardiovascular disease; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications; T1DM = type 1 diabetes; T2DM = type 2 diabetes; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.
Within each class, numerous agents are available. Six of these classes (ie, α-glucosidase inhibitors, colesevelam, bromocriptine, pramlintide, meglitinides, and thiazolidinediones) are not used frequently because of their modest efficacy, inconvenient frequency of administration, and/or limiting side effects. The 4 most commonly used non-insulin antihyperglycemic drug classes that can be added to metformin or used if a patient cannot tolerate metformin include the sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Because T2DM is a progressive disease, many patients eventually may require insulin to achieve their glycemic goals. The primary characteristics of commonly used non-insulin agents are summarized in Table 4 [4,6,29,30,33–37] and the properties of FDA-approved insulins are summarized in Table 5 [37,38].

Consider Effects on A1C
There is a paucity of high-quality, head-to-head comparison trials evaluating the ability of available agents to achieve recommended glycemic targets. This is important because the glucose-lowering effectiveness of individual medications is strongly influenced by baseline characteristics such as A1C, duration of diabetes, and previous therapy. With these limitations in mind, the relative glucose-lowering effectiveness of commonly used agents is shown in Table 4. When used as monotherapy, A1C reductions of approximately 1% to 1.5% are achieved with metformin, sulfonylureas, and GLP-1 receptor agonists [6,30,34,35,39]. DPP-4 inhibitors and SGLT-2 inhibitors have more modest glucose-lowering efficacy, with A1C reductions of approximately 0.5% to 1% [6,30,34,35,39]. Larger effects may be seen in individuals with higher baseline A1C and those who are drug naïve. Insulin is the most effective glucose-lowering agent—it can reduce virtually any level of A1C down to the normal range, with hypoglycemia being the only limiting factor. When a patient has uncontrolled hyperglycemia on metformin monotherapy, or if there is a contraindication or intolerance to metformin, clinicians should consider the potential glucose-lowering effects of other available options and should choose an agent that conceivably could bring a patient close to meeting their treatment goal.

Eliminate Options with Unacceptable Adverse Effects
When the pharmacologic options with acceptable A1C-lowering potential have been identified, the ones with contraindications and potential serious adverse effects for the individual patient can immediately be eliminated (Table 4). For example, if a patient has an eGFR < 30 mL/min/1.73 m², metformin, sulfonylureas, GLP-1 receptor agonists, most DPP-4 inhibitors, and SGLT-2 inhibitors are either contraindicated or should be used with caution. In patients with severe osteoporosis, SGLT-2 inhibitors may not be the best option. In patients with a history of diabetic ketoacidosis (DKA), caution should be used with metformin and SGLT-2 inhibitors. There have been concerns of possible acute pancreatitis and neoplasia with the incretin-based agents, the DPP-4 inhibitors and GLP-1 receptor agonists [40,41], although other clinical trials and observational data have not found increased risk [42–45]. Nevertheless, these agents potentially should be avoided in patients with a history of pancreatitis or neoplasm. SGLT-2 inhibitors may be associated with genitourinary infections and volume depletion [46–48] and probably should be avoided in patients at high risk for these conditions.
If the adverse effects are not serious, changing the way the medication is administered may allow the patient to tolerate agents with high potential benefits. For example, metformin is commonly associated with gastrointestinal (GI) adverse effects, which can be reduced or avoided with slow titration of the dose [6] or by switching to an extended-release formulation [49]. GLP-1 receptor agonists are associated with GI adverse effects [6] and in most cases slow titration is recommended.

Table 4. Characteristics of Commonly Used Antihyperglycemic Medications

<table>
<thead>
<tr>
<th>Class/Primary MOA</th>
<th>Generic Names</th>
<th>Route</th>
<th>Dosing Frequency</th>
<th>Renal Dose Adjustment</th>
<th>↓ A1C, %</th>
<th>Primary Advantages</th>
<th>Primary Disadvantages</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>Oral</td>
<td>Twice daily</td>
<td>eGFR 45 – &lt; 60: Avoid if kidney function is or is expected to become unstable. Max dose: 2000 mg daily. eGFR 30 – &lt; 45: Do not initiate but may be continued. Max dose: 1000 mg daily. eGFR &lt; 30: Do not use</td>
<td>1–1.5</td>
<td>No hypoglycemia†</td>
<td>GI adverse effects (diarrhea, abdominal cramping) Avoid if ketosis-prone, Contraindicated: eGFR &lt;30, acidosis</td>
<td></td>
</tr>
<tr>
<td>Sulfonlurea</td>
<td>Glibenclamide</td>
<td>Oral</td>
<td>Once daily</td>
<td>Use caution: increased risk of hypoglycemia in renal impairment</td>
<td>1–1.5</td>
<td>Inexpensive</td>
<td>Hypoglycemia</td>
<td>$12</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>Sitagliptin</td>
<td>Oral</td>
<td>Once daily</td>
<td>Sitagliptin: CrCl 30–50: max dose: 50 mg daily CrCl &lt; 30: max dose: 25 mg daily Saxagliptin: CrCl ≤ 50: max dose: 2.5 mg daily</td>
<td>0.6–0.8</td>
<td>No hypoglycemia†</td>
<td>Hypoglycemia, Weight neutral, ? Heart failure hospitalization</td>
<td>$440</td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td>Exenatide</td>
<td>SQ</td>
<td>Twice daily (1 hr before meals)</td>
<td>Exenatide, exenatide ER: CrCl 30–50: no dosage adjustment; use caution CrCl &lt; 30: contraindicated</td>
<td>0.7–1.5</td>
<td>No hypoglycemia†</td>
<td>Injectable, GI adverse effects (nausea, vomiting, diarrhea), ? Acute pancreatitis, Contraindicated: MTC, MEN2</td>
<td>$650</td>
</tr>
</tbody>
</table>

Evaluate Potential Risks/Benefits of Remaining Options

Hypoglycemia. The barrier of hypoglycemia generally precludes maintenance of euglycemia and full realization of the long-term benefits of good glucose control over a lifetime. Once considered a trivial issue, concerns about hypoglycemia in T2DM are increasingly being raised [19,50–55]. Clearly, hypoglycemia occurs more often as glycemic targets are lowered to near-normal values, especially in those with advanced age and multiple comorbidities [55]. Various comorbidities frequently
TREATMENT OF HYPERGLYCEMIA IN T2DM

Table 4. Characteristics of Commonly Used Antihyperglycemic Medications (continued)

<table>
<thead>
<tr>
<th>Class/Primary MOA</th>
<th>Generic Names</th>
<th>Route</th>
<th>Dosing Frequency</th>
<th>Renal Dose Adjustment</th>
<th>↓ A1C, %</th>
<th>Primary Advantages</th>
<th>Primary Disadvantages</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2 Inhibitor</td>
<td>Cangliflozin</td>
<td>Oral</td>
<td>Once daily</td>
<td>Canagliflozin: eGFR 45 – &lt; 60: max dose: 100 mg daily; eGFR 30 – &lt; 45: do not initiate; discontinue if persistent ↓ in eGFR to &lt; 45; eGFR &lt; 30: contraindicated</td>
<td>0.6–0.8</td>
<td>No hypoglycemia†</td>
<td>Weight ↓</td>
<td>GU infections Polyuria ? Risk of DKA ? Risk of fractures Risk of amputations</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>oral</td>
<td></td>
<td>Dapagliflozin: eGFR 30 – &lt; 60: do not initiate; discontinue if persistent ↓ in eGFR to 30 – &lt; 60; eGFR &lt; 30: contraindicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>oral</td>
<td></td>
<td>Empagliflozin: eGFR ≥ 45: no dose adjustment; eGFR &lt; 45: do not initiate; discontinue if persistent ↓ in eGFR to &lt; 45; eGFR &lt; 30: contraindicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A1C = hemoglobin A1C; CrCl = creatinine clearance (mL/min); CVD = cardiovascular disease; DKA = diabetic ketoacidosis; DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate (mL/min/1.73m2); ER = extended release; ESRD = end stage renal disease; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; GU = genitourinary; HD = hemodialysis; MEN2 = multiple endocrine neoplasia syndrome type 2; MOA = mechanism of action; MTC = medullary thyroid cancer; SGLT2 inhibitor = sodium-glucose co-transporter 2 inhibitor; T2DM = type 2 diabetes. (Adapted from references 4, 6, 29, 30, 33–37.)

*Costs based on the lowest estimated cash price for a 30-day supply of a commonly used agent in the class [37].
†Note that the risk of hypoglycemia may be present if added to glucose-lowering agents with such risk.
‡Refer to the Cardiovascular Outcomes section of article for details on CV risk and benefits.
§Glyburide is not recommended due to increased risk of hypoglycemia.
#Theoretically unlimited glucose-lowering efficacy; however, the effect is limited by hypoglycemia.

encountered particularly as patients age also are associated with increasing propensity for experiencing hypoglycemia and untoward outcomes from it. These include coronary artery disease, heart failure, renal and liver disease, and dementia. Hypoglycemia, when it occurs, may lead to dysrhythmias, dizziness, accidents and falls, work disability, and decreased quality of life. In addition to relaxing blood glucose targets in high-risk patients, drug selection should favor agents that do not precipitate such events (Table 4).

Fortunately, the commonly used non-insulin agents are not associated with hypoglycemia unless they are used in combination with sulfonylureas or insulin. Sulfonylureas should be used with caution and other options considered in patients with high risk for hypoglycemia. When insulin is required, regimens which minimize risk of hypoglycemia should be used. For example, adding a GLP-1 receptor agonist to basal insulin as an alternative to mealtime insulin has been shown to be equally effective with a lower risk of hypoglycemia [4,6]. Also, premixed insulin preparations should be avoided or used cautiously in individuals who miss meals frequently. Additionally, newer basal insulins that exhibit longer duration of action are now available in the United States. Preliminary studies have shown that the newly FDA-approved longer-acting basal insulins, insulin degludec and glargine U-300, may be associated with a reduced risk for hypoglycemia [56,57]. However, it remains unclear how and when these newer agents will best be incorporated into a treatment regimen.

Body weight. Nearly 90% of people living with T2DM are overweight or obese. Given the close tie between
obesity and T2DM, treating obesity is an obvious consideration in diabetes treatment. Major trials have shown the effectiveness of lifestyle modifications and weight reduction in delaying, prevention, and management of T2DM [4,58,59]. With this in mind, clinicians should consider preferentially using antihyperglycemic agents with weight-lowering or weight-neutral effects. Among commonly used antihyperglycemic agents, metformin, GLP-1 receptor agonists, and SGLT-2 inhibitors have been shown to have weight-reduction benefits, and DPP-4 inhibitors are weight neutral. On the other hand, sulfonylureas and insulin are associated with weight gain. A systematic review and meta-analysis including 204 studies with study durations ranging from 3 months to 8 years showed comparative effects of diabetes medications with a differential effect on weight of up to 5 kg (Table 4) [60].

Table 5. Summary of Commonly Used Insulins

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Concentration (Form)</th>
<th>Administration/ Other Considerations</th>
<th>Item</th>
<th>Cost*/Item, (Cost/unit)</th>
<th>Cost/1000 units (~33 units/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LONG-ACTING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>100 units/mL (human)</td>
<td>Pen dialed up to 60 units/injection in 1-unit increments</td>
<td>10-mL vial</td>
<td>$26† (0.026)</td>
<td>$26†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Box of 5 (3-mL pens)</td>
<td>$445 (0.29)</td>
<td>$445</td>
</tr>
<tr>
<td>Glargine</td>
<td>100 units/mL (analog)</td>
<td>Pen dialed up to 80 units/injection in 1-unit increments</td>
<td>10-mL vial</td>
<td>$256 (0.26)</td>
<td>$256</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Box of 5 (3-mL pens)</td>
<td>$380 (0.25)</td>
<td>$380</td>
</tr>
<tr>
<td></td>
<td>300 units/mL† (analog)</td>
<td>Caution: concentrated† insulin</td>
<td>Box of 3 (1.5-mL pens)</td>
<td>$343 (0.25)</td>
<td>$343</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pen dialed up to 80 units/injection in 1-unit increments</td>
<td>Box of 5 (1.5-mL pens)</td>
<td>$600 (0.27)</td>
<td>$600</td>
</tr>
<tr>
<td>Levemir</td>
<td>100 units/mL (analog)</td>
<td>Pen dialed up to 80 units/ injection in 1-unit increments</td>
<td>10 mL vial</td>
<td>$276 (0.28)</td>
<td>$280</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Box of 5 (3-mL pens)</td>
<td>$411 (0.27)</td>
<td>$411</td>
</tr>
<tr>
<td>Degludec</td>
<td>100 units/mL (analog)</td>
<td>Pen dialed up to 80 units/injection in 1-unit increments</td>
<td>Box of 5 (3-mL pens)</td>
<td>$451 (0.45)</td>
<td>$450</td>
</tr>
<tr>
<td></td>
<td>200 units/mL† (analog)</td>
<td>Caution: concentrated† insulin</td>
<td>Box of 3 (3-mL pens)</td>
<td>$540 (0.3)</td>
<td>$300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pen dialed up to 160 units/injection in 2- unit dose increments</td>
<td>Box of 5 (3-mL pens)</td>
<td>$600 (0.33)</td>
<td>$300</td>
</tr>
<tr>
<td>Regular insulin U-500</td>
<td>500 units/mL‡ (human)</td>
<td>Caution: concentrated‡ insulin</td>
<td>20 mL vial</td>
<td>$1385 (0.14)</td>
<td>$140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U-500 replaces basal and bolus insulins; usually start with twice daily dosing</td>
<td>Box of 2 (3-mL pens)</td>
<td>$540 (0.18)</td>
<td>$180</td>
</tr>
<tr>
<td>SHORT-ACTING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin</td>
<td>100 units/mL (human)</td>
<td>Should be administered ~30 min prior to meal(s)</td>
<td>10-mL vial</td>
<td>$26† (0.026)</td>
<td>$26†</td>
</tr>
<tr>
<td>Lispro</td>
<td>100 units/mL (analog)</td>
<td>Should be administered ~0–15 min prior to meal(s)</td>
<td>10-mL vial</td>
<td>$262 (0.26)</td>
<td>$260</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Box of 5 (3-mL pens)</td>
<td>$499 (0.33)</td>
<td>$330</td>
</tr>
<tr>
<td></td>
<td>200 units/mL† (analog)</td>
<td>Caution: concentrated† insulin</td>
<td>Box of 2 (3-mL pens)</td>
<td>$401 (0.33)</td>
<td>$330</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Should be administered ~0–15 minutes prior to meal(s)</td>
<td>Box of 5 (3-mL pens)</td>
<td>$500 (0.33)</td>
<td>$330</td>
</tr>
<tr>
<td>Aspart</td>
<td>100 units/mL (analog)</td>
<td>Should be administered ~0–15 minutes prior to meal(s)</td>
<td>10-mL vial</td>
<td>$263 (0.26)</td>
<td>$260</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Box of 5 (3-mL pens)</td>
<td>$500 (0.33)</td>
<td>$330</td>
</tr>
<tr>
<td>Glulisine</td>
<td>100 units/mL (analog)</td>
<td>Should be administered ~0–15 min prior to meal(s)</td>
<td>10-mL vial</td>
<td>$243 (0.24)</td>
<td>$243</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Box of 5 (3-mL pens)</td>
<td>$463 (0.31)</td>
<td>$310</td>
</tr>
</tbody>
</table>

continued on page 30
Metformin is associated with an average weight loss of 1.9 to 3.1 kg that was sustained with long-term use for at least 10 years in the Diabetes Prevention Program Outcomes Study [61]. A systematic review of 7 randomized trials showed that in patients with T2DM, the SGLT-2 inhibitors dapagliflozin and canagliflozin were associated with weight loss (mean weighted difference of −1.81 kg and −2.3 kg, respectively) [62]. A systematic review and meta-analysis of 25 randomized controlled trials showed greater weight loss (mean weighted difference of −2.9 kg) in overweight or obese patients with or without T2DM using GLP-1 receptor agonists when compared to placebo, insulin, or oral antihyperglycemic agents [63]. Of note, the GLP-1 receptor agonist liraglutide is now approved for weight loss in patients with or without diabetes [64]. The maximum doses approved for diabetes and obesity treatment are 1.8 and 3.0 mg/day, respectively.

Since weight loss is associated with improved glycemic control, an area of emerging interest is the use of anti-obesity medications for managing diabetes. Although most older weight-loss medications were only approved for short-term use, some newer agents are approved for longer-term use. Lorcaserin and the combination drugs topiramate/phentermine and naltrexone/bupropion are approved for chronic therapy, provided certain conditions are met. Patients on weight reduction agents should be monitored regularly. If weight loss of more than 5% is not achieved after 3 months of treatment, the therapy should be discontinued. Table 6 summarizes the efficacy and characteristics of FDA-approved weight loss medications [4,37,65–68].

An even more radical departure from conventional therapy for diabetes is the consideration of metabolic, or weight-loss, surgery, which has been found to be associated with rapid and dramatic improvements in blood glucose control. Metabolic surgery has been shown to improve glucose control more effectively than any known pharmaceutical or behavioral approach. For example, in an observational study of obese patients with T2DM, bariatric surgery led to diabetes remission rates of 72.3% 2 years after surgery and 30.4% 15 years after surgery compared to 16.4% and 6.5%, respectively, in control patients [69]. With long-term follow-up, significant decreases in microvascular and macrovascular complications were seen in the surgical group [69]. Compared with medical therapy alone, bariatric surgery plus medical therapy has been associated with more weight loss, better glycemic control, less need for diabetes medications, and improved quality of life [70]. A 2016 joint statement by numerous international diabetes organizations recommends considering metabolic surgery as a treatment for T2DM and obesity [71]. American Diabetes Association guidelines recommend consideration of bariatric surgery in individuals with

### Table 5. Summary of Commonly Used Insulins (continued)

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Concentration (Form)</th>
<th>Administration/Other Considerations</th>
<th>Item</th>
<th>Cost/Item, (Cost/Unit)</th>
<th>Cost/1000 Units (~33 Units/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMIUSED§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% NPH/30% Regular</td>
<td>100 units/mL (human)</td>
<td>Should be administered ~30 min prior to meal(s)</td>
<td>10 mL vial Box of 5 (3-mL pens)</td>
<td>$25† (0.025) $444 (0.3)</td>
<td>$25† $300</td>
</tr>
<tr>
<td>70% aspart protamine/30% aspart</td>
<td>100 units/mL (analog)</td>
<td>Should be administered –0–15 min prior to meal(s)</td>
<td>10-mL vial Box of 5 (3-mL pens)</td>
<td>$272 (0.27) $497 (0.33)</td>
<td>$272 $330</td>
</tr>
<tr>
<td>75% lispro protamine/25% lispro</td>
<td>100 units/mL (analog)</td>
<td>Should be administered –0–15 min prior to meal(s)</td>
<td>10-mL vial Box of 5 (3-mL pens)</td>
<td>$271 (0.27) $499 (0.33)</td>
<td>$271 $330</td>
</tr>
<tr>
<td>50% lispro protamine/50% lispro</td>
<td>100 units/mL (analog)</td>
<td>Should be administered –0–15 min prior to meal(s)</td>
<td>10-mL vial Box of 5 (3-mL pens)</td>
<td>$253 (0.25) $511 (0.34)</td>
<td>$253 $340</td>
</tr>
</tbody>
</table>

Adapted from references 37 and 38.

* Costs are based on the lowest price listed in the source [37].
† Price is for Walmart Relion brand.
‡ Note that concentrated insulins are for use in highly insulin-resistant individuals who require very high doses of insulin.
§ See Figure 2 for more information.
T2DM who have a body mass index greater than 35 kg/m², especially if achieving disease control is difficult by means of lifestyle modifications and medications [4].

Cardiovascular outcomes. Cardiovascular risk is about 2 to 4 times higher in patients with diabetes, and about half of patients with this condition develop heart failure [4,72]. CVD is responsible for most of the mortality in T2DM [72]. Therefore, prevention of cardiovascular morbidity and mortality is an important goal for diabetes treatment. Due to concerns about potential cardiovascular risks associated with glucose-lowering medications [73–76], the FDA has issued regulatory requirements for manufacturers to monitor the cardiovascular risk profile for these drugs [77]. Recent trials have led to a better understanding of potential cardiovascular benefits or harms of antihyperglycemic medications.

Metformin, the widely recommended first-line therapy for T2DM, carries a large body of evidence supporting its cardiovascular benefits. For example, the UKPDS found that compared to conventional therapy (mostly diet), metformin reduced cardiovascular events and mortality in obese patients with T2DM [15]. This result was supported in Hyperinsulinemia: the Outcome of its Metabolic Effect (HOME) study where, as an add-on to insulin, metformin decreased macrovascular complications when compared to placebo [78]. Research over the past decade also has assuaged concerns about metformin safety in heart failure [60]. A systematic review of observational studies involving 34,000 patients conducted

Table 6. FDA-Approved Weight Loss Medications*

<table>
<thead>
<tr>
<th>Generic Names/MOA</th>
<th>Weight Loss in 1 Year</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
<th>Cost† of 30-Day Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (GLP-1 receptor agonist)</td>
<td>Mean BW Loss, %</td>
<td>% Pts Who Lost ≥ 5% BW</td>
<td>Gl adverse effects (nausea, vomiting, diarrhea)</td>
<td>Acute pancreatitis, ARF, thyroid tumors</td>
</tr>
<tr>
<td>Lorcaserin (selective serotonin 2C receptor agonist)</td>
<td>7</td>
<td>38–48</td>
<td>Headache, dry mouth, fatigue, dizziness</td>
<td>Serotonin syndrome, heart valve disorder, ↓ heart rate, priapism</td>
</tr>
<tr>
<td>Naltrexone/bupropion (opioid antagonist/dopamine and norepinephrine reuptake inhibitor)</td>
<td>4–9</td>
<td>36–57</td>
<td>Nausea, vomiting, constipation, headache, dizziness</td>
<td>Depression, mania, hypertension</td>
</tr>
<tr>
<td>Orlistat (reversible inhibitor of intestinal lipases)</td>
<td>6</td>
<td>35–73</td>
<td>GI pain, fecal urgency, steatorrhea, ↓ absorption of vitamins</td>
<td>Hepatic failure, renal failure</td>
</tr>
<tr>
<td>Phentermine/topiramate (sympathomimetic amine/anticonvulsant)</td>
<td>14–19</td>
<td>45–70</td>
<td>Paresthesia, headache, constipation, ↓ bicarbonate, xerostomia, insomnia, dizziness</td>
<td>Glaucoma, suicidal behavior</td>
</tr>
</tbody>
</table>

ARF = acute renal failure; BW = body weight; GLP-1 = glucagon-like peptide 1; GI = gastrointestinal; MAOI = monoamine oxidase inhibitors; MEN2 = multiple endocrine neoplasia syndrome type 2; MOA = mechanism of action; MTC = medullary thyroid cancer; OTC = over the counter; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor. (Adapted from references 4,37,65–68.)

* Indications: As adjunct therapy to diet, physical activity, and behavioral modification for patients with type 2 diabetes and a body mass index (BMI) ≥ 27 kg/m² with at least 1 weight-related comorbidity or a BMI ≥ 30 kg/m². Monitoring: Assess efficacy and safety at least monthly for the first 3 months. If weight loss of ≥ 5% is achieved at 3 months, then continue to evaluate efficacy and safety at least every 3 months. If weight loss of < 5% occurs, or if there are safety or tolerability issues, discontinue the medication.

† Costs are based on the lowest estimated cash price listed in the source [37].
in 2013 showed that metformin is as safe as other glucose-lowering medications in patients with diabetes and heart failure even in the presence of CKD [4,79]. Furthermore, numerous investigations have found metformin is not associated with increased hospitalizations or risk of lactic acidosis [80]. Metformin can be used safely in patients with diabetes and heart failure [60].

Although sulfonylureas have long been a mainstay of diabetes therapy, concerns about their potential adverse cardiovascular effects have been raised by numerous studies [81]. Tolbutamide, a first-generation sulfonylurea, was removed from the market after the University Group Diabetes Program study found increased CVD deaths with this agent versus placebo. Subsequently, the FDA issued a warning for all sulfonylureas [74]. The increased cardiovascular risk associated with sulfonylureas is thought to be due to their effect on cardiac mitochondrial potassium ATP channels. Sulfonylureas bind to these channels, preventing a protective phenomenon called ischemic preconditioning and resulting in a weakened defense against myocardial injury [76]. A recent study showed an increased risk of coronary heart disease associated with long-term use of sulfonylureas in women with diabetes [81].

GLP-1 receptor agonists have recently received much attention for their potential beneficial effects on cardiovascular outcomes. In a recent trial, lixisenatide was shown to be safe in patients with T2DM and acute coronary syndrome when compared to placebo [82]. More recently, the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial demonstrated significant cardiovascular benefits with liraglutide in patients with T2DM and established or high CVD risk [83]. The composite outcome of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke, occurred less frequently in the liraglutide group compared to placebo (13% versus 14.9%, respectively), and there were fewer deaths from cardiovascular causes in the liraglutide group compared to placebo (4.7% and 6.0%, respectively) [83]. Other trials investigating the cardiovascular outcomes of this class [84,85] are in progress.

Another class with potential cardiovascular benefits is the SGLT-2 inhibitors. In a recent cardiovascular outcome study, empagliflozin significantly lowered the composite of cardiovascular death, nonfatal MI, or nonfatal stroke in T2DM patients with high cardiovascular risk compared to placebo (10.5% and 12.1%, respectively) [86]. There are several large ongoing studies evaluating the cardiovascular effects of other SGLT-2 inhibitors [87–89].

DPP-4 inhibitors were examined in recent studies and have shown no cardiovascular benefits [42,44,90]. The studies showed mixed results regarding an association between DPP-4 inhibitors and heart failure. In one study, saxagliptin was associated with increased hospitalization for heart failure compared to placebo [44], while 2 noninferiority trials did not show a significant increase in heart failure hospitalizations associated with alogliptin and sitagliptin when compared to placebo [42,90].

Administration Considerations

Many patients with T2DM require multiple agents for glycemic control. Additional medications used for comorbid conditions add to this burden. When choosing antihyperglycemic agents, the route and frequency of administration, as well as the patients’ preferences and ability, should be considered. Either once or twice daily dosing is available for most agents, and once weekly dosing is available for some of the GLP-1 receptor agonists. Once daily or once weekly formulations may improve adherence and be more desirable than preparations that are dosed twice daily. Most of the commonly used medications are dosed orally. Although many patients find this route of administration preferable to insulin or GLP-1 receptor agonists, which require injections, some patients may prefer the risk/benefit of injectable agents. All GLP-1 receptor agonists come in a pen delivery system, which eliminates mixing and provides more convenient administration. Extended-release exenatide also is available as a single-dose tray that requires mixing and may be more cumbersome to inject.

Insulin requires special consideration. There has been an enormous increase in the number of insulin products on the market in the past 2 decades. These products include insulin analogs, concentrated insulins (U-200, U-300, and U-500), premixed insulin preparations, and ultra-long-acting insulin [91]. The availability of insulin options with different concentrations, onsets, and durations of actions has made decision making on which insulin to use difficult. Clinicians need to consider patient preference, dosing frequency, and timing with regard to meals, insulin dose, administration, as well as cost. For example, concentrated insulin is preferred for a patient on high doses of insulin requiring injecting a large volume of insulin. Rapid-acting insulin analogs would be more appropriate for patients who have difficulty administering their regular insulin 20 to
30 minutes before eating. Premixed insulin preparations make it impossible to independently adjust short- and long-acting components. However, these may be good choices in patients who have consistent meal schedules and who want to simplify administration. Despite a prevailing misconception that NPH must be given twice a day, it has long been recognized that in T2DM, a single daily injection of NPH yields improvements in control similar to those achieved with 2 daily injections [92].

Cost Considerations
Treating T2DM imposes a great financial burden on individuals living with diabetes and their families due to the high cost of the medications. Table 4 and Table 5 provide information on the cost of non-insulin and insulin diabetes medications for patients who do not have prescription insurance coverage. From a practical standpoint, choice of diabetes agents is largely influenced by insurance formularies.

The older agents, metformin and the sulfonylureas, are available for a cash (no insurance) price of as little as $4 per month. This is in stark contrast to the SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, which range in cost between $400 and $600 per month. Of recent concern, the cost of insulin has been skyrocketing, with a more than 500% increase in the cost of certain insulins from 2001 to 2015 [93]. According to the Medical Expenditure Panel Survey (MEPS) from 2002 to 2013, the mean price of insulin increased by about 200% (from $4.34/mL to $12.92/mL) during this period, which was significantly higher than increases in the price of non-insulin comparators [94]. The introduction of biosimilar insulins to the market is expected to offer treatment options with lower cost. This will be tested when the biosimilar glargine, the first FDA-approved biosimilar insulin, becomes available in the U.S. market. However, a significant reduction in insulin prices is not expected soon [95].

When insulin is required, most patients with T2DM can be treated with older human insulins, which have similar efficacy and lower costs than the more expensive newer insulin analogs. A Cochrane review comparing basal insulin analogs to NPH showed similar efficacy in glycemic control with minimal clinical benefit in the form of less nocturnal hypoglycemia in the insulin analog arm [96]. Furthermore, similar glycemic control and risk of hypoglycemia was seen when regular insulin was compared with the rapid-acting insulin analogs [97]. The cost of human NPH insulin for a patient on a total daily dose of 60 units is approximately $52 per month. This contrasts with the most widely used insulin, insulin glargine, which has a cash price of about $500 per month for the same amount (Table 5). Insulin pens, which are convenient, are more expensive. Interestingly, human insulins do not require prescriptions, allowing underinsured, underfunded patients ongoing access to them.

Incorporating Patient Preferences
Research evidence is necessary but insufficient for making patient care decisions. Along with the potential benefits, harms, costs, and inconveniences of the management options, patient perspectives, beliefs, expectations, and health-related goals must be considered. Patients will undoubtedly have preferences regarding defining goals and ranking options. Clinicians should discuss therapeutic goals and treatment options and work collaboratively with patients in determining management strategies [98].

Figure 1. Treatment algorithm for hyperglycemia in type 2 diabetes. DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea. *Strong consensus. †No consensus. ‡Alternatively, agents listed in step 2 can be used as initial therapy. §Typically 2 incretin medications are not used together. ‡See Figure 2. (Adapted from references 4 and 7.)
TREATMENT OF HYPERGLYCEMIA IN T2DM

Potential treatment approaches for treating hyperglycemia in T2DM are summarized in Figure 1 and Figure 2 [4,7]. As long as there are no contraindications, metformin should be recommended concurrent with lifestyle intervention at the time of diabetes diagnosis. Even if metformin monotherapy is initially effective, glycemic control is likely to deteriorate over time due to progressive loss of β-cell function in T2DM.

There is no consensus as to what the second-line agent should be. Selection of a second agent should be made based on potential advantages and disadvantages of each agent for any given patient. A patient-centered approach is preferred over a fixed algorithm. If the patient progresses...
to the point where dual therapy does not provide adequate control, either a third non-insulin agent or insulin can be added. In patients with modestly elevated A1C (below ~8%), addition of a third non-insulin agent may be equally effective as (but more expensive than) addition of insulin.

Patients with significantly elevated A1C levels on non-insulin agents usually should have insulin added to their regimen. When insulin is added, metformin should be continued. DPP-4 inhibitors and sulfonylureas are typically stopped. If SGLT-2 inhibitors and/or GLP-1 receptor agonists are continued, this may aid with weight maintenance. However, continuing these agents is likely to be expensive and associated with problems associated with polypharmacy.

The most widely recommended strategy for initiating insulin in T2DM is to add a single bedtime injection of basal insulin (ie, NPH, glargine, detemir, or degludec) to the patient’s regimen. This regimen has been found to be effective in numerous studies and controls hyperglycemia in up to 60% of patients [99]. If the patient is treated with a single bedtime injection of insulin and the fasting glucose level is within the target range but the A1C level remains above goal, addition of mealtime insulin injections is likely to be beneficial. Alternatively, addition of a GLP-1 receptor agonist to basal insulin has been shown to be equally beneficial [4,6]. When adding mealtime insulin, a common strategy is to add a single injection of a rapid-acting insulin (eg, lispro, aspart, glulisine) before the patient’s largest meal of the day. Additional pre-meal injections of rapid-acting insulin may be added as needed, based on self-monitoring blood glucose results. If glycemia remains significantly uncontrolled on more than 200 units of insulin per day, switching to a concentrated form of insulin (eg, U-200, U-300, or U-500) should be considered.

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References


