Diabetes is a worldwide problem affecting millions of people. Glucose control is the mainstay of therapy in these patients. In recent years, a variety of new agents with novel mechanisms of action have been approved for the treatment of type 2 diabetes. While this provides more options for the treatment of these patients, the wide array of medications can lead to confusion as to which agents should be used. In general, both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommend that in addition to lifestyle modification, metformin is first-line for the treatment of type 2 diabetes in most patients.\(^1\)\(^,\)\(^2\) In general, the target A1C concentrations are 7% (ADA) or 6.5% (AACE), but the goal may be individualized in patients with other illnesses and in those at risk for hypoglycemia.\(^1\)\(^,\)\(^2\) Therapy can be started with more than one agent in patients with an A1C ≥9% (ADA) or ≥7.5% (AACE). However, for patients who fail metformin monotherapy, a broad variety of agents can be used in combination with metformin, or as monotherapy in those who cannot use metformin.\(^1\)\(^,\)\(^2\) The choice of second-line and third-line agents varies based on patient characteristics, patient preferences, and properties of the medications such as the risk of hypoglycemia or weight gain. The table below summarizes the agents available for the treatment of type 2 diabetes, including expected A1C reduction, mechanism of action, dosing, and advantages and disadvantages of each class of medication.

**Abbreviations:** BID - twice daily; CVD - cardiovascular disease; MOA - mechanism of action; PO - by mouth; SC - subcutaneously; TID - three times daily.

<table>
<thead>
<tr>
<th>Class/Estimated A1C Reduction (Monotherapy)</th>
<th>Specific Agents</th>
<th>Initial Dose(^a) (Approximate cost for 30-day supply(^b))</th>
<th>Advantages (^{a,1,3})</th>
<th>Disadvantages (^{a,1,3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>Acarbose (Precose, others)</td>
<td>Acarbose INITIAL: 25 mg PO TID ($45)</td>
<td>• Lack of hypoglycemia when used as monotherapy</td>
<td>• Modest effect on A1C</td>
</tr>
<tr>
<td>0.5% to 1%(^3)</td>
<td>Miglitol (Glyset)</td>
<td>Miglitol INITIAL: 25 mg PO TID ($145)</td>
<td>• Weight neutral</td>
<td></td>
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<tr>
<td>MOA:</td>
<td></td>
<td></td>
<td>• Reduces postprandial glucose values</td>
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<tr>
<td>Slows intestinal carbohydrate digestion/absorption.</td>
<td></td>
<td></td>
<td>• Not absorbed</td>
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<td></td>
<td></td>
<td></td>
<td>• Likely reduces CVD events (acarbose)</td>
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<td></td>
<td></td>
<td></td>
<td>• Beneficial in the treatment of prediabetes (acarbose)(^9)</td>
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<tr>
<td><strong>Amylin analog</strong></td>
<td>Pramlintide (Symlin)</td>
<td><strong>Pramlintide</strong>&lt;br&gt;INITIAL: 60 mcg SC prior to major meals (≥250 kcal or containing ≥30 g carbohydrate) ($590)</td>
<td>• Lack of hypoglycemia when used as monotherapy&lt;br&gt;• Weight loss&lt;br&gt;• Reduces postprandial glucose values&lt;br&gt;• Increases feeling of fullness after meal</td>
<td>• Modest effect on A1C&lt;br&gt;• Nausea&lt;br&gt;• Vomiting&lt;br&gt;• Hypoglycemia if insulin dose is not reduced&lt;br&gt;• Need for frequent dosing&lt;br&gt;• Injectable</td>
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<tr>
<td><strong>Biguanide</strong></td>
<td>Metformin (Glucophage, Glucophage XR)</td>
<td><strong>Metformin</strong>&lt;br&gt;INITIAL: 500 mg PO BID or 850 mg PO once daily (less than $20/month)</td>
<td>• Lack of hypoglycemia&lt;br&gt;• Weight neutral&lt;br&gt;• Likely reduces CVD events&lt;br&gt;• Beneficial in the treatment of prediabetes(^10)&lt;br&gt;• Metformin can be initiated if eGFR is &gt;45 mL/min/1.73m(^2). (Discontinue if eGFR later falls below 30 mL/min/1.73 m(^2).)(^16)</td>
<td>• Diarrhea&lt;br&gt;• Abdominal cramping&lt;br&gt;• B12 deficiency&lt;br&gt;• Lactic acidosis (rare) in patients with cardiovascular, renal, or hepatic dysfunction</td>
</tr>
<tr>
<td>Class/Estimated A1C Reduction (Monotherapy)</td>
<td>Specific Agents</td>
<td>Initial Dose(^a) (Approximate cost for 30-day supply(^b))</td>
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<td>Dipeptidyl peptidase-4 (DPP-4) inhibitor (&quot;gliptins&quot;) or incretin enhancer</td>
<td>Alogliptin (Nesina) With metformin (Kazano) With pioglitazone (Oseni) Linagliptin (Tradjenta) With metformin (Jentadueto) With empagliflozin (Glyxambi) Saxagliptin (Onglyza) With metformin (Kombiglyze XR) Sitagliptin (Januvia) With metformin (Janumet, Janumet XR)</td>
<td><strong>Alogliptin</strong> INITIAL: 25 mg PO once daily ($310) <strong>Linagliptin</strong> INITIAL: 5 mg PO once daily ($330) <strong>Saxagliptin</strong> INITIAL: 2.5 or 5 mg PO once daily ($325) <strong>Sitagliptin</strong> INITIAL: 100 mg PO once daily ($330)</td>
<td>• No hypoglycemia when used as monotherapy • Weight neutral • Generally well tolerated</td>
<td>• Dosage modification with renal impairment needed (sitagliptin, saxagliptin, alogliptin) • CYP3A4 interactions (saxagliptin, linagliptin) • May be associated with pancreatitis(^6) • New or worsening heart failure (saxagliptin, alogliptin)(^7,13,17) • May cause severe joint pain(^12)</td>
</tr>
<tr>
<td>Class/Estimated A1C Reduction (Monotherapy)</td>
<td>Specific Agents</td>
<td>Initial Dosea (Approximate cost for 30-day supplyb)</td>
<td>Advantages a,1,3</td>
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<tr>
<td>Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic</td>
<td>Albiglutide (<em>Tanzeum</em>)&lt;br&gt;Dulaglutide (<em>Trulicity</em>)&lt;br&gt;Exenatide (<em>Byetta</em>)&lt;br&gt;Exenatide extended-release (<em>Bydureon</em>)&lt;br&gt;Liraglutide (<em>Victoza</em>)</td>
<td><strong>Albiglutide</strong>&lt;br&gt;INITIAL: 30 mg SC once weekly ($325)&lt;br&gt;<strong>Dulaglutide</strong>&lt;br&gt;INITIAL: 0.75 mg SC once weekly ($490)&lt;br&gt;<strong>Exenatide</strong>&lt;br&gt;INITIAL: 5 mcg SC BID ($480)&lt;br&gt;<strong>Exenatide extended-release</strong>&lt;br&gt;INITIAL: 2 mg SC once weekly ($475)&lt;br&gt;<strong>Liraglutide</strong>&lt;br&gt;INITIAL: 0.6 mg SC once daily x 1 week, then increase to 1.2 mg SC once daily ($430)</td>
<td>• Lack of hypoglycemia when used as monotherapy&lt;br&gt;• Weight loss&lt;br&gt;• Reduces postprandial glucose values&lt;br&gt;• In patients who need more than one or two antidiabetes agents, combination injectable therapies of basal insulin and a GLP-1 agonist is an efficient, emerging strategy&lt;br&gt;• Liraglutide may reduce cardiovascular (CV) death (NNT=77 for four years) and overall mortality (NNT=71 for four years) in patients with high CV risk or CV disease&lt;sup&gt;19&lt;/sup&gt;</td>
<td>• Nausea (often transient)&lt;br&gt;• Diarrhea&lt;br&gt;• Dosage modification with renal dysfunction needed (albiglutide, dulaglutide)&lt;br&gt;• Avoid in severe renal impairment (exenatide)&lt;br&gt;• May be associated with pancreatitis&lt;sup&gt;6&lt;/sup&gt;&lt;br&gt;• Associated with thyroid cell cancer in rodents&lt;br&gt;• May be associated with renal insufficiency&lt;sup&gt;8&lt;/sup&gt;&lt;br&gt;• May be associated with gallbladder disease (liraglutide, exenatide)&lt;sup&gt;18,19&lt;/sup&gt;&lt;br&gt;• Injectable</td>
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MOA: Stimulation of GLP-1 receptors results in increased insulin secretion in response to elevated blood glucose, decreased glucagon secretion, slowed gastric emptying, and increased satiety. (GLP-1 is an incretin hormone.)

For more information, see our *PL Chart, Comparison of GLP-1 Agonists*. 

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<tr>
<th>Class/Estimated A1C Reduction (Monotherapy)</th>
<th>Specific Agents</th>
<th>Initial Dosea (Approximate cost for 30-day supplyb)</th>
<th>Advantages a,1-3</th>
<th>Disadvantagesa,1-3</th>
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</table>
| Insulin 1.5% to 3.5%5                    | Various. See our PL Chart, Comparison of Insulins and Injectable Diabetes Meds. | See our PL Charts, Initiation and Adjustment of Insulin Regimens for Type 2 Diabetes and Comparison of Insulins and Injectable Diabetes Meds. | • Effective in all patients  
• Reduced microvascular complications  
• Consider starting insulin, in combination with metformin therapy with or without other noninsulin therapies when the blood glucose is >300 mg/dL to 350 mg/dL and/or the A1C ≥10%. Insulin may be more effective than other therapies when hyperglycemia is severe, especially if the patient is symptomatic or has any catabolic features (e.g., weight loss, ketosis). | • Hypoglycemia  
• Weight gain  
• Injectable |
| Meglitinide 0.5% to 1%3                   | Nateglinide (Starlix)  
Repaglinide (Prandin, others)  
With metformin (PrandiMet) | **Nateglinide** INITIAL: 60 to 120 mg PO TID with meals ($105)  
**Repaglinide** INITIAL: 0.5 mg PO TID with meals if A1C <8%, 1 or 2 mg TID with meals if A1C ≥8% ($50) | • Reduces postprandial glucose values  
• Can be used in place of sulfonylureas in patients with irregular meal schedules or in those who develop late hypoglycemia with a sulfonylurea | • Hypoglycemia if taken without food or if severe renal impairment  
• Weight gain  
• Frequent dosing  
• Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started3 |
<table>
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<tr>
<th>Class/Estimated A1C Reduction (Monotherapy)</th>
<th>Specific Agents</th>
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<th>Advantages (^a,1-3)</th>
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</tr>
</thead>
</table>
| Sodium-glucose co-transporter 2 (SGLT2) inhibitor or “flozins” | Canagliflozin (Invokana) With metformin (Invokamet) | Canagliflozin
INITIAL: 100 mg PO once daily ($340) | • Lack of hypoglycemia
• Weight loss
• May reduce blood pressure
• Empagliflozin reduces cardiovascular (CV) mortality (NNT=45 for three years), overall mortality (NNT=39 for three years), and hospitalization due to heart failure (NNT=71 for three years) in type 2 diabetes patients with CV disease\(^2\) | • Genital fungal infections (male and female)
• Urinary tract infection (may be severe)\(^1\)
• Increased urination
• Hypotension
• Increase LDL
• Do not use if eGFR <45 mL/min/1.73m\(^2\) (canagliflozin, empagliflozin) or <60 mL/min/1.73m\(^2\) (dapagliflozin)
• Fractures (rare, in susceptible patients)\(^4\)
• Decrease in BMD (canagliflozin)\(^4\)
• May be associated with increased risk of bladder cancer (dapagliflozin)
• Association with ketoacidosis (rare)\(^1\)
• Acute kidney injury reported with canagliflozin or dapagliflozin (may require dialysis)\(^5\) |
| 0.5% to 1%\(^1\) | Dapagliflozin (Farxiga) | Dapagliflozin
INITIAL: 5 mg PO once daily ($340) | | |
| | Empagliflozin (Jardiance) With linagliptin (Glyxambi) With metformin (Synjardy) | Empagliflozin
INITIAL: 10 mg PO once daily ($340) | | |
<table>
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<tr>
<th>Class/Estimated A1C Reduction (Monotherapy)</th>
<th>Specific Agents</th>
<th>Initial Dose* (Approximate cost for 30-day supply)</th>
<th>Advantages a,1-3</th>
<th>Disadvantages a,1-3</th>
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</table>
| Sulfonylurea—first generation 1% to 1.5%³ | Chlorpropamide *(Diabinese, others)*  
Tolazamide *(Tolinase, others)*  
Tolbutamide *(Orinase, others)* | **Chlorpropamide**  
INITIAL: 100 to 250 mg PO once daily (less than $20/month)  
**Tolazamide**  
INITIAL: 250 mg PO once daily ($48)  
**Tolbutamide**  
INITIAL: 1 g PO once daily ($70) | • Initially, good efficacy  
• Inexpensive | • Hypoglycemia more common compared with second-generation sulfonylureas³  
• Weight gain³  
• Reduced efficacy over time³  
• Avoid in patients with renal dysfunction or the elderly (chlorpropamide)  
• Use of second-generation sulfonylureas preferred over first-generation sulfonylureas  
• Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started¹ |
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<th>Class/Estimated A1C Reduction (Monotherapy)</th>
<th>Specific Agents</th>
<th>Initial Dose&lt;sup&gt;a&lt;/sup&gt; (Approximate cost for 30-day supply&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>Advantages&lt;sup&gt;a,1-3&lt;/sup&gt;</th>
<th>Disadvantages&lt;sup&gt;a,1-3&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Sulfonylurea-second generation 1% to 1.5%&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Glyburide (Diabeta, Glynase, Micronase, others) With metformin (Glucovance) Glipizide (Glucotrol, Glucotrol XL, others) With metformin (Metaglip) Glimepiride (Amaryl, others) With metformin (Amaryl M) With pioglitazone (Duetact) With rosiglitazone (Avandaryl)</td>
<td>Glyburide INITIAL: 2.5 mg PO once daily (less than $10/month) Glipizide INITIAL: 5 mg PO once daily (less than $10/month) Glimepiride INITIAL: 1 mg PO once daily (less than $10/month)</td>
<td>• Initially, good efficacy • Inexpensive</td>
<td>• Hypoglycemia, especially with renal dysfunction (less with glimepiride versus glyburide)&lt;sup&gt;5&lt;/sup&gt; • Weight gain (glyburide more than glipizide, glimepiride) • Reduced efficacy over time • For the elderly and those with hepatic or renal dysfunction, start with low doses and titrate up • Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Class/Estimated A1C Reduction (Monotherapy)</td>
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<tr>
<td>Thiazolidinedione (TZD) 1% to 1.5(^%)(^3)</td>
<td>Pioglitazone (Actos) With metformin (Actoplus Met or Actoplus Met XR) With glimepiride (Duetact) With alogliptin (Oseni) Rosiglitazone (Avandia) With metformin (Avandamet) With glimepiride (Avandaryl)</td>
<td><strong>Pioglitazone</strong> INITIAL: 15 mg PO once daily (less than $20) <strong>Rosiglitazone</strong> INITIAL: 4 mg PO once daily ($115)</td>
<td>• Lack of hypoglycemia when used as monotherapy • Improves HDL cholesterol • Reduced triglycerides (pioglitazone) • May reduce CVD (pioglitazone)</td>
<td>• Weight gain • Volume retention, congestive heart failure • Increased fracture risk • Increases LDL (rosiglitazone) • May possibly increase the risk of bladder cancer (pioglitazone)</td>
</tr>
<tr>
<td>Others – bile acid sequestrant 0.5% to 1(^%)(^3)</td>
<td>Colesevelam (Welchol)</td>
<td><strong>Colesevelam</strong> INITIAL: 3.75 g PO per day (taken as six tablets once daily, or three tablets BID, with meals) ($470)</td>
<td>• No hypoglycemia • Weight neutral • Safe in CVD • Lowers LDL cholesterol</td>
<td>• Constipation • Nausea, bloating • Increased triglycerides • Drug interactions</td>
</tr>
<tr>
<td>Others – dopamine agonist 0.5% to 1(^%)(^3)</td>
<td>Bromocriptine (Cycloset)</td>
<td><strong>Bromocriptine</strong> INITIAL: 0.8 mg PO once daily ($90)</td>
<td>• No hypoglycemia • Weight neutral</td>
<td>• Dizziness/syncope • Nausea</td>
</tr>
</tbody>
</table>
a. **Information based on most current U.S. product information unless otherwise noted:** Precose (March 2015), Glyset (February 2015), Symlin (March 2015), Glucophage (March 2015), Onglyza (May 2013), Januvia (March 2015), Tradjenta (May 2014), Byetta (February 2015), Bydureon (March 2015), Victoza (March 2015), Starlix (January 2013), Prandin (March 2012), Diabeta (October 2013), Glucotrol (February 2011), Amaryl (February 2012), Actos (August 2012), Avandia (May 2012), Welchol (January 2014), Cycloset (March 2011), Diabinese (October 2013), tolazamide (Mylan; December 2009), tolbutamide (Mylan; February 2009), Invokana (March 2015), Nesina (June 2013), Farxiga (March 2015), Jardiance (August 2014), Tanzeum (March 2015), Invokamet (March 2015), Trulicity (March 2015).

b. Approximate prices based on WAC for 30-day supply (of generic product if available, generic prices may vary considerably). If WAC not available (chlorpropamide, tolazamide, tolbutamide), AWP for 30-day supply used.

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Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.
Project Leader in preparation of this PL Detail-Document: Neeta Bahal O’Mara, Pharm.D., BCPS

References

Cite this document as follows: PL Detail-Document, Drugs for Type 2 Diabetes. Pharmacist’s Letter/Prescriber’s Letter. June 2015.
Management of New-Onset Type 2 Diabetes

There are lots of medications available and many ways to start therapy. The guidelines use a variety of A1C cutoffs for treatment recommendations, such as when to initiate insulin or consider dual therapy. Ultimately, medication selection should be based on the patient’s clinical presentation, blood glucose levels or A1C, and patient specific factors (e.g., concomitant conditions, renal function, etc). Consider using these strategies to initiate therapy for any patient with new-onset type 2 diabetes, even those presenting with a very high blood glucose level (e.g., >350 mg/dL [~20 mmol/L]).

First Step: Patient Assessment

- Assess patient stability and need for urgent treatment.
  - For unstable patients, see the section below: How Should UNSTABLE Patients With High Blood Glucose Be Managed?
- Check an A1C to get a more accurate picture of the overall blood glucose levels.
  - Don’t wait on these results to start therapy, if not readily available.
- If necessary, distinguish between type 1 and type 2 diabetes:
  - It may not be clear at the time of diagnosis if a patient has type 1 or type 2 diabetes.
  - The assumption that type 2 diabetes only occurs in adults and type 1 only occurs in children is no longer accurate. Accurate classification is important to determine the most appropriate therapy.
  - Evaluate a C-peptide or serum insulin level to help distinguish type 1 from type 2 diabetes. If necessary, check autoimmune markers as type 1 diabetes is defined by the following markers:
    - Islet cell autoantibodies
    - Insulin autoantibodies (e.g., GAD [GAD65], tyrosine phosphatases [e.g., 1A-2, 1A-2β], and ZnT8)
- Address lifestyle choices for everyone:
  - Facilitate diabetes and healthy eating patient education.
  - Encourage physical activity (e.g., 150 minutes per week), smoking cessation, and weight management, if necessary.

Initiating Medication in STABLE Patients With Type 2 Diabetes:

Feel comfortable starting with a single oral medication, even in patients with significantly elevated sugars (e.g., 350 mg/dL [~20 mmol/L]).

- See our chart, Diabetes Medications and Cardiovascular Impact, for an overview of available cardiovascular data.
- See our chart, Drugs for Type 2 Diabetes (U.S. subscribers) and our algorithm, Stepwise Treatment of Type 2 Diabetes (Canadian subscribers), for the benefits and risks associated with available medications.
- First Choice:
  - Metformin 500 mg once daily, unless contraindicated (e.g., acute metabolic acidosis, creatinine clearance <30 mL/min).
  - Increase by 500 mg per day every few days to a goal dose of 2 g per day.
  - See our algorithm, Improving Tolerability to Metformin, for slower dosing titrations and other strategies to address gastrointestinal effects.
- Second Choice: (if metformin is contraindicated or not tolerated) consider any one of the following depending on concomitant conditions.
o Glucagon-like peptide-1 (GLP-1) receptor agonist
   ▪ Give preference to liraglutide due to outcomes data.

o Sodium-glucose co-transporter 2 (SGLT2) inhibitor or “flozin”
   ▪ Give preference to empagliflozin due to outcomes data.

o Dipeptidyl peptidase-4 (DPP-4) inhibitor or “gliptin”
   ▪ Give preference to sitagliptin due to outcomes data.

o Thiazolidinedione (TZD)
   ▪ Give preference to pioglitazone due to outcomes data.
   ▪ Avoid in patients with heart failure.

• **Third Choice** (if the above options aren’t tolerated or cannot be used) consider one of the following:1-3
  o Sulfonylurea
    ▪ Use these with caution due to risk of weight gain and hypoglycemia.
  o Meglitinide (repaglinide, nateglinide [U.S. only])
    ▪ Use these with caution due to risk of weight gain and hypoglycemia.
  o Alpha glucosidase inhibitor
    ▪ Use these with caution due to frequent dosing, gastrointestinal adverse effects, and modest impact on A1C.
  o Insulin
    ▪ See section below, When Should Insulin Be Considered?

• **Monitor Blood Glucose**
  o Instruct patients on monitoring blood glucose levels. See our chart, *Comparison of Blood Glucose Meters* (U.S. subscribers); (Canadian subscribers).
  o Initial monitoring may be more frequent to help patients develop a comfort level with how medicine and diet impact blood glucose control.
    ▪ Recommend testing once daily for patients on oral medications, and any time they feel hypoglycemic (e.g., shaking, sweating).10
    ▪ Monitoring may be more frequent in patients receiving insulin.10 See our commentary, *Self-Monitoring of Blood Glucose in Patients with Type 2 Diabetes*.
  o Arrange close follow-up to adjust medication doses based on blood glucose levels.

• **When to Add a Second Medication:**
  o If goal blood glucose readings are not achieved after titrating initial therapy within about three months, consider adding another medication.
  o Base medication selection on concomitant conditions. See details in the Second Choice section above.

**When Should More Than One Medication Be Started at Diagnosis?**
Guidelines recommend considering dual therapy for A1C ≥9% (≥8.5% per Canadian guidelines).1-3 However, there are no data to show that initial combination therapy improves outcomes compared to sequential therapy in otherwise asymptomatic patients.5

• Before using dual therapy for initial treatment, consider the following:
  o No data exist to show initial combination therapy improves adherence.5
  o Initial dual therapy may increase risk of hypoglycemia and potentially reduce patient buy-in on the importance of blood glucose control.
  o With dual therapy an accurate assessment of individual medication effectiveness and tolerability is difficult.5
  o In addition to increased costs, dual therapy can make it difficult to determine the specific cause if adverse effects occur.5
Regimens for Initiating Dual Therapy at Diagnosis

- Include metformin:
  - Use metformin as one of the medications unless not tolerated or contraindicated.  
  - If metformin can’t be used, follow the preferences outlined below for selecting both medications.
- First Choice:  
  - See the Second Choice section above in Initiating Medication in STABLE Patients with Type 2 Diabetes
- Second Choice:  
  - See the Third Choice section above in Initiating Medication in STABLE Patients with Type 2 Diabetes
- Monitor Blood Glucose
  - See section above, Monitor Blood Glucose.

When Should Insulin Be Considered?

- Insulin is the gold standard for managing patients with type 1 diabetes.
- Insulin may be appropriate (even if only used short-term until oral meds and dietary changes kick in) as initial therapy with metformin for patients with type 2 diabetes and an A1C ≥10% in stable patients (OR ≥9% [ADA] or ≥8.5% [CDA], in patients with symptomatic or catabolic features [e.g., ketonuria, unintended weight loss]).  
- Recommend a starting dose of basal insulin (e.g., detemir, glargine, NPH) of about 0.1 to 0.2 units/kg at bedtime.  
  - Examples:
    - 80 kg x 0.1 units/kg = 8 units
    - OR
    - 80 kg x 0.2 units/kg = 16 units
- Monitor Blood Glucose
  - See section above, Monitor Blood Glucose.

How Should Insulin Be Titrated?

- Titrate dose by 10% to 15% once or twice a week, if fasting readings remain elevated.  
  - Example:
    - 16 units X 0.1 = 1.6 units OR 16 units X 0.15 = 2.4 units.
    - OR Using an average of the above two values, you would increase the total daily dose by 2 units, to 18 units.
- Teach extremely motivated patients to self-titrate their own insulin dose daily.  
  - Example:
    - Increase insulin daily by 1 unit, if fasting blood glucose remains elevated.
- Once a total daily dose of 0.5 units/kg basal insulin is reached, consider adding rapid acting prandial insulin (e.g., aspart, lispro) 0.1 unit/kg with meals before further basal insulin titrations.
- Monitor Blood Glucose
  - See section above, Monitor Blood Glucose.

How Should UNSTABLE Patients With High Blood Glucose Be Managed?

- Unstable patients (e.g., mental status changes, acid/base imbalance, electrolyte abnormalities) require acute care.
  - Administer insulin and follow your facility’s hyperglycemia protocol.
- Patients may present with diabetic ketoacidosis (DKA) or in a hyperosmolar hyperglycemic state (HHS).  
  - DKA is the triad of hyperglycemia (>250 mg/dL [~14 mmol/L]), metabolic acidosis (pH <7.3), and urinary and serum ketones.  
  - HHS is the triad of severe hyperglycemia (>600 mg/dL [~33 mmol/L]), hyperosmolality (>320 mOsm/kg), and dehydration without ketoacidosis.  
  - Patients presenting with DKA or HHS require prompt treatment to reduce mortality.
Follow your facility protocol for management of DKA or HHS.
- Replace fluids initially with normal saline (as long as no cardiac compromise), to restore volume and ensure perfusion.\(^8,9\)
  - Additional fluid choice will be based on hemodynamics, hydration status, electrolytes, and urinary output.\(^8\)
- Administer intravenous (IV) insulin to bring down blood glucose and assist with correcting acidosis.\(^8,9\)
- Replace potassium as necessary.\(^8,9\)
- Administer sodium bicarbonate to maintain a pH >7.\(^8,9\)

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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References

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