Diet, exercise, and weight loss can improve glycemic control, but almost all patients with type 2 diabetes eventually require drug therapy. Treating to a glycated hemoglobin (A1C) concentration of <7% can prevent microvascular complications (retinopathy, nephropathy, and neuropathy), but whether it prevents macrovascular complications and death is unclear. An A1C target of <8% may be appropriate for older patients and those with underlying cardiovascular disease (CVD), a history of severe hypoglycemia, diabetes-related complications, a limited life expectancy, or a long duration of disease.1,2

METFORMIN — The oral biguanide metformin (Glucophage, and others) is generally the drug of choice for initial treatment of type 2 diabetes.1,2 Its mechanism of action is complex.3,4 Metformin decreases hepatic glucose production and increases secretion of glucagon-like peptide-1 (GLP-1). It may also reduce intestinal absorption of glucose and (to a lesser extent) increase peripheral glucose uptake. Metformin monotherapy reduces A1C by 1-1.5%, is weight-neutral or causes modest weight loss, and does not cause hypoglycemia.

Cardiovascular Benefits — In a 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS), initial treatment with metformin was associated with a 33% reduction in the risk of myocardial infarction and a 27% reduction in the risk of death from any cause, compared to dietary restriction alone.5

Renal Impairment — Metformin is contraindicated for use in patients with an eGFR <30 mL/min/1.73 m², and starting the drug in patients with an eGFR of 30-45 mL/min/1.73 m² is not recommended.6 A retrospective cohort study in 49,478 patients with type 2 diabetes who continued taking metformin or a sulfonylurea after developing renal impairment (eGFR <60 mL/min/1.73 m²) found that metformin monotherapy was associated with a significantly lower risk of major adverse cardiovascular events, compared to sulfonylurea monotherapy.7

Other Comorbidities — In a review of 17 observational studies, use of metformin was associated with reduced all-cause mortality in patients with type 2 diabetes and moderate to severe chronic kidney disease (CKD), heart failure (HF), or chronic liver disease.8

SGLT2 INHIBITORS — SGLT2 (sodium-glucose co-transporter 2) inhibitors decrease renal glucose reabsorption and increase urinary glucose excretion, reducing fasting and postprandial blood glucose levels. They reduce A1C by 0.5-1%; other beneficial effects include a reduction in systolic blood pressure, weight loss, reduction in cardiovascular death in patients with CVD or high cardiovascular risk, and improved renal outcomes in patients with nephropathy.

Canagliflozin (Invokana) — In two randomized, double-blind trials (CANVAS and CANVAS-R) with a median follow-up of 126 weeks in a total of 10,142
<table>
<thead>
<tr>
<th>Drug Class (A1C Reduction)</th>
<th>Some Advantages</th>
<th>Some Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanide (1-1.5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Inexpensive; durable A1C lowering; weight-neutral or modest weight loss; no hypoglycemia when used as monotherapy; reduced risk of micro- and macrovascular events</td>
<td>GI effects (metallic taste, nausea, diarrhea, abdominal pain); vitamin B12 deficiency; lactic acidosis</td>
</tr>
<tr>
<td><strong>SGLT2 Inhibitors (0.5-1%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin</td>
<td>Weight loss; reduced systolic blood pressure; no hypoglycemia when used as monotherapy; reduced incidence of CV events, heart failure, and nephropathy</td>
<td>Genital mycotic infections; Fournier’s gangrene; volume depletion; acute kidney injury; hypotension; ketoacidosis; fractures; increase in LDL-cholesterol; possible increased risk of lower limb amputation, primarily at the level of the toe or metatarsal, with canagliflozin</td>
</tr>
<tr>
<td><strong>GLP-1 Receptor Agonists (1-1.5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide, exenatide, lixisenatide, semaglutide</td>
<td>Weight loss; no hypoglycemia when used as monotherapy; reduced incidence of CV events and nephropathy; dulaglutide, extended-release exenatide and semaglutide are administered SC once weekly; semaglutide is available in an oral formulation</td>
<td>GI effects (nausea, vomiting, diarrhea); renal impairment and acute renal failure associated with dehydration caused by GI toxicity; injection-site reactions; possible risk of acute pancreatitis; thyroid C-cell carcinoma has been reported in animals and thyroid C-cell hyperplasia has been reported in humans</td>
</tr>
<tr>
<td><strong>DPP-4 Inhibitors (0.5-1%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin, linagliptin, saxagliptin, sitagliptin</td>
<td>Weight-neutral; hypoglycemia rare when used as monotherapy</td>
<td>Possible risk of acute pancreatitis; fatal hepatic failure; possible severe and disabling joint pain</td>
</tr>
<tr>
<td><strong>Sulfonylureas (1-1.5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride, glipizide, glyburide</td>
<td>Inexpensive; long-term reduction in micro- and macrovascular complications; reductions in albuminuria</td>
<td>Hypoglycemia; weight gain; glyburide has a higher incidence of hypoglycemia and mortality than glimepiride or glipizide</td>
</tr>
<tr>
<td><strong>Thiazolidinediones (1-1.5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone, rosiglitazone</td>
<td>Durable A1C lowering; low risk of hypoglycemia</td>
<td>Weight gain; heart failure; macular edema; possible decrease in bone mineral density and increased incidence of fractures, especially in women; hepatic failure; pioglitazone has been associated with an increased risk of bladder cancer</td>
</tr>
<tr>
<td><strong>Meglitinides (0.5-1%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide, repaglinide</td>
<td>Short-acting</td>
<td>Hypoglycemia, especially in patients with severe renal impairment taking nateglinide; weight gain</td>
</tr>
<tr>
<td><strong>Alpha-Glucosidase Inhibitors (0.5-1%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose, miglitol</td>
<td>No hypoglycemia when used as monotherapy</td>
<td>Abdominal pain, diarrhea, flatulence; transaminase elevations with acarbose</td>
</tr>
<tr>
<td><strong>Others (0.5%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Weight loss; reduced postprandial glucose excursions</td>
<td>Nausea, vomiting, anorexia; headache; severe hypoglycemia (when given with insulin)</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>No hypoglycemia; decreased LDL cholesterol</td>
<td>Constipation, nausea, dyspepsia; increased serum triglyceride concentrations</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>No hypoglycemia; may reduce risk of cardiovascular events</td>
<td>Nausea, vomiting, fatigue; headache; dizziness; somnolence; syncope</td>
</tr>
</tbody>
</table>

**CV = cardiovascular; LDL = low-density lipoprotein**

1. Gastrointestinal adverse effects usually decrease over time and can be avoided by starting with a low dose. Use of extended-release formulations may also reduce GI adverse effects.
3. Occurs rarely. Metformin should not be administered for 48 hours after an iodinated contrast imaging procedure in patients with an eGFR < 60 mL/min/1.73 m² or a history of liver disease, alcoholism, or heart failure, or in those receiving intra-arterial contrast, and eGFR should be re-evaluated before treatment is restarted.
6. Slow titration can minimize these effects.
9. Contraindicated in patients with NYHA class III or IV heart failure.
11. If hypoglycemia occurs, it should be treated with oral glucose because these drugs interfere with the breakdown of sucrose.
patients with type 2 diabetes and high cardiovascular risk, the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower with addition of canagliflozin to standard treatment, compared to addition of placebo (26.9 vs 31.5 cases per 1000 patient-years). However, the risk of toe, foot, or leg amputation was higher with canagliflozin (6.3 vs 3.4 cases per 1000 patient-years); this association has not been reported in trials with other SGLT2 inhibitors. Canagliflozin is approved to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established CVD.

A randomized, double-blind trial (CREDENCE) in 4401 patients with type 2 diabetes, albuminuria (urine albumin-to-creatinine ratio [UACR] >300 mg/g), and an eGFR of 30–<90 mL/min/1.73 m² was stopped early based on data that the risk of end-stage kidney disease, doubling of serum creatinine levels, or death from renal or cardiovascular causes was reduced by 30% with canagliflozin, compared to placebo. The canagliflozin group also had a reduced risk of cardiovascular death, myocardial infarction, stroke, and hospitalization for HF, and there was no increased risk of amputation compared to placebo in this trial. Based on these results, canagliflozin was approved by the FDA to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular death, and hospitalization for HF in adults with type 2 diabetes and diabetic nephropathy with albuminuria.

Dapagliflozin (Farxiga) — In a randomized, double-blind trial (DECLARE-TIMI 58) in 17,160 patients with type 2 diabetes who had or were at risk for artherosclerotic cardiovascular disease (ASCVD), dapagliflozin did not reduce the composite endpoint of major adverse cardiovascular events (cardiovascular death, myocardial infarction, or ischemic stroke) compared to placebo, but did reduce the rate of hospitalization for HF. In another randomized, double-blind trial (DAPA-HF) in 4744 patients with HF and a left ventricular ejection fraction ≤40%, the composite endpoint of worsening HF or cardiovascular death was significantly lower with addition of dapagliflozin to standard treatment than with addition of placebo (16.3% vs 21.2%), whether or not patients had diabetes. Dapagliflozin is FDA-approved to reduce the risk of hospitalization for HF in adults with type 2 diabetes.

Empagliflozin (Jardiance) — In a randomized, double-blind trial (EMPA-REG OUTCOME) in 7020 patients with type 2 diabetes and established CVD, addition of empagliflozin to standard care reduced the rates of cardiovascular death, hospitalization for HF, and death from any cause, compared to addition of placebo. Empagliflozin also reduced the risk of nephropathy (progression to macroalbuminuria, doubling of serum creatinine levels, initiation of renal-replacement therapy). In a subset of patients with an eGFR <60 mL/min/1.73 m² and/or albuminuria, empagliflozin reduced the risks of cardiovascular death by 29%, all-cause mortality by 24%, and hospitalization for HF by 39%, compared to placebo. Empagliflozin is FDA-approved to reduce the risk of cardiovascular death in adults with type 2 diabetes and established CVD.

Ertugliflozin (Steglatro) — There are no completed clinical trials of the effect of ertugliflozin on cardiovascular or renal outcomes.

Class Benefits — In a population-based cohort study (EASEL) in 25,258 patients with type 2 diabetes and established CVD, initiation of an SGLT2 inhibitor was associated with lower rates of all-cause mortality, hospitalization for HF, and major adverse cardiovascular events, compared to initiation of a non-SGLT2 inhibitor. A meta-analysis of 3 cardiovascular outcome trials of SGLT2 inhibitors (empagliflozin, dapagliflozin, and canagliflozin) in 34,322 patients with type 2 diabetes (60% with established ASCVD) found that these drugs reduced the risk of major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death) by 11%, but only in those with established ASCVD. Reductions in the risk of cardiovascular death or hospitalization for HF (23%) and in progression of renal disease (45%) occurred independently of the patient’s history of ASCVD or HF.

GLP-1 RECEPTOR AGONISTS — Glucagon-like peptide-1 (GLP-1) receptor agonists potentiate glucose-dependent secretion of insulin, suppress glucagon secretion, slow gastric emptying, and promote satiety. They reduce A1C by 1–1.5% and cause weight loss. GLP-1 receptor agonists can reduce the incidence of major adverse cardiovascular events and may have a beneficial effect on proteinuria, but whether they prevent progression of CKD is not clear.

Dulaglutide (Trulicity) — Meta-analyses have found no increase or decrease in the risk of major adverse cardiovascular events with use of dulaglutide. However, in a randomized, double-blind trial (REWIND) with a median follow-up of 5.4 years in 9901 patients who had a cardiovascular event or cardiovascular risk factors, the composite endpoint of nonfatal myocardial
Table 2. Formulations, Dosage, and Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Formulations</th>
<th>Usual Adult Dosage</th>
<th>Cost 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin2 – generic</td>
<td></td>
<td>500, 850, 1000 mg tabs</td>
<td>1500-2550 mg/day PO divided bid-tid2</td>
</tr>
<tr>
<td>Glucophage (BMS)</td>
<td></td>
<td>500 mg/5 mL soln (4, 16 oz)</td>
<td>1500-2550 mg/day PO divided bid-tid2</td>
</tr>
<tr>
<td>Riomet (Sun)</td>
<td>500, 750, 1000 mg tabs</td>
<td>1500-2000 mg PO once/day</td>
<td>8.10</td>
</tr>
<tr>
<td>Glumetza (Santarus)</td>
<td></td>
<td>500, 1000 mg ER tabs</td>
<td>4.884.30</td>
</tr>
<tr>
<td>Riomet ER</td>
<td>500 mg/5 mL ER susp (16 oz)</td>
<td>1500-2550 mg/day PO divided bid-tid2</td>
<td>N.A</td>
</tr>
<tr>
<td><strong>SGLT2 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin – Invokana (Janssen)</td>
<td>100, 300 mg tabs</td>
<td>100-300 mg PO once/day</td>
<td>494.30</td>
</tr>
<tr>
<td>Dapagliflozin – Farxiga (AstraZeneca)</td>
<td>5, 10 mg tabs</td>
<td>5-10 mg PO once/day</td>
<td>492.40</td>
</tr>
<tr>
<td>Empagliflozin – Jardiance (Boehringer Ingelheim/Lilly)</td>
<td>10, 25 mg tabs</td>
<td>10-25 mg PO once/day</td>
<td>492.90</td>
</tr>
<tr>
<td>Ertugliflozin – Steglatro (Merck)</td>
<td>5, 15 mg tabs</td>
<td>5-15 mg PO once/day</td>
<td>281.40</td>
</tr>
<tr>
<td><strong>GLP-1 Receptor Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide – Trulicity (Lilly)14</td>
<td>0.75 mg/0.5 mL, 1.5 mg/0.5 mL single-dose pens</td>
<td>0.75 or 1.5 mg SC once/wk</td>
<td>759.40</td>
</tr>
<tr>
<td>Exenatide – Byetta (AstraZeneca)</td>
<td>250 mcg/mL (1.2, 2.4 mL)</td>
<td>5 or 10 mcg SC bid15,16</td>
<td>729.60</td>
</tr>
<tr>
<td>Liraglutide – Victoza (Novo Nordisk)14</td>
<td>6 mg/mL (3 mL)</td>
<td>1.2 or 1.8 mg SC once/day</td>
<td>614.50</td>
</tr>
<tr>
<td>Lixisenatide – Adlyxin (Sanoﬁ)</td>
<td>50 mcg/mL 100 mcg/mL (3 mL)</td>
<td>20 mcg SC once/day</td>
<td>620.20</td>
</tr>
<tr>
<td>Semaglutide – Ozempic (Novo Nordisk)14</td>
<td>1.34 mg/mL (1.5 mL)</td>
<td>0.5 or 1 mg SC once/wk</td>
<td>772.40</td>
</tr>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin – generic Nesina (Takeda)</td>
<td>6.25, 12.5, 25 mg tabs</td>
<td>25 mg PO once/day</td>
<td>195.00</td>
</tr>
<tr>
<td>Linagliptin – Tradjenta (Boehringer Ingelheim/Lilly)</td>
<td>5 mg tabs</td>
<td>5 mg PO once/day</td>
<td>436.20</td>
</tr>
<tr>
<td>Saxagliptin – Onglyza (AstraZeneca)</td>
<td>2.5, 5 mg tabs</td>
<td>2.5-5 mg PO once/day</td>
<td>420.50</td>
</tr>
<tr>
<td>Sitagliptin – Januvia (Merck)</td>
<td>25, 50, 100 mg tabs</td>
<td>100 mg PO once/day</td>
<td>451.20</td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride – generic Amaryl (Sanofi)</td>
<td>1, 2, 4 mg tabs</td>
<td>1-4 mg PO once/day</td>
<td>2.70</td>
</tr>
<tr>
<td>Glipizide – generic Glucotrol (Pfizer)</td>
<td>5, 10 mg tabs</td>
<td>10-20 mg PO once/day or divided bid</td>
<td>2.40</td>
</tr>
<tr>
<td>Glyburide26 – generic micronized tablets – generic Glynase Prestab (Pfizer)</td>
<td>1.25, 2.5, 5 mg tabs</td>
<td>1.25-20 mg PO once/day or divided bid</td>
<td>1.80</td>
</tr>
</tbody>
</table>

ER = extended release; soln = solution; susp = suspension; N.A. = cost not available
1. Approximate WAC for 4 weeks or 30 days’ treatment with the lowest usual adult dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. October 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
2. Metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m2. Starting metformin therapy in patients with an eGFR of 30-45 mL/min/1.73 m2 is not recommended. If the eGFR falls below 45 mL/min/1.73 m2 in patients already taking metformin, the benefits and risks of continuing treatment should be assessed.
3. Taken with meals.
4. Cost of one 16-ounce bottle.
5. Taken with the evening meal.
6. Tablets should be swallowed whole not split, crushed, or chewed.
7. Taken with breakfast or first meal of the day.
8. Maximum dose is 100 mg in patients with an eGFR of 30–60 mL/min/1.73 m². Should not be started in patients with an eGFR <30 mL/min/1.73 m2 with albuminuria >300 mg/day or in those with an eGFR <45 mL/min/1.73 m2 with albuminuria <300 mg/day.
9. Contraindicated in patients with an eGFR <30 mL/min/1.73 m2.
10. Taken in the morning, with or without food.
11. Should not be started in patients with an eGFR <45 mL/min/1.73 m2 or in those with active bladder cancer.
12. Should not be started in patients with an eGFR <45 mL/min/1.73 m2.
13. Should not be started in patients with an eGFR of 30–60 mL/min/1.73 m2.
14. Contraindicated in patients with or who have a family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2.
### Table 2. Formulations, Dosage, and Cost (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Formulations</th>
<th>Usual Adult Dosage</th>
<th>Cost1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone – generic Actos (Takeda)</td>
<td>15, 30, 45 mg tabs</td>
<td>15-45 mg PO once/day27,28</td>
<td>$4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>388.60</td>
</tr>
<tr>
<td>Rosiglitazone – Avandia (GSK)</td>
<td>2, 4 mg tabs</td>
<td>4-8 mg PO once/day or divided bid29</td>
<td>169.40</td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide – generic</td>
<td>60, 120 mg tabs</td>
<td>60-120 mg PO tid30</td>
<td>41.60</td>
</tr>
<tr>
<td>Repaglinide – generic</td>
<td>0.5, 1, 2 mg tabs</td>
<td>1-4 mg PO tid30,31</td>
<td>19.10</td>
</tr>
<tr>
<td><strong>Alpha-Glucosidase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose – generic Preceose (Bayer)</td>
<td>25, 50, 100 mg tabs</td>
<td>50-100 mg PO tid132</td>
<td>41.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>90.00</td>
</tr>
<tr>
<td>Miglitol – generic Glyset (Pfizer)</td>
<td>25, 50, 100 mg tabs</td>
<td>50-100 mg PO tid133</td>
<td>170.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>271.80</td>
</tr>
<tr>
<td><strong>Combination Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin/glipizide1 – generic</td>
<td>250/2.5, 500/2.5, 500/5 mg tabs</td>
<td>500/2.5 mg PO bid1</td>
<td>24.00</td>
</tr>
<tr>
<td>Metformin/gliburide1,26 – generic</td>
<td>250/1.25, 500/2.5, 500/5 mg tabs</td>
<td>500/5 mg PO bid2</td>
<td>35.20</td>
</tr>
<tr>
<td>Metformin/pioglitazone1 – generic Actoplus Met (Takeda)</td>
<td>500/15, 850/15 mg tabs</td>
<td>500/15 mg PO bid137</td>
<td>75.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin/alogliptin2 – generic Kazano (Takeda)</td>
<td>500/12.5, 1000/12.5 mg tabs</td>
<td>1000/12.5 mg PO bid13</td>
<td>195.00</td>
</tr>
<tr>
<td>Metformin/linaglaptin2 – Jentadueto</td>
<td>500/2.5, 850/2.5, 1000/2.5 mg tabs</td>
<td>500/2.5-1000/2.5 mg PO bid1</td>
<td>436.20</td>
</tr>
<tr>
<td>(Boehringer Ingelheim/Lilly)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jentadueto XR</td>
<td>1000/2.5, 1000/5 mg ER tabs</td>
<td>1000/5-2000/5 mg PO once/day45,46</td>
<td>420.50</td>
</tr>
<tr>
<td>Metformin/saxagliptin2 – Kombiglyze XR (BMS)</td>
<td>500/5, 1000/2.5, 1000/5 mg ER tabs</td>
<td>1000/5-2000/5 mg PO once/day45,46</td>
<td>420.50</td>
</tr>
<tr>
<td>Metformin/stiglaptin2 – Janumet (Merck) Janumet XR</td>
<td>500/50, 1000/50 mg tabs</td>
<td>500/50-1000/50 mg PO bid4</td>
<td>225.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin/canagliflozin2 – Invokamet (Janssen)</td>
<td>500/50, 1000/50, 500/150, 1000/150 mg tabs</td>
<td>500/50-500/150 mg PO bid130</td>
<td>494.30</td>
</tr>
<tr>
<td>Invokamet XR</td>
<td>500/50, 1000/50, 500/150, 1000/150 mg tabs</td>
<td>1000/100-1000 mg PO once/day4,4,29</td>
<td>494.30</td>
</tr>
<tr>
<td>Metformin/dapagliflozin2 – Xigduo XR (AstraZeneca)</td>
<td>1000/2.5, 500/5, 1000/5, 1000/10 ER tabs</td>
<td>1000/5-1000/10 mg PO once/day4,4,29</td>
<td>492.40</td>
</tr>
<tr>
<td>Metformin/empagliflozin2 – Synjardy (Boehringer Ingelheim/Lilly)</td>
<td>500/5, 1000/5, 500/12.5, 1000/12.5 mg tabs</td>
<td>500/5-1250/12.5 mg PO bid40</td>
<td>492.90</td>
</tr>
<tr>
<td>Synjardy XR</td>
<td>1000/5, 1000/10, 1000/12.5, 1000/25 mg ER tabs</td>
<td>1000/5-1000/25 mg PO once/day4,4,40</td>
<td>246.40</td>
</tr>
<tr>
<td>Metformin/ertugliflozin2 – Segluromet (Merck)</td>
<td>500/2.5, 500/7.5, 1000/2.5, 1000/7.5 mg tabs</td>
<td>500/2.5-1000/7.5 mg PO bid13</td>
<td>281.40</td>
</tr>
<tr>
<td>Metformin/dapagliflozin/saxagliptin2 – Qternmet XR (AstraZeneca)</td>
<td>1000/2.5/2.5, 1000/5/2.5, 1000/5/5, 1000/10/5 mg ER tabs</td>
<td>1000/5-5000/10/5 mg PO once/day4,4,31</td>
<td>N.A.</td>
</tr>
<tr>
<td>Glimepiride/pioglitazone – generic Duetact (Takeda)</td>
<td>2/30, 4/30 mg tabs</td>
<td>2/30-4/30 mg PO once/day4,37</td>
<td>390.50</td>
</tr>
</tbody>
</table>

15. Starting dosage is 5 mg twice daily, up to an hour before morning and evening meals. After one month, the dosage can be increased to 10 mg twice daily.
16. The immediate-release formulation is not recommended for patients with a CrCl <30 mL/min and the extended-release products are not recommended for those with an eGFR <45 mL/min/1.73 m².
17. Must be reconstituted before administration.
18. Starting dosage is 0.6 mg once daily for 7 days, followed by 1.2 mg thereafter.
19. Starting dosage is 10 mcg once daily, up to an hour before the morning meal, for 14 days, followed by 20 mcg thereafter.
20. Starting dosage is 0.25 mg once weekly for 4 weeks.
21. Starting dosage is 3 mg once daily for 30 days. Tablets should be swallowed whole with no more than 4 ounces of water 30 minutes before first food, drink, or other oral drugs.
22. The recommended dosage is 12.5 mg once daily in patients with a CrCl of 30-59 mL/min and 6.25 mg once daily in those with a CrCl <30 mL/min.
23. The recommended dosage is 2.5 mg once daily in patients with an eGFR <45 mL/min/1.73 m².
24. The recommended dosage is 50 mg once daily in patients with an eGFR of 30-45 mL/min/1.73 m² and 25 mg once daily in those with an eGFR <30 mL/min/1.73 m².
25. Doses >15 mg/day should be divided and given before meals of adequate caloric content.
27. Should not be started in patients with ALT >3 times upper limit of normal (ULN) with serum total bilirubin >2 times ULN. Contraindicated in patients with NYHA class III or IV heart failure.
28. The starting dosage of pioglitazone is 15 mg once daily in patients with NYHA class I or II heart failure.
infarction, nonfatal stroke, or cardiovascular death was significantly lower with addition of dulaglutide to standard treatment, compared to addition of placebo (12.0% vs 13.4%).

Long-term (~5 years) use of dulaglutide has been associated with a reduced incidence of the composite endpoint of new macroalbuminuria, sustained decline in eGFR, or chronic renal replacement therapy.

**Exenatide (Byetta, Bydureon)** – In a randomized, double-blind trial (EXSCEL) in 14,752 patients (73% had CVD), the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was 11.4% with addition of once-weekly exenatide to standard treatment and 12.2% with addition of placebo; exenatide was noninferior to placebo in safety but not superior with regard to efficacy.

**Liraglutide (Victoza)** – In a randomized, double-blind trial (ELLIPSE) in children 10–<17 years old with type 2 diabetes, liraglutide (added to metformin, with or without basal insulin) was superior to placebo in reducing A1C over 52 weeks (-0.50% vs +0.80%). Liraglutide is FDA-approved for use in patients ≥10 years old with type 2 diabetes.

In a randomized, double-blind trial (LEADER) with a median follow-up of 3.8 years in 9340 patients with type 2 diabetes at high risk for CVD, addition of liraglutide to standard treatment significantly reduced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, compared to addition of placebo (13.0% vs 14.9%). Liraglutide is FDA-approved to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes.

In a prespecified secondary analysis of renal outcomes in the LEADER trial, the composite endpoint of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease occurred in 5.7% of patients who received liraglutide and in 7.2% of those who received placebo. This difference was primarily due to reductions in new-onset persistent macroalbuminuria with liraglutide.

---

### Table 2. Formulations, Dosage, and Cost (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Formulations</th>
<th>Usual Adult Dosage</th>
<th>Cost†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combination Products (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin/pioglitazone – Oseni (Takeda)</td>
<td>12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg tabs</td>
<td>25/15-25/45 mg PO once/day&lt;sup&gt;10,27,28,41&lt;/sup&gt;</td>
<td>$195.00 385.60</td>
</tr>
<tr>
<td>Dapagliflozin/saxagliptin – Qtern (AstraZeneca)</td>
<td>5/5, 10/5 mg tabs</td>
<td>10/5 mg PO once/day&lt;sup&gt;11,42&lt;/sup&gt;</td>
<td>492.40</td>
</tr>
<tr>
<td>Empagliflozin/linagliptin – Glyxambi (Boehringer Ingelheim/Lilly)</td>
<td>10/5, 25/5 mg tabs</td>
<td>10/5-25/5 mg PO once/day&lt;sup&gt;11,42&lt;/sup&gt;</td>
<td>539.30</td>
</tr>
<tr>
<td><strong>Long-Acting Insulin/GLP-1 Receptor Agonist Combinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin degludec/lixisenatide – Xultophy 100/3.6 (Novo Nordisk)</td>
<td>3 mL prefilled pens&lt;sup&gt;43&lt;/sup&gt;</td>
<td>16-50 units SC once/day&lt;sup&gt;44,45&lt;/sup&gt;</td>
<td>831.90&lt;sup&gt;46&lt;/sup&gt;</td>
</tr>
<tr>
<td>Insulin glargine/lixisenatide – Soliqua 100/33 (Sanofi)</td>
<td>3 mL prefilled pens&lt;sup&gt;47&lt;/sup&gt;</td>
<td>15-60 units SC once/day&lt;sup&gt;44,49&lt;/sup&gt;</td>
<td>565.40&lt;sup&gt;46&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

29. Should not be started in patients with active liver disease or ALT >2.5 times ULN. Contraindicated in patients with NYHA class III or IV heart failure.
30. Doses should be taken 15-30 minutes before meals. Should not be taken if meal is missed.
31. A starting dose of 0.5 mg tid with meals is recommended for patients with a CrCl of 20-40 mL/min.
32. Not recommended for patients with a serum creatinine >2 mg/dL.
33. Not recommended in patients with a CrCl <25 mL/min.
34. Contraindicated in women who are breastfeeding.
35. Should be taken within 2 hours of waking in the morning.
36. Cost of a 30-day supply of packets.
37. Should be taken immediately before meals that contain ≥30 g of carbohydrate. Insulin dose should be reduced by 50%.
38. Patients who need 2000 mg/day of metformin should take two 1000/2.5 mg tablets once daily.
39. Maximum daily dose is 2000/300 mg in patients with an eGFR <50 mL/min/1.73 m². Patients with an eGFR of 45–<60 mL/min/1.73 m² should not receive more than 50 mg of canagliflozin bid.
40. Contraindicated in patients with an eGFR <45 mL/min/1.73 m².
41. Reduce the albiglutin dose to 12.5 mg/day in patients with a CrCl of 30-59 mL/min.
42. Starting dosage is 5 mg/5 mg in patients already taking dapagliflozin.
43. Contains 100 units/mL of insulin degludec and 3.6 mg/mL of lixisenatide.
44. Should be given at the same time each day with or without food.
45. Basal insulin or a GLP-1 receptor agonist should be discontinued before starting treatment. Starting dosage is 10 units/0.36 mg in patients naive to basal insulin or a GLP-1 receptor agonist and is 16 units/0.56 mg in those on basal insulin or a GLP-1 receptor agonist; titrate up or down by 2 units every 3–4 days to achieve desired fasting plasma glucose.
46. Cost of 30 days’ treatment for a patient using Xultophy 40 units/1.44 mg daily or Soliqua 40 units/13.3 mcg daily.
47. Contains 100 units/mL of insulin glargine and 33 mcg/mL of lixisenatide.
48. Within one hour before first meal of the day.
49. Basal insulin or a GLP-1 receptor agonist should be discontinued before starting treatment. Starting dosage is 15 units/5 mcg in patients naive to basal insulin or a GLP-1 receptor agonist, or ~30 units of basal insulin, or on a GLP-1 receptor agonist, and is 30 units/10 mcg in those on 30–60 units of basal insulin; titrate up or down by 2–4 units/week to achieve desired fasting plasma glucose.
Lixisenatide (Adlyxin) – In a randomized, double-blind trial (ELIXA) in 6068 patients with type 2 diabetes who had a recent acute coronary event, addition of lixisenatide to standard treatment was noninferior, but not superior, to addition of placebo in reducing the rate of major adverse cardiovascular events.34

Among 5978 patients with acute coronary syndrome in the ELIXA trial, addition of lixisenatide to standard treatment reduced the UACR by 21% in patients with microalbuminuria and by 39% in those with macroalbuminuria, compared to addition of placebo. Lixisenatide also reduced the risk of new-onset macroalbuminuria, but there were no significant differences in eGFR decline between the two groups at 108 weeks.35

Semaglutide (Ozempic; Rybelsus) – In a randomized, double-blind trial (SUSTAIN-6) in 3297 patients with type 2 diabetes who were at high cardiovascular risk, addition of once-weekly injections of semaglutide to standard treatment was noninferior to addition of placebo in reducing the incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (6.6% vs 8.9%). The incidence of new or worsening nephropathy was 3.8% with semaglutide and 6.1% with placebo, a significant difference due primarily to a reduction in persistent macroalbuminuria. Rates of new or worsening nephropathy were lower with semaglutide, but rates of retinopathy complications were higher, mostly in patients with pre-existing retinopathy.38 In January 2020, the FDA approved use of semaglutide to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease.

An oral formulation of semaglutide (Rybelsus) was recently approved by the FDA. In clinical trials, addition of oral semaglutide to standard treatment was superior to addition of placebo, the SGLT2 inhibitor empagliflozin, or the DPP-4 inhibitor sitagliptin and noninferior to addition of liraglutide in reducing A1C.36–37 In a randomized safety trial (PIONEER 6) in 3183 patients at high cardiovascular risk, oral semaglutide was noninferior to placebo in the incidence of major adverse cardiovascular events (3.8% vs 4.8%).46

Class Benefits – A meta-analysis of 7 placebo-controlled trials of cardiovascular outcomes with albiglutide (no longer available commercially), exenatide, liraglutide, lixisenatide, and semaglutide found that these GLP-1 receptor agonists significantly reduced the risk of major adverse cardiovascular events (12%), all-cause mortality (12%), and a composite endpoint of adverse renal outcomes (17%).47 Dulaglutide has also demonstrated cardiovascular benefits.

Pancreatitis – Incretin-based drugs (GLP-1 receptor agonists and DPP-4 inhibitors) have been associated with acute pancreatitis.48 A review of data by the FDA and the European Medicines Agency did not find a causal link between use of these drugs and pancreatic disease, but both agencies will continue to consider pancreatitis a risk associated with these drugs until more data become available.49

DPP-4 INHIBITORS – The dipeptidyl peptidase-4 (DPP-4) inhibitors alogliptin (Nesina), linagliptin (Tradjenta), saxagliptin (Onglyza), and sitagliptin (Januvia) potentiate glucose-dependent secretion of insulin and suppress glucagon secretion. They reduce A1C by 0.5-1%, are weight-neutral, and are generally well tolerated.

Cardiovascular Safety – DPP-4 inhibitors have not increased or decreased the risk of ischemic cardiovascular events in large randomized trials in patients with type 2 diabetes. In a meta-analysis of 236 trials including 176,310 patients, SGLT2 inhibitors and GLP-1 receptor agonists were associated with significantly lower cardiovascular and all-cause mortality compared to DPP-4 inhibitors or placebo; DPP-4 inhibitors were not associated with lower all-cause mortality compared to controls.50

In trials with saxagliptin and alogliptin, more patients were hospitalized for HF in the DPP-4 inhibitor treated group.51 An increased risk of HF was not detected in either sitagliptin- or linagliptin-dedicated trials.52–54 In a case-control analysis (CNODES) that included 29,741 patients with type 2 diabetes who were hospitalized for HF, use of incretin-based drugs (DPP-4 inhibitors or GLP-1 receptor agonists) was not associated with an increased risk of hospitalization for HF, compared to use of other oral antihyperglycemic drugs.52

Nephropathy – Long-term data on the effects of DPP-4 inhibitors on albuminuria and nephropathy are not available.

Pancreatitis – DPP-4 inhibitors have been associated with acute pancreatitis.48

SULFONYLUREAS – Sulfonylureas interact with ATP-sensitive potassium channels in the beta-cell membrane to increase secretion of insulin. The sulfonylureas glimepiride (Amaryl, and generics), glipizide (Glucotrol, and others), and glyburide (Glynase Prestab, and others), reduce A1C by 1-1.5%, but the reductions are less durable than those with metformin, and these drugs can cause weight gain.
and hypoglycemia. A meta-analysis of long-term trials found that use of sulfonylureas was associated with a reduced risk of microvascular and macrovascular complications of diabetes.\(^6\) Their effectiveness and low cost have led to wide use of these drugs as second-line agents.

**Cardiovascular Safety** – Until recently, the cardiovascular safety of sulfonylureas was suspect because of a 1970 report,\(^4\) but in a recent randomized controlled trial (CAROLINA) in 6042 patients with type 2 diabetes and increased cardiovascular risk, addition of glimepiride to standard treatment was noninferior to addition of the DPP-4 inhibitor linagliptin in cardiovascular safety.\(^5\) In an earlier trial (CARMELINA), addition of linagliptin to standard treatment was noninferior to addition of placebo in cardiovascular safety.\(^6\)

**THIAZOLIDINEDIONES (TZDs)** – Pioglitazone (Actos, and generics) and rosiglitazone (Avandia) increase the insulin sensitivity of adipose tissue, skeletal muscle, and the liver, and reduce hepatic glucose production. They reduce A1C by 1-1.5%. Whether the benefits of TZDs outweigh their risks (weight gain, heart failure, anemia, increased fracture risk) remains unclear.

**Cardiovascular Risk** – Both pioglitazone and rosiglitazone have been associated with an increased risk of heart failure,\(^7\) but in a randomized controlled trial, there was no significant difference between rosiglitazone and metformin plus a sulfonylurea in the risk of cardiovascular death, myocardial infarction, or stroke.\(^8\) Restrictions placed on rosiglitazone in 2010 because of concerns about its cardiovascular safety have been lifted.\(^9\)

**MEGLITINIDES** – Nateglinide and repaglinide, although structurally different from the sulfonylureas, also bind to ATP-sensitive potassium channels on beta cells and increase insulin release. Repaglinide is more effective than nateglinide in lowering A1C (1% vs 0.5%) and has the advantage of being safe for use in patients with renal failure. Both are rapidly absorbed and cleared; plasma levels of insulin peak 30-60 minutes after each dose and multiple daily doses are required. These drugs permit more dosing flexibility than sulfonylureas, but they also can cause hypoglycemia and they have not been shown to reduce microvascular complications or to have a beneficial effect on cardiovascular outcomes.

**ALPHA-GLUCOSIDASE INHIBITORS** – Acarbose (Precose, and generics) and miglitol (Glyset, and generics) inhibit the alpha-glucosidase enzymes that line the brush border of the small intestine, interfering with hydrolysis of carbohydrates and delaying absorption of glucose and other monosaccharides. They reduce A1C by 0.5-1%. To lower postprandial glucose concentrations, these drugs must be taken with each meal.

**OTHER AGENTS** – Other FDA-approved agents for type 2 diabetes include the immediate-release formulation of the ergot-derived dopamine agonist bromocriptine mesylate (Cyprold), the bile acid sequestrant colesvelem\(^10\) (Welchol, and generics) and the subcutaneously-injected amylin mimetic pramlintide (Symlin). None of these agents are recommended as monotherapy and they are minimally effective at reducing A1C (~0.5% reduction).

**INSULIN** – Many patients with type 2 diabetes eventually require insulin to achieve glycemic control. Insulin therapy for type 2 diabetes was reviewed in a previous issue.\(^7\)

**PREGNANCY** – Insulin is the drug of choice for treatment of pregnant women with type 2 diabetes because it does not cross the placenta. It is excreted in human breast milk, but women who use insulin can breastfeed safely. Metformin also appears to be relatively safe for use in pregnant women.\(^12\) Data on the safety of other antihyperglycemic drugs during pregnancy are insufficient to recommend their use.

68. KW Mahaffey et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J 2013; 166:249.
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Mark Abramowicz, M.D., President – The Medical Letter; no disclosure or potential conflict of interest to report.
Jean-Marie Pflomm, Pharm.D., E — The Medical Letter; no disclosure or potential conflict of interest to report.
Mark Abramowicz, M.D., President – The Medical Letter; no disclosure or potential conflict of interest to report.
Eric J. Epstein, M.D., Contributing Editor – The Medical Letter; no disclosure or potential conflict of interest to report.

In addition to the Principal Faculty above, the following have also contributed to this activity:
Brida M. Shah, Pharm.D., Consulting Editor — The Medical Letter; no disclosure or potential conflict of interest to report.
F. Peter Swanson, M.D., Consulting Editor — The Medical Letter; no disclosure or potential conflict of interest to report.

INFORMATION ON NEXT PAGE

The Medical Letter’s Continuing Medical Education Program is to support the professional development of healthcare providers including physicians, nurse practitioners, pharmacists, and physician assistants by providing independent, unbiased drug information and prescribing recommendations that are free of industry influence. The program content includes current information and unbiased reviews of FDA-approved and off-label uses of drugs, their mechanisms of action, clinical trials, dosage and administration, adverse effects, and drug interactions. The Medical Letter delivers educational content in the form of self-study material.

The expected outcome of the CME program is to increase the participant’s ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in The Medical Letter.

The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of healthcare providers through Core Competencies by providing continuing medical education that is unbiased and free of industry influence. The Medical Letter does not sell advertising or receive any commercial support.

GOAL:
Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

LEARNING OBJECTIVES:
Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in The Medical Letter with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this activity, the participant will be able to:
1. Explain the current approach to the management of a patient with type 2 diabetes.
2. Discuss the pharmacologic options available for treatment of type 2 diabetes and compare them based on their efficacy, dosage and administration, and potential adverse effects.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient with type 2 diabetes.

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Have any questions? Call us at 800-211-2769 or 914-235-0500 or e-mail us at: custserv@medicalletter.org

Questions on next page
### Drugs for Type 2 Diabetes

1. Advantages of metformin for initial monotherapy of type 2 diabetes include:
   - a. low cost
   - b. durable A1C reductions
   - c. reduction in micro- and macrovascular events
   - d. all of the above

2. A 74-year-old woman with type 2 diabetes has an A1C >8.5% on metformin monotherapy. Because cost is an issue, she suggests that she take glimepiride in addition to metformin to reduce her A1C. You tell her that, unlike metformin, glimepiride can cause:
   - a. reduced bone mineral density
   - b. weight gain
   - c. vitamin B12 deficiency
   - d. genital mycotic infections

3. SGLT2 inhibitors:
   - a. increase secretion of insulin
   - b. decrease secretion of glucagon
   - c. decrease renal glucose reabsorption
   - d. decrease glucose absorption from the GI tract

4. SGLT2 inhibitors have improved outcomes in patients with:
   - a. cirrhosis
   - b. nephropathy
   - c. atrial fibrillation
   - d. all of the above

5. Which of the following drug classes is most effective in reducing A1C?
   - a. SGLT2 inhibitors
   - b. GLP-1 receptor agonists
   - c. DPP-4 inhibitors
   - d. meglitinides

6. DPP-4 inhibitors have been shown to decrease:
   - a. the risk of a cardiovascular event
   - b. the risk of nephropathy
   - c. the risk of hospitalization for heart failure
   - d. A1C by 0.5-1%

7. A 30-year-old woman with cardiovascular disease and type 2 diabetes has been taking metformin for years. Her A1C is 7.5% and her endocrinologist suggested that she add a GLP-1 receptor agonist. She refuses to give herself injections. Which GLP-1 receptor agonist would you recommend?
   - a. dulaglutide
   - b. lixisenatide
   - c. semaglutide

8. A 64-year-old man with type 2 diabetes has been treated with metformin for the past year. Liraglutide was added to his regimen about one week ago. He presents to urgent care today complaining of diarrhea and vomiting for the past few days. His serum creatinine is 1.8 mg/dl today (was 0.9 mg/dl at his last office visit). The increase in serum creatinine is most likely due to:
   - a. renal injury caused by metformin
   - b. a hypersensitivity reaction to liraglutide
   - c. dehydration caused by gastrointestinal toxicity of liraglutide
   - d. hypoglycemia caused by the addition of liraglutide

9. Saxagliptin and alogliptin have been associated with hospitalization due to:
   - a. genital mycotic infections
   - b. cardiovascular events
   - c. nephropathy
   - d. heart failure

10. Which of the following is the drug of choice for treatment of pregnant women with type 2 diabetes?
    - a. metformin
    - b. canagliflozin
    - c. liraglutide
    - d. insulin

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**Issue 1584 Questions**

(Respond to questions #81-90 in Comprehensive Activity #81, available January 2020)