What next when metformin isn't enough for type 2 diabetes?

This patient-centered case vignette offers insight into how best to choose among additional oral agents, basal insulin, or the newer GLP-1 receptor agonists.

The "Standards of Medical Care in Diabetes" guidelines published in 2015 by the American Diabetes Association (ADA) state that metformin is the preferred initial pharmacotherapy for managing type 2 diabetes. Metformin, a biguanide, enhances insulin sensitivity in muscle and fat tissue and inhibits hepatic glucose production. Advantages of metformin include the longstanding research supporting its efficacy and safety, an expected decrease in the glycated hemoglobin (HbA1c) level of 1% to 1.5%, low cost, minimal hypoglycemic risk, and potential reductions in cardiovascular (CV) events due to decreased low-density lipoprotein (LDL) cholesterol.

To minimize adverse gastrointestinal effects, start metformin at 500 mg once or twice a day and titrate upward every one to 2 weeks to the target dose. To help guide dosing decisions, use the estimated glomerular filtration rate (eGFR) instead of the serum creatinine (SCr) level, because the SCr can translate into a variable range of eGFRs (TABLE 1). Factors that will affect the choice of the second agent include patient preference, cost, potential adverse effects, impact on weight, efficacy, and risk of hypoglycemia.

What if metformin alone isn't enough?

CASE Richard C, age 50, has type 2 diabetes, hypertension, hyperlipidemia, and obesity. He takes metformin 1 g twice a day for his diabetes. After 3 months on this regimen, his HbA1c is 8.8%. How would you manage Mr. C's diabetes going forward?
Based on cost, familiarity, and long-standing safety data, you decide to give Mr. C an SU, while cautioning him about hypoglycemia.

CASE Mr. C has now been taking metformin and an SU at maximum doses for 2 years and continues with lifestyle modifications. Though his HbA1c level dropped after adding the SU, over 2 years it has crept up to 8.6% and his mean blood glucose is 186 mg/dL. What are your treatment options now?

If the target HbA1c level is not achieved on dual therapy, consider triple therapy combinations (TABLE 3). In Mr. C’s case, a third oral agent could be added, but DPP-4 and SGLT2 are unlikely to get his HbA1c below 7%. TZD may get his HbA1c into the desired range but is associated with adverse effects such as heart failure, edema, and weight gain. Mr. C agrees instead to start a basal insulin in conjunction with metformin. You could continue the SU, but you decide to stop it because the additive effect of these medications increases the risk of hypoglycemia.

CASE Six months later Mr. C is taking metformin and insulin glargine, a basal insulin, adjusted to a fasting blood glucose of 80 to 130 mg/dL. His HbA1c is still above target at 8.4%, and the mean postprandial blood glucose is 232 mg/dL.

Mr. C is still above target for HbA1c and for postprandial blood glucose (goal: <180 mg/dL), so he needs pharmacotherapy that targets postprandial glucose elevations. His fasting blood glucose readings are at goal, so increasing his insulin glargine is not recommended because it could cause hypoglycemia. An oral agent other than SU could be added, but none is potent enough to lower the HbA1c to goal (TABLE 2). There are 3 other options:

- add a mealtime bolus of insulin
- add a GLP-1 receptor agonist
- switch to premixed (biphasic) insulin.

What to do when basal insulin isn’t enough—with or without oral meds
For type 2 diabetes poorly controlled on basal insulin with or without oral agents, the 2015 ADA treatment guidelines recommend adding a GLP-1 receptor agonist or mealtime insulin. A less desirable alternative is to switch from basal insulin to a twice-daily premixed (biphasic) insulin analog (70/30 aspart mix or 75/25 or 50/50 lispro mix). The human NPH-Regular premixed formulations (70/30) are less costly alternatives. The disadvantage with all premixed insulins is they only cover 2 postprandial glucose elevations a day.

Insulin requires multiple daily injections, can lead to weight gain, and carries the risk of hypoglycemia, which causes significant morbidity. Daily or weekly administration of a GLP-1 receptor agonist combined with basal insulin can offer a more convenient alternative to mealtime boluses of insulin.

What are GLP-1 receptor agonists?
GLP-1 receptor agonists exert their maximum influence on blood glucose levels during the postprandial period by mimicking the body’s natural incretin hormonal response to oral

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**TABLE 1**

A guide for metformin use based on eGFR

<table>
<thead>
<tr>
<th>eGFR level (mL/min per 1.73 m²)</th>
<th>Metformin recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>Not contraindicated. Monitor renal function annually.</td>
</tr>
<tr>
<td>≥45 to &lt;60</td>
<td>Continue use. Monitor renal function every 3-6 months.</td>
</tr>
<tr>
<td>≥30 to &lt;45</td>
<td>Continue with caution. Use lower dose. Monitor renal function every 3 months. If caring for a new patient, do not initiate him or her on metformin.</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Stop metformin.</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate.

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When prescribing medication for T2DM, consider efficacy, cost, tolerability, impact on body weight, comorbidities, risk of hypoglycemia, and patient preference.

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glucose ingestion. They delay gastric emptying, promote satiety, decrease glucagon secretion, and increase insulin secretion. This mechanism blunts the spiking of postprandial blood glucose after a meal and improves blood glucose control and weight reduction.

A systematic review and meta-analysis by Eng and colleagues compared the safety and efficacy of combined GLP-1 agonist and basal insulin with other treatment regimens. Fifteen randomized controlled trials were included involving 4348 participants with a mean trial duration of 25 weeks.

Compared with all other treatment regimens, the GLP-1 receptor agonist and basal insulin combination not only reduced HbA1c by 0.44% (95% confidence interval [CI], -0.60 to -0.29) and increased the likelihood of attaining an HbA1c of <7.0% (relative risk [RR]=1.92; 95% CI, 1.43 to 2.56) but also reduced weight by 3.22 kg (-4.90 to -1.54) with no increased risk of hypoglycemia (RR=0.99; 0.76 to 1.29).

**GLP-1 agonist vs bolus insulin**

Compared with basal-bolus insulin regimens, the combination of a GLP-1 receptor agonist with basal insulin has led to a significantly lowered risk of hypoglycemia (RR=0.67; 95% CI, 0.56 to 0.80), greater weight loss (-5.66 kg; 95% CI, -9.8 to -1.51) and an average reduction in HbA1c of 0.1% (95% CI, -0.17 to -0.02).

There are 5 GLP-1 receptor agonists that have US Food and Drug Administration approval for the treatment of type 2 diabetes: albiglutide, dulaglutide, exenatide, exenatide XR, and liraglutide (Table 4). All 5 agents...
are administered subcutaneously and packaged in pen-injector form. Adverse effects include nausea, which is transient and diminishes within the first few weeks of therapy, and less commonly, pancreatitis.3,12 All of the GLP-1 receptor agonists, except short-acting exenatide, carry a warning about the risk of worsening renal function and a possible association with medullary thyroid carcinomas, which were identified in rats, but have not been observed in humans.3,12 Medications in this drug class have a low risk for precipitating hypoglycemia.11 Cost is their chief disadvantage, although copay reduction cards are available online for most of the products. Evaluate efficacy, ease of use, tolerability, and cost when selecting a GLP-1 receptor agonist.3,12

**CASE** Mr. C prefers a more convenient option than adding another daily injection. Given his obesity, a GLP-1 receptor agonist can help

### TABLE 4
Comparison of GLP-1 receptor agonists3,12

<table>
<thead>
<tr>
<th>Drug name, cost per month</th>
<th>Dose</th>
<th>Preparation</th>
<th>Efficacy</th>
<th>Adverse effects</th>
<th>Use in renal/hepatic impairment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide (Tanzeum) −$330</td>
<td>30-50 mg/wk</td>
<td>Pen needle provided. Reconstitute 15 minutes (30-mg dose) or 30 minutes (50-mg dose) before injection.</td>
<td>−1% HbA1c reduction. −1 kg mean weight loss</td>
<td>Diarrhea, 13%; nausea, 11%; injection site reaction, 11%-18%; URI, 14%</td>
<td>No dose adjustment needed. Use caution when initiating or escalating doses in renal dysfunction.</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity) −$500</td>
<td>0.75-1.5 mg/wk</td>
<td>Pen needle provided. No reconstitution needed.</td>
<td>−1.5% HbA1c reduction. −2.5 kg mean weight loss</td>
<td>Nausea, 12%-21%; diarrhea, 9%-13%; vomiting, 6%-13%; injection site reactions, 0.5%</td>
<td>No dose adjustment needed.</td>
</tr>
<tr>
<td>Exenatide (Byetta) −$430</td>
<td>5-10 mcg bid</td>
<td>Pen needles not supplied with pen. No reconstitution needed.</td>
<td>−1% HbA1c reduction. −2 kg mean weight loss</td>
<td>Nausea, 8%-44%; diarrhea, 6%-20%; vomiting, 4%-18%; headache, 8%-14%; injection site reactions, 12.7%</td>
<td>Avoid use in severe renal impairment or end-stage renal disease. Use caution in patients with renal transplantation or moderate renal impairment. No dose adjustment for hepatic impairment.</td>
</tr>
<tr>
<td>Exenatide XR (Bydureon) −$440</td>
<td>2 mg/wk</td>
<td>Pen needle provided. Both the vial and pen forms must be reconstituted immediately prior to use.</td>
<td>−1.5% HbA1c reduction. −2.5 kg mean weight loss</td>
<td>Nausea, 13%-24%; diarrhea, 6%-20%; headache, 8%-14%; injection site nodules, 6%-77%</td>
<td>Avoid use in severe renal impairment or end-stage renal disease. Use caution in patients with renal transplantation or moderate renal impairment. No dose adjustment for hepatic impairment.</td>
</tr>
<tr>
<td>Liraglutide (Victoza) −$400−$600, depending on dose</td>
<td>0.6-1.8 mg/d</td>
<td>Pen needles not supplied with pen. No reconstitution needed.</td>
<td>−1.5% HbA1c reduction. −2.5 kg mean weight loss</td>
<td>Nausea, 28%-34.6%; diarrhea, 17%; vomiting, 11%; headache, 14%; injection site reactions, 2%</td>
<td>Use caution when initiating or increasing dose in patients with renal impairment. Use caution in hepatic impairment.</td>
</tr>
</tbody>
</table>

* Moderate renal impairment: CrCl, 30-50 mL/min; severe renal impairment: CrCl, <30 mL/min.

bid, twice a day; CrCl, creatinine clearance; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; URI, upper respiratory infection.
with weight loss and lower his risk for hypo-
glycemia. To further increase the convenience in dosing, you lean toward either weekly ex-
enatide XR or dulaglutide over basal-bolus combination insulin. Weekly albiglutide is less potent than exenatide XR and dulaglutide in decreasing HbA1c. Mr. C’s insurance plan provides preferred coverage for exena-
tide XR and he is eligible for a copay savings

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ceptor agonist and basal insulin combination treatment for the

PART 2 Tumor biology and
genomics: The first element
By Bobby Daly, MD, MBA, and Olufumilayo I. Olopade, MD, FACP, OON

The series was adapted from an article originally published in CA: A Cancer Journal for Clinicians
(journal of the American Cancer Society) and reviews innovative interventions to close this survival

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