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Drugs for Type 2 Diabetes

Glucose control is the mainstay of diabetes management. 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, it may 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.[1,2,49] 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.[1,2,21] 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.[1,2,49] The choice of second-line and third-line agents varies based on patient characteristics, patient preferences, potential adverse effects (e.g., hypoglycemia, weight gain), and cost.[49] The table below summarizes the agents available in the U.S. for the treatment of type 2 diabetes, including expected A1C reduction when added to metformin, cost, adverse effects, and other pertinent information (e.g., frequency of dosing, cardiovascular benefits). For additional details on cardiovascular benefits associated with drugs for type 2 diabetes, see our chart, *Diabetes Medications and Cardiovascular Impact*.

Abbreviations: BID = two times daily; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; MOA = mechanism of action; TID = three times daily; UTI = urinary tract infection.

Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Alpha-glucosidase inhibitors Acarbose (*Precose*, generics) Miglitol (*Glyset*, generics)	0.7% to 0.8% (acarbose) 0.7% (miglitol, when added to sulfonylurea, not metformin)[36] MOA: slows intestinal carbohydrate digestion/absorption.[21,24]	**Acarbose** 300 mg, divided TID (~$50) **Miglitol** 300 mg, divided TID (~$200)	• GI (e.g., flatulence, diarrhea).[23] • Low risk of hypoglycemia when used as monotherapy.[23]	• Weight neutral.[23] • Taken with meals.[24] • Reduces postprandial glucose.[21] • Requires frequent dosing (e.g., TID).[21] • Beneficial in the treatment of prediabetes (acarbose).[9]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Amylin analog Pramlintide (*Symlin*)	~0.36% when added to insulin with or without metformin and/or a sulfonylurea[33] MOA: slows gastric emptying, increases the feeling of fullness, and reduces postprandial glucagon secretion.[21,24]	**Pramlintide** 120 mcg/dose (usually 360 mcg/day; divided, prior to major meals) (~$2,200)	• GI (e.g., nausea, vomiting).[21] • Hypoglycemia rare, unless insulin dose not reduced.[21]	• Weight loss.[21] • Increased feeling of fullness after meal.[21] • Injectable.[21] • Taken immediately before meals.[24] • Reduces postprandial glucose.[21] • Requires frequent dosing.[21]

Biguanide
Metformin (*Glucophage*, *Glucophage XR*, generics)
 	
Available in combination with alogliptin, canagliflozin, dapagliflozin, glimepiride, glipizide, glyburide, linagliptin, pioglitazone, repaglinide, rosiglitazone, saxagliptin, and sitagliptin. See specific agents.
	1%–2% as monotherapy
	
	MOA: inhibits production of glucose, intestinal absorption of glucose, and increases insulin sensitivity in muscle and fat.[21,24]
		Metformin
		2,000 to 2,550 mg, divided BID to TID
		(~$10)
		
		Metformin XR
		2,000 mg to 2,500 mg, divided BID
		(~$15)
			• B12 deficiency.[23,49]
			• GI (e.g., diarrhea, nausea, cramping).[21,23]
			• Lactic acidosis (rare) in patients with cardiovascular, renal, or hepatic dysfunction.[21,24]
			• Low risk of hypoglycemia when used as monotherapy.[23]
				• Weight neutral.[21,23]
				• Ameliorates insulin-associated weight gain.[23]
				• First-line after diet and exercise for most patients.[21]
				• Beneficial in the treatment of prediabetes.[10]
				• May reduce cardiovascular mortality.[42]
				• Safe in patients with stable heart failure and moderate renal impairment:[3,16,25,26]
				  ○ Can be initiated in patients with an eGFR >45 mL/min/1.73m^2.[24]
				  ○ Discontinue if eGFR falls below 30 mL/min/1.73m^2.[24]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Dipeptidyl peptidase-4 (DPP-4) inhibitor ("gliptins") or incretin enhancer Alogliptin (*Nesina*, others, with metformin [*Kazano*], with pioglitazone [*Oseni*]) Linagliptin (*Tradjenta*, with metformin [*Jentadueto*, *Jentadueto XR*], with empagliflozin [*Glyxambi*]) Saxagliptin (*Onglyza*, with metformin [*Kombiglyze XR*], with dapagliflozin [*Qtern*], with metformin and dapagliflozin [*Qternmet XR*]) Sitagliptin (*Januvia*, with metformin [*Janumet*, *Janumet XR*])	0.5% to 0.7% MOA: increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, increases sense of fullness, and slows gastric emptying.[21,24]	**Alogliptin** 25 mg (~$195) **Linagliptin** 5 mg (~$440) **Saxagliptin** 5 mg (~$410) **Sitagliptin** 100 mg (~$450)	• May be associated with pancreatitis.[6,21] • New or worsening heart failure (saxagliptin and alogliptin).[7,8,13,17,21,43] • May cause severe joint pain.[12] • Low risk of hypoglycemia when used as monotherapy.[21,23]	• Dosage modification with renal impairment needed (sitagliptin, saxagliptin, alogliptin).[24] • CYP3A4 interactions (saxagliptin, linagliptin).[24] • Reduces postprandial glucose.[44] • Weight neutral.[23] • Generally, well tolerated.[21]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic Dulaglutide (*Trulicity*) Exenatide (*Byetta*) and exenatide extended-release (*Bydureon*, *Bydureon BCise*) Liraglutide (*Victoza*, with insulin degludec [*Xultophy*]) Lixisenatide (*Adlyxin*, with insulin glargine [*Soliqua*]) Semaglutide (*Ozempic*)	1% (See GLP-1 agonist chart for individual agents) MOA: increases insulin secretion in response to elevated blood glucose, decreases glucagon secretion, leading to reduced hepatic glucose production and slowed gastric emptying.[21,24]	See our chart, *Comparison of GLP-1 Agonists*, for dosing and cost info.	• GI (diarrhea, nausea).[21] • May be associated with pancreatitis (rare).[6,21] • May be associated with gallbladder disease (liraglutide, exenatide).[18,19] • Low risk of hypoglycemia when used as monotherapy.[21] • May lead to retinopathy complications (semaglutide).[41]	• Weight loss.[21] • Injectable.[21] • Linked to thyroid cell cancer in rats.[21] • Avoid if eGFR <45 mL/min/1.73m^2 (extended-release exenatide) or <30 mL/min/1.73m^2 (immediate-release exenatide).[24] • Reduces postprandial glucose.[21] • CV benefit (albiglutide, liraglutide, semaglutide).[19,22,40] • In patients who need more than one or two diabetes meds, combination therapy with basal insulin and a GLP-1 agonist is an emerging strategy.[1]
Insulin Various	0.9% to 1.2% or more MOA: promotes storage of glucose in muscle and fat tissues, and inhibits production of glucose.[21,24]	No maximum dose[23] See our chart, *Comparison of Insulins*, for cost info.	• Hypoglycemia (educate patient to prevent, recognize, and manage).[21] • Highest risk of weight gain.[21,23]	• Consider initial therapy with insulin plus metformin if blood glucose is ≥300 mg/dL and/or A1C is ≥10%.[21]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Meglitinide Nateglinide (*Starlix*, generics) Repaglinide (*Prandin*, others, with metformin [*PrandiMet*])	0.7% to 1.1% MOA: stimulates pancreatic insulin secretion.[21,24]	**Nateglinide** 360 mg, divided TID (~$130) **Repaglinide** 16 mg, divided TID (~$80)	• Hypoglycemia (educate patient to prevent, recognize, and manage).[21] • Weight gain.[21]	• Requires frequent dosing.[21] • Reduces postprandial glucose.[21] • Provides flexible dosing (e.g., can hold dose if skipping meal).[21,24] • Consider over sulfonylureas (less hypoglycemia, better postprandial control).[2]
Sodium-glucose co-transporter 2 (SGLT2) inhibitors Canagliflozin (*Invokana*, with metformin [*Invokamet*, *Invokamet XR*]) Dapagliflozin (*Farxiga*, with metformin [*Xigduo XR*], with saxagliptin [*Qtern*], with saxagliptin and metformin [*Qternmet XR*]) *Continued…*	0.4% to 0.7% MOA: blocks glucose reabsorption in the kidney, and increases urinary excretion of glucose.[21,24]	**Canagliflozin** 300 mg (~$495) **Dapagliflozin** 10 mg (~$495) **Empagliflozin** 25 mg (~$495) **Ertugliflozin** 15 mg (~$280)	• Genital fungal (yeast) infections (male/female).[2] • UTI (may be severe), ketoacidosis (rare).[14] • Dizziness, hypotension, hypoglycemia (rare), increased LDL/urination.[21] • Hyperkalemia, especially in patients with renal impairment.[35] • Fractures (rare, in susceptible patients).[4] • Decrease in BMD (canagliflozin).[11] • May be associated with increased risk of bladder cancer (dapagliflozin).[39] • Acute kidney injury, may require dialysis (canagliflozin, dapagliflozin).[15] • May be associated with **acute** pancreatitis (rare).[46,48]	• Weight loss.[21] • Do not use if eGFR <45 mL/min/1.73m^2 (canagliflozin, dapagliflozin, empagliflozin) or <60 mL/min/1.73m^2 (ertugliflozin).[24] • CV benefit (canagliflozin, empagliflozin).[20,37] • Renal benefit (canagliflozin).[50]

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Drug or Drug Class	Expected A1C Drop When Added to Metformin[23] MOA	Maximum Daily Dose[24] (Cost/30 Days)[a]	Notable Adverse Effects	Comments
SGLT2 inhibitors, continued Empagliflozin (*Jardiance*, with linagliptin [*Glyxambi*], with metformin [*Synjardy*, *Synjardy XR*]) Ertugliflozin (*Steglatro*, with metformin [*Segluromet*], with sitagliptin [*Steglujan*])			• Rare cases of Fournier's gangrene in men and women, with onset early (days) and late (~2 years) in therapy.[47] • Amputations may occur in about 6 of every 1,000 patients treated with canagliflozin over 1 year, compared to about 3 in every 1,000 patients on other diabetes meds.[27,37] • Canagliflozin use in patients at high CV risk for about 3.5 years may increase risk of amputations, NNH ~77 [Evidence level A-1].[37,38]	
Sulfonylurea–first generation Chlorpropamide (*Diabinese* [discontinued], generics) Tolazamide (*Tolinase* [discontinued], generics) Tolbutamide (*Orinase* [discontinued], generics)	1% to 1.5% as monotherapy[45] MOA: stimulates pancreatic insulin secretion.[21,24]	**Chlorpropamide** 750 mg[24] (~$70) **Tolazamide** 1,000 mg (doses >500 mg divide BID)[24] (~$170) **Tolbutamide** 3,000 mg (given once daily or divided up to TID)[24] (~$170)	• Hypoglycemia (educate patient to prevent, recognize, and manage).[21] ○ More common than with second-generation sulfonylureas.[5] • Weight gain.[5] • Increased CV mortality (tolbutamide).[29]	• Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started.[1] • Second-generation sulfonylureas preferred over first-generation sulfonylureas, due to lower risk of hypoglycemia.[5] • Relatively short-lived efficacy.[1] • Avoid chlorpropamide in patients with renal dysfunction or the elderly.[24]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Sulfonylurea-second generation Glyburide (*DiaBeta* [discontinued], *Glynase*, *Micronase*, generics, with metformin [*Glucovance*]) Glipizide (*Glucotrol*, *Glucotrol XL*, generics, with metformin [*Metaglip*]) Glimepiride (*Amaryl*, generics, with pioglitazone [*Duetact*], with rosiglitazone [*Avandaryl*])	0.7% to 1.3% MOA: stimulates pancreatic insulin secretion.[21,24]	**Glimepiride** 8 mg (~$15) **Glipizide IR** 40 mg (doses >30 mg should be divided BID) (less than $10) **Glipizide XL** 20 mg (~$20) **Glyburide** 20 mg (standard formulation; doses >10 mg can divide BID); 12 mg (micronized product; once daily or in divided doses) (~$20)	• Hypoglycemia, especially with renal dysfunction (educate patient to prevent, recognize, and manage).[21] ○ Less with glimepiride versus glyburide.[5] Avoid both in the elderly.[51] • Weight gain. ○ Less with glipizide and glimepiride versus glyburide.[5]	• Discontinue when more complex insulin regimens (e.g., basal plus prandial insulins) are started.[1] • Relatively short-lived efficacy.[1] • For the elderly and those with hepatic or renal dysfunction, start with low doses and titrate up.[21]
Thiazolidinedione (TZD) Pioglitazone (*Actos*, generics, with metformin [*ACTOplus Met* or *ACTOplus Met XR*], with glimepiride [*Duetact*], with alogliptin [*Oseni*]) *Continued…*	0.8% to 0.9% MOA: increases insulin sensitivity in muscle and fat.[21,24]	**Pioglitazone** 45 mg (less than $10) **Rosiglitazone** 8 mg (~$340)	• Low risk of hypoglycemia when used as monotherapy.[21] • Edema.[21] • Weight gain.[21] • Heart failure.[21] • Increased fracture risk.[21] • Increased LDL (rosiglitazone).[21]	• Glycemic control better sustained over diabetes course than metformin or sulfonylureas.[21] • Pioglitazone may improve lipid profile (e.g., lowers triglycerides).[21] • Avoid in patients with symptomatic heart failure.[21] • CV benefit (pioglitazone).[30]

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Drug or Drug Class	**Expected A1C Drop When Added to Metformin**[23] **MOA**	**Maximum Daily Dose**[24] **(Cost/30 Days)**[a]	**Notable Adverse Effects**	**Comments**
Thiazolidinedione, continued Rosiglitazone (*Avandia*, with metformin [*Avandamet*])			• Possible increased risk of bladder cancer (pioglitazone). Assess risk factors and counsel patients to report hematuria.[31,34]	
Others – bile acid sequestrant Colesevelam (*Welchol*, generic)	0.5%[32] MOA: may reduce hepatic glucose production, increase incretin levels, and decrease glucose absorption.[21]	**Colesevelam** 3.75 gm, given once daily or divided BID (~$550 [powder for suspension]; ~$260 [tablets])	• GI (e.g., constipation, nausea, bloating).[21] • May increase triglycerides.[21] • Rare hypoglycemia.[21]	• Lowers LDL cholesterol.[21] • May decrease absorption of other meds.[21]
Others – dopamine agonist Bromocriptine (*Cycloset*)	0.5% when added to metformin and a sulfonylurea[28] MOA: may centrally regulate metabolism, increases insulin sensitivity.[21]	**Bromocriptine** 4.8 mg (~$750)	• Fatigue.[21] • Dizziness/syncope.[21] • Nausea.[21] • Rare hypoglycemia.[21]	• Weight neutral.[28] • CYP3A4 interactions.[24]

a. Pricing (for generic when available) based on wholesale acquisition cost (WAC). Medication pricing by Elsevier, accessed May 2019.

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Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality RCT 2. SR/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*****	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).
RCT = randomized controlled trial; **SR** = systematic review
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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March 2019 ~ Resource #350304

Improving Diabetes Outcomes

Below is our toolbox of practical tips and resources to help improve outcomes in your patients with diabetes, with a focus on nonpregnant **adults**.

Guidelines from the ADA and Diabetes Canada are available at:

- ADA: http://care.diabetesjournals.org/content/diacare/suppl/2018/12/17/42.Supplement_1.DC1/DC_42_S1_Combined_FINAL.pdf
- Diabetes Canada: http://guidelines.diabetes.ca/docs/CPG-2018-full-EN.pdf

Abbreviations: ABI = ankle-brachial index; ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; ADA = American Diabetes Association; AHA = American Heart Association; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CCS = Canadian Cardiovascular Society; DC = Diabetes Canada; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ISH = International Society of Hypertension; JNC8 = Eighth Joint National Committee; SGLT2 = sodium-glucose cotransporter 2 (flozins).

Goal	Suggested Strategies or Resources
Set an appropriate **A1C target**.	• Recommend an A1C <7% (ADA) or ≤7% (DC) in many patients with diabetes to reduce complications.[1,2] • Select less stringent targets, such as <8% (ADA) or ≤8.5% (DC), in certain diabetes patients such as those at risk for severe hypoglycemia, with limited life expectancy, or with advanced vascular complications.[1,2] • Select more stringent targets, such as <6.5% (ADA) or ≤6.5% (DC), to further reduce the risk of microvascular complications when the benefit outweighs the risk of hypoglycemia.[1,2] • Diabetes Canada has an online tool providers can use to individualize your patient's A1C target at http://guidelines.diabetes.ca/reduce-complications/a1ctarget. • Read about *A Personalized Approach for A1C Goals*.
Choose the **most appropriate agent(s)** to achieve the A1C target. *Continued…*	• Start with **metformin** in most patients with type 2 diabetes without severe renal impairment.[1,2] (U.S.: do not start if eGFR <45 mL/min/1.73 m^2).[1] Metformin has negligible risk of hypoglycemia, does not cause weight gain, and may reduce cardiovascular risk.[1,2] – See our commentary, *Clinical Use of Metformin in Special Populations*, for details on metformin use in renal impairment, heart failure, and liver impairment. – Metformin is associated with **B12 deficiency**. Consider checking levels periodically (every two to three years), especially in patients with anemia or neuropathy (Canada: check every one to two years).[1,13,14] For details on monitoring, diagnosis, and treatment, see our commentary, *Management of Vitamin B12 Deficiency*. • Add meds to metformin for patients with type 2 diabetes based on A1C lowering, side effects, and cost.[1,2]

More. . .

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<table>
<tr><th>Goal</th><th>Suggested Strategies or Resources</th></tr>
<tr><td>Choose the most appropriate agent(s) to achieve the A1C target, continued</td><td>
<table>
<tr><th>Drug Class</th><th>Consider for…[9,19]</th><th>Avoid or Use Caution in…[1,2,4,9,19]</th></tr>
<tr><td>SGLT2 inhibitor</td><td>CV disease risk,* heart failure, overweight</td><td>Renal impairment, diuretic use, risk factors for amputation, history of genital fungal infections, fracture risk</td></tr>
<tr><td>GLP-1 Agonists</td><td>CV disease risk,* overweight</td><td>Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2</td></tr>
<tr><td>Sulfonylurea</td><td>Cost concerns</td><td>Hypoglycemia risk, overweight</td></tr>
<tr><td>Insulin</td><td>High A1C</td><td>Hypoglycemia risk, overweight[9]</td></tr>
<tr><td>Glitazone</td><td>High triglycerides, CV risk</td><td>Heart failure, risk of bladder cancer, patients on insulin</td></tr>
<tr><td>DDP-4 Inhibitor</td><td>Post-prandial effect desired, overweight</td><td>Heart failure (saxagliptin, alogliptin)</td></tr>
<tr><td>α-glucosidase inhibitor</td><td>Post-prandial effect desired, overweight</td><td>A1C ≥8.5%</td></tr>
</table>
*In patients with clinical cardiovascular disease, consider empagliflozin, canagliflozin, liraglutide, or semaglutide.[1,2] They reduce major CV events when added to standard care in patients with CV disease or high CV risk (liraglutide, canagliflozin, semaglutide),[1] including all-cause and CV mortality (empagliflozin, liraglutide).[1] See our chart, Diabetes Medications and Cardiovascular Impact, for details on study outcomes for each agent.

• When goals aren't met, scrutinize the patient's med list for Drugs That Significantly Increase Blood Glucose.
• For more information on drug therapy for type 2 diabetes, see our resources:
• Management of New-Onset Type 2 Diabetes
• Drugs for Type 2 Diabetes (U.S. subscribers)
• Stepwise Treatment of Type 2 Diabetes (Canadian subscribers)
• Initiation and Adjustment of Insulin Regimens for Type 2 Diabetes (U.S. subscribers, Canadian subscribers)
• How to Switch Insulin Products (U.S. subscribers, Canadian subscribers)
• Comparison of Insulins (U.S. subscribers, Canadian subscribers)
• Insulin Analogs vs Human Insulin
• Insulin Pumps: What You Need to Know
</td></tr>
<tr><td>Ensure safe use of diabetes meds.</td><td>• New insulin concentrations and products can create confusion. For strategies and resources to help prevent errors with insulin, see our chart, Tips to Improve Insulin Safety.
• Give patients our patient education handout, How to Handle Low Blood Sugar (U.S. subscribers, Canadian subscribers).
• For notable adverse effects of flozins, glitazones, and more, see our charts, Drugs for Type 2 Diabetes (U.S. subscribers) and Stepwise Treatment of Type 2 Diabetes (Canadian subscribers).</td></tr>
</table>

More. . .

Goal	Suggested Strategies or Resources
Use a **statin** when appropriate.	• Use a statin for **primary prevention** for most diabetes patients 40 years of age and older.[5,6] • **AHA/ACC**:[5] • Statins are indicated for adults 40 to 75 years of age with diabetes and an LDL ≥70 mg/dL • In adults 20 to 39 years of age with diabetes that is longstanding (≥10 years for type 2 or ≥20 years for type 1), albuminuria (≥30 mcg/mg creatinine), eGFR <60 mL/min/1.73 m^2, ABI <0.9, retinopathy, or neuropathy, starting a statin may be reasonable. • In patients >75 years of age with diabetes, continuing or even starting a statin may be reasonable after a risk/benefit discussion. • **CCS**: statins are indicated for diabetes and age ≥40 years, or diabetes >15 years' duration and age ≥30 years, or diabetes with microvascular disease.[6] • A statin is indicated for secondary prevention in patients with diabetes and ASCVD.[5,6] • For a complete list of statin indications, see our charts, *2018 ACC/AHA Cholesterol Guidelines* (U.S. subscribers) or *Canadian Cardiovascular Society Dyslipidemia Recommendations* (Canadian subscribers). • For more information on choosing and using a statin, see our charts: • *Characteristics of the Various Statins* • *Statin Dose Comparison* • To help promote safe statin use, give patients our patient education handout, *What You Should Know About Statins*.
Meet an appropriate **blood pressure goal**.	• Aim for a BP <140/90 mmHg in most diabetes patients (JNC 8, ISH, ADA).[1,7] The ADA states that a target of <130/80 mmHg may be suitable for patients with CV disease or 10-year CV risk >15% if it can be safely achieved.[1] ACC/AHA guidelines recommend a BP of <130/80 mmHg for most patients in general,[7] and Canadian guidelines (DC, CCS) recommend a goal of <130/80 mmHg for most patients with diabetes.[2,8] • Pharmacotherapy should include an antihypertensive shown to reduce CV events in diabetes patients: ACEI, ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker.[1,2,8] (ISH guidelines give preference to ACEI or ARB in non-black patients.[7]) • For more information about blood pressure goals and choosing appropriate antihypertensives, see our resources: • *Treatment of Hypertension* (U.S. subscribers) • *Stepwise Treatment of Hypertension* (Canadian subscribers) • Help pharmacy technicians brush up on treatment of high blood pressure with our technician tutorial, *Hypertension 101*. • Give patients our patient education handout, *Blood Pressure Medications and You.*

More. . .

Goal	Suggested Strategies or Resources
Choose safe and effective treatment for patients with concomitant **heart failure.**	• Choose **metformin** first for most heart failure patients with type 2 diabetes.[1,2,4] Hold if patient becomes unstable (e.g., acute heart failure exacerbation), or eGFR <30 mL/min/1.73 m^2, due to rare risk of lactic acidosis.[1,4] Preliminary evidence suggests that metformin may improve outcomes (e.g., reduced hospitalization and mortality).[1,20] • **SGLT2 inhibitors** are second-line agents.[1,2] Empagliflozin, canagliflozin, and dapagliflozin have been shown to reduce heart failure hospitalization in patients with CV disease (and high CV risk [canagliflozin]).[1,15,16] • Studies are underway to determine SGLT2 inhibitor benefits specifically in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.[4] • Be aware that SGLT2 inhibitors may cause volume depletion in patients taking a diuretic.[1] Do not start an SGLT2 inhibitor if eGFR <45 mL/min/1.73m^2 (canagliflozin, empagliflozin) or <60 mL/min/1.73m^2 (dapagliflozin, ertugliflozin).[1,2,17,18] • **GLP-1 agonists** can be used in heart failure, but do not seem to specifically benefit heart failure (i.e., neutral effect).[1,2] Concerns have been raised about increased heart rate in heart failure patients in some studies.[4] • **Sulfonylureas** and **insulin** appear to have a neutral effect.[1,4] • **Saxagliptin**, and **alogliptin** have been associated with heart failure hospitalization.[4] For more on gliptins and heart failure, see our commentary, *DPP-4 inhibitors (Gliptins) and Risk of Heart Failure*. • **Glitazones** are associated with fluid retention and increased risk of heart failure and heart failure hospitalization, and should be avoided in patients with (symptomatic [ADA]) heart failure .[1,2,4] • Patients with diabetes are at increased risk of renal impairment and hyperkalemia due to renin-angiotensin-aldosterone system blockade. In patients with eGFR <60 mL/min/1.73 m2 and/or using s**pironolactone** or **eplerenone**, consider starting their **ACEI** or **ARB** at half-dose; checking electrolytes, renal function, blood pressure, and heart failure symptoms within seven to ten days of initiation or dosage increase; and increasing the dose cautiously.[2] • **Beta-blockers** reduce morbidity and mortality in patients with heart failure with reduced ejection fraction and diabetes.[4] They do not seem to worsen glycemic control, and hypoglycemic unawareness was not reported in clinical trials.[4]
Start **low-dose aspirin** if appropriate.	• Use low-dose aspirin (e.g., 81 mg/day) in diabetes patients for **secondary prevention** in patients with a history of atherosclerotic cardiovascular disease (e.g., heart attack, stroke).[1,2] • Aspirin's benefit for **primary prevention** in patients with diabetes appears similar to that of the general population, and is controversial.[1,10] Low-dose aspirin could be considered for primary prevention in diabetes patients ≥50 years of age with at least one major risk factor (family history, hypertension, smoking, kidney disease, dyslipidemia) and low bleeding risk, after a risk/benefit discussion (ADA).[1] Patients >70 years of age, risk appears greater than benefit.[1] Similarly, Diabetes Canada does not recommend routine use.[2] • Get more information on the evidence regarding low-dose aspirin benefits and risks from our chart, *Aspirin for CV Primary Prevention and More*. • Give patients our handout, *Aspirin and Your Heart*.

More. . .

Goal	Suggested Strategies or Resources
Make sure patients are up-to-date on **vaccines**.	• People with diabetes should receive immunizations per the latest immunization schedule recomendations.[1,2] Encourage administration of pneumococcal vaccine, influenza vaccine, hepatitis B (ADA), and herpes zoster (DC) vaccine to patients with diabetes.[1,2] • **ADA**: Annual vaccination against **influenza** is recommended for all persons ≥6 months of age.[1] Vaccination against **pneumonia** with pneumococcal polysaccharide vaccine (PPSV23; *Pneumovax 23*) is recommended for people with diabetes two through 64 years of age. In children, complete the pneumococcal conjugate vaccine (PCV13; *Prevnar 13*) series before age two years.[1] For immunocompetent patients ≥65 years give **one** dose of PCV13 (if not previously given and 1 year has passed since any previous PPSV23 dose), then PPSV23 ≥1 year after PCV13 and ≥5 years after the last dose of PPSV23.[3] Give the **hepatitis vaccine** series to unvaccinated adults with diabetes who are age 19 to 59 years. Also consider the hepatitis B vaccine series for unvaccinated adults with diabetes who ≥60 years of age.[1] • **Diabetes Canada**: For adults, give **influenza** vaccine annually.[2] Vaccination against **pneumonia** with pneumococcal polysaccharide vaccine (PPSV23) should be offered to adults 19 to 64 years of age.[2] For those ≥65 years give **one** dose of PPSV23, provided five years have elapsed since any dose given at age <65 years.[2] For patients ≥65 years of age, PCV13 can also be considered (if not previously given) at least one year after any previous PPSV23 dose, then a one-time PPSV23 dose ≥8 weeks after PCV13, allowing five years to elapse since any PPSV23 dose given at age <65 years.[2] Give the herpes zoster vaccine to adults ≥60 years of age.[2] • Immunization schedules can be found at http://www.cdc.gov/vaccines/schedules/hcp/adult.html (U.S.; adults ≥19 years of age), https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html (U.S.; ages ≤18 years), and http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-chroni-eng.php#a7 (Canada; immunizations for persons with chronic diseases).
Ensure patients stay on appropriate medications through **transitions of care**.	• Use our *Transitions of Care Checklist* at admission, at transfer between units at the same facility, and at the patient's first post-admission outpatient visit to keep patients on track with their medications and out of the hospital. • For tips of reducing bouncebacks, see our toolbox, *Reducing Hospital Readmissions*. • Use the toolbox from AHRQ to optimize medication reconciliation (http://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/match/match.pdf). • Pharmacy technicians can learn to assist patients with med lists using our technician tutorial, *Mastering Medication Lists and Histories.*
Help improve **medication adherence**. *Continued…*	• Tailor medication regimens and educate patients with diabetes to help them adhere. • See our resources on improving adherence: • *Medication Adherence Strategies* toolbox • *Conversation Starter: Med Adherence Quick Guide* • *Guide for Helping Patients Afford Their Medications* (U.S. subscribers) • *Strategies for Communicating Effectively with Patients* (pharmacist CE)

More. . .

Goal	Suggested Strategies or Resources
Help improve **medication adherence**, continued	• *Using Motivational Interviewing to Create Change* (pharmacist CE) • When patients are part of the decision-making process, they are more likely to be adherent. Most conditions have several reasonable treatment options, each carrying a different balance of risks and benefits. In these situations, "shared decision making," which involves providing balanced information on the benefits and risk of each option, can be used.[11] • An online diabetes decision aid to use with your patients is available from the Mayo Clinic at https://diabetesdecisionaid.mayoclinic.org. • Use our resources to help educate diabetes patients about the need to tailor their medication regimens in specific situations: • *Sick Day Management of Diabetes* • Patient education handout, *How to Manage Sick Days with Diabetes* (U.S. subscribers, Canadian subscribers)
Prevent and manage **diabetes complications**.	• See our resources: • *Pharmacotherapy of Neuropathic Pain* • *Diabetic Foot Infections* • *Management of Albuminuria: Focus on Pharmacotherapy*
Use **self-monitoring of blood glucose** appropriately.	• Recommend self-monitoring of blood glucose for patients who can benefit, such as those with type 1 diabetes, those with type 2 diabetes treated with insulin, or those with poorly controlled type 2 diabetes.[1,2] • In type 2 patients not taking hypoglycemic agents, multiple daily self-monitoring is not necessary except when therapy adjustments may be needed (e.g., acute illness, poor control, new meds, etc).[12] • For more information about self-monitoring of blood glucose, see our resources: • *Comparison of Blood Glucose Meters* (U.S. subscribers, Canadian subscribers) • *Lancets and Lancing Devices* (U.S. subscribers, Canadian subscribers) • Give patients our handout: *Understanding Your Blood Sugar Numbers* (U.S. subscribers, Canadian subscribers).
Educate patients about **diet, exercise, and other lifestyle changes**. *Continued…*	• Encourage beneficial lifestyle changes such as maintaining a healthy weight, smoking cessation, and regular physical activity for diabetes patients.[1,2] • Diabetes is best-managed by a multidisciplinary care team.[1.2] To find an accredited diabetes education program, go to https://www.diabeteseducator.org/living-with-diabetes/find-an-education-program (U.S.) • Consider referral to a registered dietitian.[1,2] To find a registered dietitian, go to http://www.eatright.org/programs/rdfinder/. • For more information on beneficial lifestyle changes for patients with diabetes, see our resources: • *Weight Loss: Helping Your Overweight and Obese Patients* • *Lifestyle Changes to Reduce Cardiovascular Risk* • *Smoking Cessation: Helping Patients Who Use Tobacco*

More. . .

Goal	Suggested Strategies or Resources
Educate patients about **diet, exercise, and other lifestyle changes**, continued	• *Smoking Cessation Drug Therapy* • *Tackling a Growing Problem: Childhood Obesity* (pharmacist, technician CE) • *Pharmacotherapy for Smoking Cessation* (pharmacist CE) • *The Pharmacist's Role in Promoting Tobacco Cessation* (pharmacist CE) • Give patients our patient education handouts to take home: • *Tips for Getting to a Healthy Weight* • *How to Eat a Heart-Healthy Diet* • *How to Kick the Smoking Habit* • *Have Diabetes? Take Care of Your Feet!*
Help schedule **screenings** as appropriate.	• Encourage adults with type 2 diabetes to schedule eye exams at least every two years (or at least every year if there is evidence of retinopathy), get screened for nephropathy annually, get screened for neuropathy annually, and get comprehensive foot exams at least annually.[1,2] • Give patients our patient education handout to take home: *Have Diabetes? Take Care of Your Feet!*
Learn about **quality measures**.	• Learn more about quality measures for patients with diabetes from our toolbox: • *Quality Measures for Pharmacies* (U.S. subscribers)
Use **medication therapy management (MTM)** to optimize treatment for patients with diabetes (U.S. pharmacists).	• Medicare Part D patients with diabetes are eligible for MTM. • U.S. pharmacists can use our conversation starter, *Improving Diabetes Care*, as a guide when talking with diabetes patients during medication reviews or other patient interactions. • For more information on MTM, see our resources: • *Medication Therapy Management* (U.S. subscribers) • *MTM in the Community Pharmacy: Comprehensive Medication Reviews* (pharmacist CE [U.S.]) • *MTM in the Community Pharmacy: Targeted Interventions* (pharmacist CE) • Use our technician tutorials to engage pharmacy technicians in the process of MTM: • *Diabetes 101* • *Dispensing Insulin and Other Injectable Diabetes Meds* • *Patient Profiles 101* • *Optimizing Pharmacy Workflow*

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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