Learning Objectives
Upon completion of this activity, participants should be better able to:

- Recognize blood glucose (BG) patterns that indicate a need to address postprandial glucose control in patients who are treated with basal insulin
- Review therapeutic approaches for improving glucose control in patients with type 2 diabetes mellitus (T2DM) who are treated with basal insulin therapy
- Identify steps to overcome potential barriers to successful intensification of basal insulin therapy
- Apply knowledge regarding approaches to improve BG control in patients with T2DM who are treated with basal insulin

Introduction
Individualizing Glycemic Targets
Glycemic control is important for minimizing the risk of developing microvascular complications in patients with type 2 diabetes mellitus (T2DM), but results from landmark clinical trials have indicated that not all patients benefit from low glycemic targets.1-3 In their current guidelines, the American Diabetes Association (ADA) recommends a general glycemic target of glycated hemoglobin (A1C) <7.0% (Table 1); the American Association of Clinical Endocrinologists (AACE) recommends a general glycemic goal of A1C ≤6.5% (Table 1) and has an insulin-specific target of A1C <7.0%.5,6 Both organizations recognize that more or less stringent goals may be appropriate for some individuals; younger patients without comorbid disease or complications who are at low risk for hypoglycemia may derive more benefit from tighter glycemic control than older patients with severe comorbid disease who are at high risk for

Demystifying Insulin Intensification: Stepping Beyond Basal Therapy in T2DM
Consider patient characteristics and disease status when setting goals for glycemic control.
hypoglycemia. However, deliberately permitting lax control exposes patients to the risks of acute and chronic complications of hyperglycemia without alleviating the risk of hypoglycemia: epidemiologic analyses have shown that adult patients with A1C <6.0% are at higher risk for severe hypoglycemia than those with A1C between 6.0% and 8.9%, but contrary to expectations, A1C >9.0% does not further protect against severe hypoglycemia. Accordingly, the ADA/European Association for the Study of Diabetes (EASD) recommend individualizing glycemic targets based on multiple patient characteristics. The Elements of Diabetes Care Scale (EDCS) has been proposed to provide clinical guidance in setting specific patient-centered glycemic targets (Table 2); A1C goals using the EDCS system range from 6.5% to 8.5% (Table 3).

Although getting patients with severely elevated A1C to their individualized glycemic goal should be a treatment priority, it is not a race. Rapid reduction of blood glucose (BG) may cause unpleasant symptoms in patients accustomed to high BG levels even if their levels are still far above target. Aim for progressive improvement of glycemia with each 3-month office visit. In randomized trials, a decline of 0.5% every 3 months is common; Canadian diabetes guidelines discuss setting intermediate A1C targets for patients who are severely hyperglycemic.

### Recognizing the Need for Intensification of Postprandial Glucose Control

A1C is 1 of 3 interrelated measures of glycemic control and reflects both preprandial and postprandial glucose (PPG) control. A1C measures glucose control over relatively long periods of time, whereas self-monitored blood glucose (SMBG) measurements provide essentially instantaneous BG readings. Patients with T2DM need to be aware of their BG goals, the benefits of performing SMBG, and when to perform SMBG. SMBG performed before breakfast assesses fasting plasma glucose (FPG); SMBG performed 2 hours after a meal assesses PPG. General FPG and PPG goals are shown in Table 1.

Structured BG monitoring (also known as episodic intensive BG monitoring) can help clinicians determine when medication adjustments are needed to improve glycemic control. This method uses a 7-point glucose profile (before and after each meal and at bedtime) over 3 separate days; the AACE recommends that this be done before each routine follow-up appointment. Patients who find meter downloads challenging may prefer a paper form to record this data. Importantly, clinician review of SMBG records is crucial—not only to ensure that appro-

### Table 1. General Glycemic Targets for Individuals With T2DM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AACE</th>
<th>ADA/EASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>≤6.5</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>&lt;110</td>
<td>70-130</td>
</tr>
<tr>
<td>Preprandial glucose (mg/dL)</td>
<td>&lt;110</td>
<td>70-130</td>
</tr>
<tr>
<td>Postprandial glucose (mg/dL)</td>
<td>&lt;140</td>
<td>&lt;180</td>
</tr>
<tr>
<td>Bedtime glucose (mg/dL)</td>
<td>NS</td>
<td>100-140</td>
</tr>
</tbody>
</table>

NS = not specified.
appropriate adjustments are made to medications, but also to assess meal and activity patterns and adherence to therapy.\textsuperscript{15,18,19} Notably, patients report being frustrated by the effort expended to prepare SMBG records, only to have them given cursory review, if any.\textsuperscript{20} On the other hand, SMBG review allows clinicians to acknowledge the patient’s significant role in self-management.\textsuperscript{21}

### Table 2. EDCS Factor Weights for Individualizing Glycemic Targets\textsuperscript{10}

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>Classification and Point Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
<td>Patient age (y)</td>
<td>&lt;40 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-55 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56-65 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65-79 1.5</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycemic control history</td>
<td>Good 1</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>None 1</td>
<td></td>
</tr>
<tr>
<td>Vascular complications</td>
<td>None 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microvascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Established 2</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia risk</td>
<td>Low 1</td>
<td></td>
</tr>
<tr>
<td>Personal characteristics</td>
<td>Attitudes and diabetes knowledge</td>
<td>Well versed/up-to-date 0</td>
</tr>
<tr>
<td>Psychosocio-economic factors</td>
<td>Resources/support system</td>
<td>Readily available 0</td>
</tr>
<tr>
<td></td>
<td>QoL/psychological status</td>
<td>Good 0</td>
</tr>
<tr>
<td></td>
<td>Economic issues</td>
<td>Minimal 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QoL = quality of life.

### Table 3. Suggested Glycemic Targets Based on EDCS Score\textsuperscript{10}

<table>
<thead>
<tr>
<th>EDCS Score</th>
<th>&lt;5</th>
<th>5-10</th>
<th>11-15</th>
<th>&gt;16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested A1C target (%)</td>
<td>≤6.5</td>
<td>6.6-7.5</td>
<td>7.6-8.0</td>
<td>≈ 8.0-8.5</td>
</tr>
</tbody>
</table>
PPG levels become more important the closer a patient is to attaining his or her A1C goal; even patients with “good” A1C numbers may have wide variations in their BG levels. If A1C is >8.4%, FPG is likely the primary contributor; conversely, if A1C is <8.4%, PPG is likely the primary contributor. The ADA/EASD generally recommend initiating basal insulin in a single dose of 0.1 to 0.2 units/kg/d and titrating until the FPG goal is reached. There are at least 4 ways to identify the need to stop titrating basal insulin and add a different antihyperglycemic agent for PPG control—the specific method used depends on what data are available to the clinician. If you have SMBG data, look for an in-range FPG but persistently elevated PPG (BG >180 mg/dL). If you have the patient’s FPG and A1C, look for an in-range FPG but elevated A1C. Another indicator is that the basal insulin dose has increased from 0.5 to 1.0 units/kg/d. Finally, if further increases in the basal dose are likely to result in hypoglycemia, an agent targeting PPG should be considered. For patients with elevated A1C who are already using basal insulin, it may be tempting (but not recommended) to increase the basal dose to reduce PPG peaks. If the FPG is in range, increasing the basal dose may cause hypoglycemia. Potential consequences of hypoglycemia include cardiac arrhythmias, other cardiovascular events, and falls in older adults.

Exploring Options and Overcoming Barriers to Intensification Beyond Basal Insulin Therapy: Non-Insulin Strategies

Diet and activity patterns must be considered prior to adding medications to intensify antihyperglycemic therapy. BG rises after meals, and the PPG peak is highest when foods high in simple sugars are consumed. However, exercise before or after a meal can reduce PPG. A brief walk (10-15 minutes) can reduce BG by 30 to 50 mg/dL, and a 10-minute walk after each meal may reduce the need for additional medications. That said, T2DM is a progressive disease, and even the most conscientious patients are likely to require therapeutic intensification to maintain their individualized glycemic targets.

In patients with T2DM, insulin can—and likely should—be used in combination with oral antihyperglycemic agents (OHAs). A recent nationally representative survey of emergency department utilization found that hypoglycemia rates in individuals with T2DM treated with insulin-only regimens were 3 to 10 times higher than those in individuals using insulin in combination with an OHA (Figure 1). Current evidence indicates that the combination of metformin with basal insulin is beneficial, with lower rates of hypoglycemia than with insulin-only regimens. However, this combination may be insufficient to maintain glycemic control as T2DM progresses. As newer agents with a lower risk of hypoglycemia and minimal to favorable impact on weight have become available, the sulfonylurea class is losing favor. In addition to the risk of hypoglycemia associated with these agents, there are other concerns regarding cardiovascular safety. Of the 3 sulfonylureas available in the United States, glimepiride appears to be the safest in terms of mortality risk in patients with coronary artery disease.

There are 4 classes of non-insulin agents offering PPG control that can be added to metformin and basal insulin: thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4)
inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors.\textsuperscript{6,8} It is important for clinicians to be aware of the benefits and limitations of these classes of antihyperglycemic therapy so that treatment of patients with T2DM can be appropriately individualized. A summary of key glycemic and nonglycemic outcomes for these agents is shown in Table 4.

**TZDs**
There are 2 TZDs available in the United States: rosiglitazone and pioglitazone.\textsuperscript{36,37} TZDs reduce BG levels by increasing insulin sensitivity and reducing hepatic glucose output.\textsuperscript{8} Pioglitazone has been shown to reduce A1C by approximately 0.6%.\textsuperscript{38} Adding pioglitazone to basal insulin can improve glycemic control without significantly increasing the risk of severe hypoglycemia (Table 4)\textsuperscript{38}; rosiglitazone is not recommended for use in combination with insulin.\textsuperscript{36} Pioglitazone may be used without dose adjustment in patients with any degree of renal impairment, but it is not recommended for use by patients at risk of or with symptomatic or established heart failure, as it can cause fluid retention and lead to edema, especially when used in combination with insulin.\textsuperscript{37} Furthermore, pioglitazone may result in weight gain\textsuperscript{38} and increase the risk of bone fracture and should not be used in patients with active bladder cancer.\textsuperscript{37}
DPP-4 Inhibitors

Currently, 4 DPP-4 inhibitors have been approved for use in the United States: alogliptin, linagliptin, saxagliptin, and sitagliptin.39-42 DPP-4 inhibitors reduce BG by delaying the breakdown of the gut hormone GLP-1, which enhances postprandial insulin secretion and reduces hypoglycemia. In Table 4, we summarize the efficacy and safety outcomes for selected non-insulin agents added to basal insulin.

Table 4. Summary of Efficacy and Safety Outcomes for Selected Non-Insulin Agents Added to Basal Insulin

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Δ A1C (%)</th>
<th>Hypoglycemia, Nonsevere/Severe (% of patients)</th>
<th>Δ Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD</td>
<td>Pioglitazonea,38</td>
<td>–0.58b</td>
<td>40.5/ NR</td>
<td>2.91 (range, 1.4-4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DPP-4 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alogliptinc,43</td>
<td>–0.71b</td>
<td>22.5/0.80</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Linagliptin44</td>
<td>–0.58b (24 wk) –0.48b (52 wk)</td>
<td>22/0.30 (24 wk) 31.4/1.7 (52 wk)</td>
<td>–0.16 (24 wk) –0.3 (52 wk)</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin45</td>
<td>–0.73b</td>
<td>18.4/1.00</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin46</td>
<td>–0.6b</td>
<td>16/0.62</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>GLP-1 RAsf,54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albiglutide qwg,59</td>
<td>–0.8 (26 wk)</td>
<td>15.8/0 (26 wk)</td>
<td>–0.73 (26 wk)</td>
</tr>
<tr>
<td></td>
<td>Exenatide bidg,60</td>
<td>–1.7 (30 wk)h</td>
<td>25/0 (30 wk)</td>
<td>–1.78 (30 wk)h</td>
</tr>
<tr>
<td></td>
<td>Liraglutide once dailyg,j,58</td>
<td>–1.3 (26 wk)h</td>
<td>18.2/0 (26 wk)</td>
<td>–3.54 (26 wk)h</td>
</tr>
<tr>
<td></td>
<td>SGLT2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canagliflozin62</td>
<td>–0.63ab,k to –0.72ab,l</td>
<td>49b,k/1.8k to 2.7l</td>
<td>–1.8b to –2.3l</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin63</td>
<td>–0.64b,m to –0.8b,n</td>
<td>59n to 67n/1.4n to 2.0m</td>
<td>–0.99b,o to –1.50b,o</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin64</td>
<td>–0.6hc to –0.7hc (18 wk)</td>
<td>19.5 to 28.4c/0 to 1.3c (18 wk)</td>
<td>–1.7b,o to –1.3b,c (18 wk)</td>
</tr>
</tbody>
</table>

*Patients receiving basal, bolus, or basal-bolus insulin; bP ≤ .05 vs placebo; c25-mg dose; dBG <60 mg/dL; eOverall hypoglycemia, including nonsevere and severe; fDulaglutide once weekly has not been evaluated in combination with basal insulin; gAlbiglutide, exenatide, and liraglutide have not been studied in combination with prandial insulin; hP ≤ .05 vs baseline; iBG <54 mg/dL; jSimilar vs increasing insulin; k100-mg dose; l300-mg dose; m2.5-mg dose; n5/10-mg dose; o10-mg dose.

NR = not reported.
glucagon secretion. A1C reductions with DPP-4 inhibitors reported in clinical trials range from 0.6% to 0.8%, and adding a DPP-4 inhibitor to basal insulin has been shown to modestly reduce A1C with a low risk of severe hypoglycemia but without weight gain (Table 4). While experience with these agents in patients with renal disease is limited, available data suggest that linagliptin (unlike alogliptin, saxagliptin, or sitagliptin) does not require dose reduction. Furthermore, although the absolute incidence of acute pancreatitis in the SAVOR-TIMI 53 trial was low, it was higher in patients treated with saxagliptin than in those treated with placebo. Accordingly, DPP-4 inhibitors should be promptly discontinued in patients who develop symptoms of pancreatitis, such as severe abdominal pain. Conflicting signals for heart failure with DPP-4 inhibitors have been found in large database analyses. A small but statistically significant increase in the incidence of heart failure has been noted in 2 long-term clinical trials of saxagliptin and alogliptin, but more studies are needed to clarify these unexpected findings.

**GLP-1 RAs**

In the United States, there are 5 approved GLP-1 RAs: albiglutide once weekly (qw), dulaglutide qw, exenatide twice daily (bid), exenatide qw, and liraglutide once daily. GLP-1 RAs are synthetic analogues of the gut hormone GLP-1; unlike their native counterparts, GLP-1 RAs resist breakdown by DPP-4, enhancing postprandial insulin secretion and reducing glucagon secretion. A1C reductions reported in clinical trials for this class of agents range from 0.7% to 1.7%, and adding a GLP-1 RA to basal insulin is associated with reductions in BG, with a low risk of severe hypoglycemia and weight loss (Table 4). (Note: exenatide qw is not recommended for use in combination with insulin, and dulaglutide qw has not been studied in combination with basal insulin.) Auspiciously, observational data indicate that the weight loss is durable, lasting at least 2 years. However, when used in patients with renal impairment, monitoring and dose reduction may be needed with all of the GLP-1 RAs (although dose adjustment is not specifically recommended for albiglutide, dulaglutide, or liraglutide). Exenatide bid and exenatide qw may be used with caution in patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-50 mL/min) but should not be used in patients with severe renal disease (eGFR <30 mL/min). Albiglutide, dulaglutide, and liraglutide can be used with caution in patients with mild, moderate, or severe renal impairment. Furthermore, GLP-1 RAs should not be used in patients with a history of pancreatitis; in patients who develop symptoms of acute pancreatitis, these agents should be discontinued promptly. Albiglutide, dulaglutide qw, exenatide qw, and liraglutide are also contraindicated in patients with personal or family histories of 2 rare types of thyroid tumors—medullary thyroid carcinoma and multiple endocrine neoplasia type 2.

**SGLT2 Inhibitors**

SGLT2 inhibitors are the newest class of agents for the treatment of T2DM. Currently, 3 agents

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Some patients with T2DM may not achieve glycemic goals even with basal insulin therapy, but other options are available to advance therapy.
are approved in the United States: canagliflozin, dapagliflozin, and empagliflozin.\textsuperscript{62-64} SGLT2 inhibitors reduce BG by reducing renal glucose reabsorption, thereby increasing renal glucose excretion.\textsuperscript{65} Similar to the other OHAs discussed previously, A1C reductions of 0.6\% to 0.9\% have been observed in clinical trials of these agents.\textsuperscript{62-64,66,67} Adding an SGLT2 inhibitor to basal insulin modestly reduces BG and body weight, with a low risk of severe hypoglycemia (Table 4).\textsuperscript{62-64,66,67} Since SGLT2 inhibitors increase urinary excretion, before initiating these agents hypovolemia should be assessed and corrected in patients with renal impairment or low systolic blood pressure; elderly patients; or those using diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers.\textsuperscript{62-64} Furthermore, because renal glucose reabsorption is impaired in patients with renal disease, SGLT2 inhibitors are ineffective and therefore contraindicated in patients with severe renal impairment (including dialysis).\textsuperscript{62-64} The dosage of canagliflozin cannot exceed 100 mg if eGFR is \textless 60 mL/min and should be discontinued if eGFR is \textless 45 mL/min.\textsuperscript{62} Dapagliflozin cannot be used at all in patients with eGFR \textless 60 mL/min.\textsuperscript{63} Empagliflozin should not be initiated if eGFR is \textless 45 mL/min; no dose adjustment is required in patients with lesser degrees of renal impairment, but empagliflozin should be discontinued if eGFR falls below 45 mL/min.\textsuperscript{64} Patients using these agents should also be monitored for development of genital mycotic infections, and treatment should be initiated as indicated.\textsuperscript{62-64} Additionally, patients using empagliflozin should also be monitored for urinary tract infections and treated as indicated.\textsuperscript{64}

### Table 5. Initiating and Titrating Prandial Insulin After Optimization of Basal Insulin\textsuperscript{6,8,72}

<table>
<thead>
<tr>
<th>Measure</th>
<th>ADA/EASD\textsuperscript{6,72}</th>
<th>AACE\textsuperscript{6}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>Test premeal values, add before the meal with the highest reading</td>
<td>Total daily dose 0.3 to 0.5 units/kg, administered as:</td>
</tr>
<tr>
<td></td>
<td>Add \approx 4 units</td>
<td>• 50% basal analogue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 50% prandial analogue</td>
</tr>
<tr>
<td>Uptitration for hyperglycemia</td>
<td>1 to 2 units every 3 days</td>
<td>If premeal BG is \textgreater 180 mg/dL, increase the prandial insulin dose by 10% at the meal</td>
</tr>
<tr>
<td></td>
<td>If FPG is \textgreater 180 mg/dL, can increase by 4 units every 3 days</td>
<td>BE\textit{FORE} the one with the high PPG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If 2-h PPG is \textgreater 180 mg/dL, add 10% at that meal</td>
</tr>
<tr>
<td>Downtitration for hypoglycemia</td>
<td>If FPG is \textless 70 mg/dL, reduce bedtime basal dose by 4 units or 10%, whichever is greater</td>
<td>• If fasting AM, reduce basal dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If nighttime, reduce basal and/or presupper or pre-evening snack insulin dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If between meals, reduce previous premeal insulin dose</td>
</tr>
</tbody>
</table>

Rapid-acting analogues are preferred over regular human insulin due to improved PPG control and predictability.\textsuperscript{6,8}
Exploring Options and Overcoming Barriers to Intensification Beyond Basal Insulin Therapy: Insulin Strategies

Prandial insulin is a well-validated strategy recommended in clinical guidelines for addressing elevated PPG in patients with T2DM. With appropriate dose adjustment, insulin can be used in patients with comorbid diseases, such as renal impairment or heart failure, that may limit use of other agents.

Basal-bolus therapy (BBT), consisting of 1 or 2 basal insulin injections daily and 1 prandial insulin injection with each meal, is the standard insulin regimen for patients with type 1 diabetes mellitus. BBT has also been shown to be an effective insulin regimen for patients with T2DM, with more than half of patients in clinical trials meeting a target of A1C <7.0% or more relaxed treatment goals (Figure 2). However, patients with T2DM may be able to attain their individualized goals with less intensive insulin regimens.

Premixed insulin, which combines an intermediate-acting and a prandial insulin in a single injection, may be an acceptable option for patients with consistent schedules and carbohydrate intake but is associated with a greater increase in body mass index (BMI) than basal insulin or BBT. Relative to BBT, premixed insulin is also less effective: fewer than half of patients are able to attain A1C <7.0% using premixed insulin (Figure 2). The risk of hypoglycemia with premixed insulin appears similar to that with BBT.

Stepwise initiation of prandial insulin can be used to overcome a number of barriers to intensifying insulin therapy (Table 5). This strategy adds prandial doses 1 at a time to basal insulin. It is associated with equivalent efficacy but less weight gain and less hypoglycemia.
than transitioning directly from a basal-only regimen to BBT.\textsuperscript{6,8,73,74} Stepwise insulin initiation also minimizes the number of insulin injections and the number of SMBG finger sticks, advantages that may improve patients’ adherence to intensified insulin therapy. Basal and prandial insulin dose self-titration offers another tool to overcome barriers to insulin intensification by further enhancing patient satisfaction.\textsuperscript{75} Self-titration using insulin analogues (which have more predictable actions and are less likely to cause hypoglycemia than human insulins\textsuperscript{6}) and a simple algorithm can be as effective and as safe as clinician-directed dose adjustments.\textsuperscript{75-78}

For some patients with T2DM who need to advance beyond basal insulin, adding a GLP-1 RA may be a reasonable alternative to prandial insulin. Several trials have demonstrated that adding a GLP-1 RA to basal insulin is as effective as adding 1 or 3 prandial insulin doses (A1C reductions of 0.7%-1.1% vs 0.4%-1.1%, respectively), with less weight gain (weight loss of 0.7-2.8 kg vs weight gain of 0.8-2.1 kg, respectively) and nonsevere hypoglycemia (1.0-2.1 vs 5.0-8.2 episodes per person-year, respectively).\textsuperscript{59,79,80} To this end, investigational coformulations of basal insulin and a GLP-1 RA have been evaluated in phase 3 clinical trials.\textsuperscript{81,82} The coformulations demonstrated high efficacy (A1C reduction from baseline of 1.8%), with less hypoglycemia and weight gain than basal insulin without a GLP-1 RA but lower rates of gastrointestinal adverse events than a GLP-1 RA without a basal insulin.\textsuperscript{81,82}

**Conclusion**

Diabetes is a chronic, self-managed disease, and patients rely heavily on well-informed clinicians to help make wise decisions about their care, beginning with appropriately individualized glycemic targets based on clinical, personal, and psychosocioeconomic characteristics. Thoughtful review of SMBG records at every follow-up visit is essential to determine whether adjustments to diet or activity, or additional antihyperglycemic agents, are needed and whether patients have achieved their individualized A1C goals. Steady improvement in BG levels is more important than rapid reduction and is less likely to cause hypoglycemia, as illustrated by the outcomes of clinical trials comparing stepwise prandial insulin therapy with BBT.

Using non-insulin agents in combination with appropriately dosed basal insulin can be an effective and safe strategy for improving glycemic control that is generally associated with lower risks of hypoglycemia than insulin-only regimens. Many antihyperglycemic agents can be used in combination with basal insulin and metformin:

- Pioglitazone, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 RAs (ie, albiglutide, exenatide bid, and liraglutide), and prandial insulin are all associated with improved efficacy relative to placebo
- Pioglitazone, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 RAs are associated with a low risk of severe hypoglycemia
- DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 RAs are associated with a low risk of weight gain

Treatment selection, like glycemic targets, should be individualized to patient characteristics. Insulin therapy offers great flexibility in terms of regimen and dosing. Multiple barriers to prandial insulin therapy can be overcome by stepwise insulin initiation and dose self-titration. Clinicians should apply the principles of individualized patient-centered care and carefully review patients’ personal and family medical histories before prescribing any agent.
CASE: A 47-Year-Old Woman With T2DM

History and Presentation
Eileen, aged 47 years, works nights (11 PM to 7 AM) as a cashier and has expressed concern about gaining weight since initiating basal insulin 12 months ago. When T2DM was diagnosed 7 years ago, she had been treated with metformin with and without a sulfonylurea (discontinued after 2 episodes of severe hypoglycemia). She feared insulin therapy until her A1C increased to 10%, when once-daily basal insulin was initiated. She performs SMBG once daily, before breakfast. At her current visit, she mentions that she is “starving after work,” so she frequently eats a large breakfast and then goes to bed. Her A1C typically fluctuates between 7.0% and 7.5%. Her SMBG meter download shows FPG between 80 and 125 mg/dL.

Physical Examination
- Height: 64 in (162 cm)
- Weight: 172 lb (78 kg)
- BMI: 29.5 kg/m²
- Blood pressure: 129/84 mm Hg
- Mild ankle edema that worsens while at work

Laboratory Results
- A1C: 7.7%

Current Medications
- Metformin extended release 1000 mg once daily (maximum tolerated dose)
- Basal insulin analogue 32 units at 9:00 AM

Clinical Decision Point
According to current guidelines from the ADA/EASD and AACE, what would be an appropriate A1C target for Eileen?
A. <6.0%
B. <7.0%
C. <8.0%
D. <9.0%

Comment
The ADA/EASD recommend a general target of A1C <7.0% but encourage individualization of glycemic goals, with lower targets reserved for patients with a low risk of hypoglycemia. For exam-
ple, a relaxed target of A1C <8.0% is recommended for older patients with longer disease duration and multiple or severe comorbidities. The AACE recommends a general glycemic target of A1C ≤6.5% or an insulin-specific glycemic target of A1C <7.0%. Correct answer: B

Clinical Decision Point
Which inference can be made from Eileen’s BG numbers?
A. She is in excellent glycemic control
B. She has nocturnal hypoglycemia
C. She has fasting hyperglycemia
D. She has postprandial hyperglycemia

Comment
Eileen’s FPG falls within the 70 to 130 mg/dL target range specified by the ADA/EASD, but her A1C is elevated above her individualized target of 7.0%. Nocturnal hypoglycemia would not elevate her A1C relative to her FPG. This pattern of BG data indicates that she has postprandial hyperglycemia. Correct answer: D

Clinical Decision Point
Which of the following SMBG strategies would the AACE recommend to help you and Eileen determine whether she is currently experiencing hypoglycemia?
A. Before and after every meal and at bedtime every day of the week
B. Before and after every meal and at bedtime for 3 days prior to her next follow-up appointment
C. Every night of the week at bedtime
D. SMBG is not necessary for patients with T2DM

Comment
The AACE recommends intensive monitoring for 3 days prior to follow-up visits to assess preprandial, postprandial, and nocturnal BG values. In addition to review of SMBG records at each office visit, clinicians should ask patients whether they are experiencing hypoglycemic episodes. Correct answer: B

Clinical Decision Point
Which of the following strategies would you recommend to improve Eileen’s glycemic control without increasing her risk of hypoglycemia?
A. Tell her that hypoglycemia is an unfortunate consequence of improved glycemic control; review the signs and symptoms to help her recognize and prevent it
B. Increase her basal insulin dose by 10%
C. Decrease her basal insulin dose by 10%
D. Add a GLP-1 RA, a DPP-4 inhibitor, or an SGLT2 inhibitor to her current regimen

Comment
Hypoglycemia is not an inevitable consequence of improved glycemic control, but all patients with diabetes should know how to prevent and treat it. Increasing Eileen’s basal dose may reduce
her PPG, but it will also increase her risk of hypoglycemia because it will reduce her FPG, which is already on the low side of the target range. Decreasing her basal dose will reduce her risk of hypoglycemia, but it will not improve her glycemic control. GLP-1 RAs, DPP-4 inhibitors, and SGLT2 inhibitors have all been shown to reduce PPG and have an intrinsically low risk of hypoglycemia. Correct answer: D

Case (cont’d)
Eileen has had a positive experience with basal insulin self-injection, but if another agent needs to be added, she would prefer an OHA. You consider prescribing a DPP-4 inhibitor or an SGLT2 inhibitor, but they are not in her health plan’s formulary.

Clinical Decision Point
Which individualized treatment intensification plan would you recommend for Eileen?
A. Add a TZD
B. Switch from basal insulin to premixed insulin
C. Increase her basal insulin dose by 10%
D. Present the advantages and disadvantages of prandial insulin or a GLP-1 RA

Comment
Adding a TZD is a potential option; pioglitazone is the only TZD recommended for use in combination with basal insulin, but it causes weight gain and edema. Premixed insulin may help her to meet her glycemic goal, but it causes more weight gain than separate basal and bolus injections. Increasing her basal insulin dose may address her elevated PPG but will increase her risk of hypoglycemia. Adding either prandial insulin or a GLP-1 RA might help Eileen reach her glycemic goals. When used in combination with basal insulin, GLP-1 RAs have a low risk of severe hypoglycemia and weight gain; prandial insulin has a lower risk of hypoglycemia or weight gain when initiated stepwise. A GLP-1 RA might also increase satiety, potentially reducing her hunger after work.83 Correct answer: D

Case Conclusion
A general target of A1C <7.0% has been shown to reduce the risk of developing microvascular complications while avoiding the increased risk of hypoglycemia associated with lower A1C targets. While several different classes of antihyperglycemic agents could be added to Eileen’s current regimen to improve glycemic control, current guidelines from the ADA/EASD and AACE emphasize the need to collaborate with patients to individualize treatment options without significantly increasing the risk of severe hypoglycemia. For effective patient-centered diabetes care, Eileen’s needs and wants should be addressed, including improved PPG control, low risk of hypoglycemia, and little to no weight gain. GLP-1 RAs, DPP-4 inhibitors, SGLT2 inhibitors, TZDs, and stepwise prandial insulin have different advantages and disadvantages for addressing PPG in this patient. Eileen should continue her schedule of 3-month follow-up visits to ensure that adjustments to her therapeutic regimen are having the desired effects.

Click here to access the self-assessment and evaluation form.
References


54. Trulicity (dulaglutide) [prescribing information]. Indianapolis, IN: Eli Lilly and


70. Owen V, Seetho I, Idris I. Predictors of responders to insulin therapy at 1 year among adults with type 2 diabetes. Diabetes
Demystifying Insulin Intensification: Stepping Beyond Basal Therapy in T2DM


Frequently Asked Questions About Insulin

Q. When should PPG be measured?
A. The ADA and AACE have slightly different general guidelines. The ADA recommends measuring 1 to 2 hours after eating and a BG target of <180 mg/dL.¹ The AACE recommends measuring 2 hours after eating and a BG target <140 mg/dL.² It may be hard for patients to remember to test PPG. Some patients test only at times they know will yield good numbers.

Q. Why are A1C targets of 5.7% to 6.2% no longer recommended?
A. The risk of hypoglycemia is very high at low A1C targets; 7.0% balances the risk of hyperglycemia and complications fairly well for most patients. Very aggressive management may be deadly for patients who are older, have complications, or have heart disease.³

Q. Is there a role for measuring C-peptide levels in adjusting medications?
A. This expensive test quantifies insulinopenia and is mainly used to prove to an insurance company that a patient has type 1 diabetes mellitus (T1DM). It can be helpful in diagnosing latent autoimmune diabetes.⁴ Practically, the SMBG log contains the information needed to determine regimen changes. For example, if a patient has had T2DM for a number of years and isn’t responding to a sulfonylurea, this can be addressed clinically.

Q. Is continuous glucose monitoring (CGM) more effective than SMBG?
A. Absolutely, but it is often difficult to persuade insurance companies to cover the cost of CGM for patients with T1DM, let alone T2DM. However, as the cost of these systems decreases, more insurers are likely to cover them. Patients considering personal CGM systems (owned by the patient) need to be aware that they will need to wear the sensor on most days for the devices to be effective as an aid to reducing A1C.⁵ Professional CGM systems (owned by the clinician) can be very helpful if asymptomatic hypoglycemia is suspected. Professional CGM devices offering 3-day blinded data collection and 7-day blinded or unblinded data collection are available.⁶,⁷

Q. What should I do when patients get conflicting information about diabetes management from their primary care provider and their endocrinologist?
A. One of the goals of the patient-centered medical home is to coordinate care between providers; communication is crucial to avoid putting the patient in the middle of a disagreement between providers.

Q. Can sulfonylureas be used in combination with insulin?
A. Opinions vary regarding the discontinuation of sulfonylureas. The AACE, but not the ADA, recommends dose reduction or discontinuation of sulfonylureas when basal insulin is added.⁸,⁹ The ADA suggests discontinuing sulfonylureas when advancing beyond basal insulin.⁹
References


