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Drugs for Type 2 Diabetes

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The goal of drug therapy for type 2 diabetes is to achieve and maintain a near-normal glycated hemoglobin (A1C) concentration without inducing hypoglycemia; the target is generally an A1C of <7%.[1] Treating to this target has been shown to prevent microvascular complications (retinopathy, nephropathy, and neuropathy), but whether it prevents macrovascular outcomes is unclear. An A1C target of <8% may be appropriate for older patients and those with underlying cardiovascular disease, a history of severe hypoglycemia, diabetes-related complications or comorbidities, or a long duration of disease.[2,3]

LIFESTYLE MODIFICATIONS — Diet, exercise, and weight loss can improve glycemic control and are recommended for all patients, but most patients with type 2 diabetes ultimately require drug therapy. In a 10-year randomized controlled trial in 5145 overweight or obese patients with type 2 diabetes, an intensive lifestyle modification program reduced weight, lowered A1C, and improved cardiovascular risk factors, but did not reduce the incidence of cardiovascular events.[4]

METFORMIN — The oral biguanide metformin (*Glucophage*, and others) is the drug of choice for initial treatment of type 2 diabetes for most patients.[1,3,5] Its mechanism of action is complex.[6,7] 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. A meta-analysis of 177 trials comparing use of metformin to either a sulfonylurea, a thiazolidinedione, a DPP-4 inhibitor, or an alpha-glucosidase inhibitor found that metformin was more effective than all the other drugs in achieving A1C goals.[8] Metformin produces about the same reduction in A1C as a sulfonylurea (1-1.5%), but metformin-induced reductions are more durable and metformin does not cause weight gain and rarely causes hypoglycemia.

Recommendations for Treatment of Type 2 Diabetes

- For most patients, the target of drug therapy is an A1C of <7%.
- Oral antihyperglycemic drugs lower A1C by 0.5-1.5%.
- Metformin is generally the drug of choice for initial treatment of type 2 diabetes.
- If metformin alone does not achieve the desired A1C goal, a second drug is usually added. Most patients with type 2 diabetes eventually require multi-drug therapy to maintain glycemic control.
- Reasonable second-line agents include a sulfonylurea, GLP-1 receptor agonist, DPP-4 inhibitor, or SGLT2 inhibitor.
- If maximum doses of two drugs prove insufficient, adding insulin may be appropriate to achieve glycemic control.
- Some diabetes experts favor early use of insulin if A1C remains poorly controlled on maximal-dose single-drug therapy.

Cardiovascular Benefits — Metformin has been associated with decreases in both microvascular and macrovascular complications. In a 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS), use of metformin reduced the risk of myocardial infarction by 33% and death from any cause by 27%, compared to dietary restriction alone.[9]

Renal Impairment — The FDA has removed earlier restrictions on use of metformin in patients with mild to moderate chronic kidney disease because recent studies indicate that it does not increase the risk of lactic acidosis in such patients.[10] Metformin is now contraindicated in patients with an eGFR <30 mL/min/1.73 m^2, and starting treatment with the drug in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended.[11]

SULFONYLUREAS — The sulfonylureas **glimepiride** (*Amaryl*, and generics), **glipizide** (*Glucotrol*, and others), and **glyburide** reduce A1C by 1-1.5%. They interact with ATP-sensitive potassium channels in the beta-cell membrane to increase secretion of insulin. In a 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS), use of a sulfonylurea or insulin reduced the risk of myocardial infarction by 15%, microvascular disease by 24%, and death from any cause by 13%, compared to dietary restriction alone.[9] Hypoglycemia and weight gain are the main deterrents to use of sulfonylureas.

Revised 1/12/17: In the dulaglutide section, we mistakenly stated that *Xultophy* is a combination of **albiglutide**/insulin degludec; the correct combination of *Xultophy* is **liraglutide**/insulin degludec. We have also moved that sentence to the liraglutide paragraph.

Table 1. Advantages and Adverse Effects

Drug Class (A1C Reduction[1])	Some Advantages	Some Adverse Effects
Biguanide (1-1.5%)		
Metformin	Inexpensive; durable A1C lowering; weight neutral or weight loss (2-3 kg); hypoglycemia is rare when used as monotherapy; reduction in micro- and macrovascular events	GI effects (metallic taste, nausea, diarrhea, abdominal pain)[2]; vitamin B12 deficiency[3]; lactic acidosis[4]; decrease in hemoglobin and hematocrit (first year of treatment)
Sulfonylureas[5] (1-1.5%)		
Glimepiride, glipizide, glyburide	Inexpensive; long-term reduction in micro- and macrovascular complications	Hypoglycemia; weight gain; possible aggravation of myocardial ischemia; glyburide has a higher incidence of hypoglycemia and mortality than glimepiride or glipizide[6]; increased risk of hip and other fractures[7]
GLP-1 Receptor Agonists (1-1.5%)		
Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide[8]	Weight loss (1.5-2.8 kg); no hypoglycemia when used as monotherapy; albiglutide, dulaglutide, and extended-release exenatide *(Bydureon)* are administered once weekly; decrease in cardiovascular events with liraglutide in high-risk patients	Nausea[9]; vomiting; diarrhea; renal insufficiency and acute renal failure with nausea and vomiting[10]; possible risk of acute pancreatitis; thyroid C-cell carcinomas have been reported in animals and thyroid C-cell hyperplasia has been reported in humans (liraglutide and extended-release exenatide)[11]
DPP-4 Inhibitors (0.5-1%)		
Alogliptin, linagliptin, saxagliptin, sitagliptin	Weight neutral; hypoglycemia is rare when used as monotherapy[12]	Hypersensitivity reactions (urticaria, angioedema, anaphylaxis, Stevens-Johnson syndrome, and vasculitis); possible risk of acute pancreatitis; fatal hepatic failure; higher rate of hospitalization for heart failure in one study with saxagliptin; possible severe and disabling joint pain
SGLT2 Inhibitors (0.5-1%)		
Canagliflozin, dapagliflozin, empagliflozin	Weight loss (0.1-4 kg); risk of hypoglycemia comparable to placebo[13]; reduction in blood pressure, cardiovascular mortality and risk of nephropathy with empagliflozin[14]	Genital mycotic infections in men and women; recurrent urinary tract infections; volume depletion; increased urinary frequency and volume; hypotension; ketoacidosis; increased serum creatinine and decreased eGFR; hyperphosphatemia with canagliflozin and dapagliflozin; hyperkalemia and hypermagnesemia with canagliflozin; fractures; increase in LDL-cholesterol; increase in hemoglobin and/or hematocrit; possible increased risk of bladder cancer with dapagliflozin

1. When used as monotherapy.
2. 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. VR Aroda et al. J Clin Endocrinol Metab 2016; 101:1754.
4. Occurs rarely. Metformin should be not be administered for 48 hours after an iodinated contrast imaging procedure in patients with an eGFR <60 mL/min/1.73 m^2 or a history of liver disease, alcoholism, or decompensated heart failure, or in those receiving intra-arterial contrast, and eGFR should be re-evaluated before treatment is restarted.
5. First-generation sulfonylureas, such as tolbutamide and chlorpropamide, have been associated with an increased risk of cardiovascular mortality.
6. Because of its adverse effects, many experts no longer recommend use of glyburide (MC Riddle. J Clin Endocrinol Metab 2010; 95:4867).
7. J Starup-Linde et al. Bone 2016; 95:136.

Cardiovascular Safety – A review of the Nurses' Health Study, which followed 4902 women with diabetes and no cardiovascular disease, found an association between duration of sulfonylurea use and increased risk of coronary heart disease, but not stroke.[12] However, a meta-analysis of 47 randomized controlled trials found no increase in the risk of myocardial infarction, stroke, or cardiovascular or all-cause mortality with use of sulfonylureas, and long-term trials found that sulfonylureas reduced both microvascular and macrovascular complications of diabetes.[13]

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 lower A1C by 1-1.5% and have been associated with weight loss.

Exenatide is injected subcutaneously twice daily *(Byetta)*[14] or once weekly *(Bydureon)*.[15] Immediate-release exenatide can be used with basal insulin; use of once-weekly exenatide with basal insulin has not been studied.

Liraglutide *(Victoza)* is injected subcutaneously once daily and can be used with basal insulin. Liraglutide is also available in combination with insulin degludec *(Xultophy)*. In a randomized double-blind trial in 9340 patients with type 2 diabetes at high risk for cardiovascular events, addition of liraglutide to standard therapy significantly reduced the composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, compared to addition of placebo. This effect was seen mainly in patients who had a cardiovascular event before enrollment.[16]

Dulaglutide *(Trulicity)* and **albiglutide** *(Tanzeum)* are injected subcutaneously once weekly. Dulaglutide

Table 1. Advantages and Adverse Effects (continued)

Drug Class (A1C Reduction[1])	Some Advantages	Some Adverse Effects
Meglitinides (0.5-1%)		
Nateglinide, repaglinide	Short-acting	Hypoglycemia; weight gain; increased risk of hypoglycemia in patients with severe renal impairment taking nateglinide
Thiazolidinediones (1-1.5%)		
Pioglitazone, rosiglitazone	Durable A1C lowering; low risk of hypoglycemia	Weight gain (2-3 kg over 6-12 months)[15]; peripheral edema; anemia; increased risk of heart failure[16,17]; macular edema; possible decrease in bone mineral density and increased incidence of fractures, especially in women[18]; hepatic failure; pioglitazone has been associated with an increased risk of bladder cancer[19]
Alpha-Glucosidase Inhibitors (0.5-1%)		
Acarbose, miglitol	No hypoglycemia when used as monotherapy[20]	Abdominal pain, diarrhea, and flatulence[21]; acarbose can cause transaminase elevations
Others (0.5%)		
Pramlintide	Weight loss; reduces postprandial glucose excursions	Nausea; vomiting; headache; anorexia; severe hypoglycemia (when taken with insulin)
Colesevelam	No hypoglycemia; decreased LDL cholesterol	Constipation; nausea; dyspepsia; increased serum triglyceride concentrations
Bromocriptine	No hypoglycemia; may reduce risk of cardiovascular events	Nausea, vomiting, fatigue, headache, and dizziness (more common during titration and lasting for a median of 14 days); somnolence; orthostatic hypotension; syncope, especially in patients taking antihypertensives; lowers prolactin levels

8. Albiglutide and extended-release exenatide *(Bydureon)* must be reconstituted before use.
9. Titrating the dose over one week for liraglutide and over one month for exenatide can help reduce nausea.
10. In patients with pre-existing kidney disease or taking other nephrotoxic drugs (TD Filippatos and MS Elisaf. World J Diabetes 2013; 4:190).
11. Albiglutide, dulaglutide, liraglutide, and extended-release exenatide should not be used in patients with or who have a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
12. The risk of hypoglycemic events increases significantly when taken with a sulfonylurea (AR Chacra et al. Int J Clin Pract 2009; 63:1395) or insulin.
13. WT Cefalu et al. Lancet 2013; 382:941.
14. B Zinman et al. N Engl J Med 2015; 373:2117; C Wanner et al. N Engl J Med 2016; 375:323.
15. Weight gain can be greater if used in combination with insulin.
16. Contraindicated in patients with NYHA class III or IV heart failure.
17. CB Maxwell and AT Jenkins. Am J Health Syst Pharm 2011; 68:1791.
18. YK Loke et al. CMAJ 2009; 180:32.
19. FDA safety communication. Available at: www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm532772.htm.
20. If hypoglycemia occurs, it should be treated with oral glucose because these drugs interfere with the breakdown of sucrose.
21. Slow titration can minimize these effects.

has reduced A1C by 0.8-1.6% when added to metformin alone, to metformin plus pioglitazone or glimepiride, or to prandial insulin. Albiglutide has reduced A1C by 0.6-0.8% when added to metformin alone, to metformin plus pioglitazone or a sulfonylurea, or to basal insulin glargine. It causes less weight loss than dulaglutide and more injection-site reactions.[17] A systematic review and meta-analysis of 34 randomized controlled trials found that extended-release exenatide and dulaglutide were more effective than albiglutide in reducing A1C and body weight, without increasing hypoglycemia.[18]

Lixisenatide *(Adlyxin)* is injected subcutaneously once daily.[19] It is also available in combination with insulin glargine *(Soliqua)*. Lixisenatide has reduced A1C by 0.6-1% when added to metformin, a sulfonylurea, pioglitazone, or basal insulin (or a combination of these agents) and reduced weight by 0.2-2.8 kg. In a randomized placebo-controlled trial in 6068 patients with type 2 diabetes who had either a myocardial infarction or an unstable angina event within the last 6 months, addition of lixisenatide to standard treatment neither increased nor decreased the risk of major cardiovascular events over a median follow-up of 25 months.[20]

Pancreatitis – GLP-1 receptor agonists have been associated with acute pancreatitis (see p. 15).[21]

DPP-4 INHIBITORS — The oral dipeptidyl peptidase-4 (DPP-4) inhibitors **alogliptin** *(Nesina)*,[22] **linagliptin** *(Tradjenta)*,[23] **saxagliptin** *(Onglyza)*,[24] and **sitagliptin** *(Januvia)*[25] potentiate glucose-dependent secretion of insulin and suppress glucagon secretion. They produce small reductions in A1C (0.5-1%) when used as monotherapy.

Cardiovascular Safety – Saxagliptin neither increased nor decreased the risk of ischemic events compared to placebo in 16,492 patients with type 2 diabetes who either had a history of cardiovascular disease or were at risk for cardiovascular events, but more patients taking saxagliptin were hospitalized for heart failure (3.5% vs 2.8%).[26] In 5380 patients with type 2 diabetes who had a recent acute coronary syndrome, **alogliptin** did not increase the incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke,

Revised 11/13/17: The price for *Victoza* was changed to $498.40 (from $249.20).

Table 2. Formulations, Dosage, and Cost

Drug	Some Available Formulations	Usual Adult Dosage	Cost[1]
Biguanide			
Metformin[2] – generic	500, 850, 1000 mg tabs	1500-2550 mg/d PO divided bid-tid[3]	$9.10
Glucophage (BMS)			88.20
liquid – *Riomet* (Ranbaxy)	500 mg/5 mL soln (4, 16 oz)	1500-2550 mg/d PO divided bid-tid[3]	615.90[4]
extended-release – generic	500, 750, 1000 mg ER tabs	1500-2000 mg PO once/d[5]	35.00
Glucophage XR (BMS)	500, 750 mg ER tabs		30.00
Glumetza (Salix)	500, 1000 mg ER tabs		1544.40
Fortamet (Shionogi)	500, 1000 mg ER tabs		1990.90
Sulfonylureas			
Glimepiride – generic	1, 2, 4 mg tabs	1-4 mg PO once/d[6]	6.30
Amaryl (Sanofi)			39.60
Glipizide – generic	5, 10 mg tabs	10-20 mg PO once/d[6] or divided bid[7]	2.70
Glucotrol (Pfizer)			70.50
extended-release – generic	2.5, 5, 10 mg tabs	5-20 mg PO once/d[6]	8.70
Glucotrol XL			37.60
Glyburide[8] – generic	1.25, 2.5, 5 mg tabs	5-20 mg PO once/d[6] or divided bid[3]	7.40
micronized tablets – generic	1.5, 3, 6 mg tabs	0.75-12 mg PO once/d[6]	2.30
Glynase Prestab (Pfizer)		or divided bid[3]	20.40
GLP-1 Receptor Agonists			
Albiglutide – *Tanzeum* (GSK)[9]	30, 50 mg single-dose pens[10]	30 or 50 mg SC once/wk	478.90
Dulaglutide – *Trulicity* (Lilly)[9]	0.75 mg/0.5 mL, 1.5 mg/0.5 mL single-dose pens or syringes	0.75 or 1.5 mg SC once/wk	626.00
Exenatide – immediate-release			
Byetta (BMS/AstraZeneca)	250 mcg/mL (1.2, 2.4 mL) prefilled pens	5 or 10 mcg SC bid[11,12]	607.50[13]
extended-release			
Bydureon (BMS/AstraZeneca)[9]	2 mg single-dose pen or powder for injectable suspension[10]	2 mg SC once/wk[12]	576.70
Liraglutide – *Victoza* (Novo Nordisk)[9]	6 mg/mL (3 mL) prefilled pens	1.2 or 1.8 mg SC once/d[14]	498.40[15]
Lixisenatide – *Adlyxin* (Sanofi)	50 mcg/mL, 100 mcg/mL (3 mL) prefilled pens	20 mcg SC once/d[16]	577.20
DPP-4 Inhibitors			
Alogliptin – generic	6.25, 12.5, 25 mg tabs	25 mg PO once/d[17]	195.00
Nesina (Takeda)			363.40
Linagliptin – *Tradjenta* (Boehringer Ingelheim)	5 mg tabs	5 mg PO once/d	357.10
Saxagliptin – *Onglyza* (AstraZeneca)	2.5, 5 mg tabs	2.5-5 mg PO once/d[18]	363.30
Sitagliptin – *Januvia* (Merck)	25, 50, 100 mg tabs	100 mg PO once/d[19]	363.40
SGLT2 Inhibitors			
Canagliflozin – *Invokana* (Janssen)	100, 300 mg tabs	100-300 mg PO once/d[6,20]	391.70
Dapagliflozin – *Farxiga* (AstraZeneca)	5, 10 mg tabs	5-10 mg PO once/d[6,21]	391.70
Empagliflozin – *Jardiance* (Boehringer Ingelheim/Lilly)	10, 25 mg tabs	10-25 mg PO once/d[6,22]	391.70
Meglitinides			
Nateglinide – generic	60, 120 mg tabs	60-120 mg PO tid[23]	103.50
Starlix (Novartis)			283.00
Repaglinide – generic	0.5, 1, 2 mg tabs	1-4 mg PO tid[23,24]	118.50
Prandin (Novo Nordisk)			563.00

ER = extended release; soln = solution; N.A. = Cost not available

1. Approximate WAC for 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. December 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.
2. Metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2. Starting metformin therapy in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended. If the eGFR falls below 45 mL/min/1.73 m^2 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. Taken with breakfast or first meal of the day.
7. Doses >15 mg/day should be divided and given before meals of adequate caloric content.
8. Because of its adverse effects, many experts no longer recommend use of glyburide (MC Riddle. J Clin Endocrinol Metab 2010; 95:4867).
9. Contraindicated in patients with or who have a family history of medullary thyroid carcinoma, and in patients with multiple endocrine neoplasia syndrome type 2.
10. Must be reconstituted before administration.
11. Starting dose is 5 mcg twice daily, up to an hour before the morning and evening meals. After one month, the dose can be increased to 10 mcg twice daily.
12. Not recommended for patients with a CrCl <30 mL/min.
13. Cost of one 1.2-mL prefilled pen.
14. Starting dosage is 0.6 mg once daily for 7 days, followed by 1.2 mg thereafter.
15. Cost of two 18 mg/3 mL pens.
16. Starting dosage is 10 mcg once daily, up to an hour before the morning meal, for 14 days, followed by 20 mcg thereafter.
17. The recommended dosage is 12.5 mg once daily for patients with a CrCl of 30 to 59 mL/min and 6.25 mg once daily for a CrCl <30 mL/min.
18. The recommended dosage is 2.5 mg once daily for patients with a CrCl ≤50 mL/min.
19. The recommended dosage is 50 mg once daily for patients with a CrCl of ≥30 to 49 mL/min and 25 mg once daily for a CrCl <30 mL/min.
20. Maximum dose is 100 mg in patients with moderate renal impairment (eGFR 45-59 mL/min/1.73 m^2). It should not be given to patients with an eGFR <45 mL/min/1.73 m^2.
21. Should not be started in patients with an eGFR <60 mL/min/1.73 m^2 or in those with active bladder cancer.
22. Should not be started in patients with an eGFR <45 mL/min/1.73 m^2.
23. Doses should be taken 15-30 minutes before meals. Should not be taken if meal is missed.

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

Drug	Some Available Formulations	Usual Adult Dosage	Cost[2]
Thiazolidinediones			
Pioglitazone – generic	15, 30, 45 mg tabs	15-45 mg PO once/d[25,26]	$9.00
Actos (Takeda)			388.57[39]
Rosiglitazone – *Avandia* (GSK)	2, 4 mg tabs	4-8 mg PO once/d or divided bid[27]	148.10
Alpha-Glucosidase Inhibitors			
Acarbose – generic	25, 50, 100 mg tabs	50-100 mg PO tid[3,28]	47.70
Precose (Bayer)			96.90
Miglitol – generic	25, 50, 100 mg tabs	50-100 mg PO tid[3,28]	170.30
Glyset (Pfizer)			207.30
Other			
Colesevelam – *Welchol* (Daiichi Sankyo)	625 mg tabs; 3.75 g/packet	3.75 g PO once/d or divided bid[3]	565.20
Bromocriptine[29] – *Cycloset* (Valeant/VeroScience)	0.8 mg tabs	1.6-4.8 mg PO once/d[30]	199.70
Pramlintide – *Symlin* (AstraZeneca)	1000 mcg/mL (1.5, 2.7 mL prefilled pen)	60-120 mcg SC tid[31]	885.00
Combination Products			
Metformin/glipizide[2] – generic	250/2.5, 500/2.5, 500/5 mg tabs	500/2.5 mg PO bid[3]	40.90
Metformin/glyburide[2] – generic	250/1.25, 500/2.5, 500/5 mg tabs	500/5 mg PO bid[3]	5.20
Glucovance (BMS)	500/2.5, 500/5 mg tabs		77.90
Metformin/repaglinide[2] – generic	500/1 mg tabs	500/1 mg PO bid-tid[23]	294.60
Metformin/pioglitazone[2] – generic	500/15, 850/15 mg tabs	500/15 mg PO bid[3,25]	191.80
Actoplus Met (Takeda)			573.20
Actoplus Met XR	1000/15, 1000/30 mg ER tabs	1000/15 mg PO once/d[3,25]	310.40
Metformin/rosiglitazone[2] – *Avandamet* (GSK)	500/2, 500/4, 1000/2, 1000/4 mg tabs	500/2 mg PO bid[3,27]	137.80
Metformin/alogliptin[2] – generic	500/12.5, 1000/12.5 mg tabs	500/12.5-1000/12.5 mg PO bid[3]	195.00
Kazano (Takeda)			363.40
Metformin/linagliptin[2] – *Jentadueto* (Boehringer Ingelheim)	500/2.5, 850/2.5, 1000/2.5 mg tabs	500/2.5-1000/2.5 mg PO bid[3]	357.10
Jentadueto XR	1000/2.5, 1000/5 mg ER tabs	1000/5-2000/5 mg PO once/d[3,32]	357.10
Metformin/saxagliptin[2] – *Kombiglyze XR* (BMS)	500/5, 1000/2.5, 1000/5 mg ER tabs	1000/5-2000/5 mg PO once/d[5]	363.30
Metformin/sitagliptin[2] – *Janumet* (Merck)	500/50, 1000/50 mg tabs	500/50-1000/50 mg PO bid[3]	363.40
Janumet XR	500/50, 1000/50, 1000/100 mg ER tabs	1000/100-2000/100 mg PO once/d[5]	363.40
Metformin/canagliflozin[2] – *Invokamet* (Janssen)	500/50, 1000/50, 500/150, 1000/150 mg tabs	500/50-500/150 mg PO bid[3,33]	391.70
Invokamet XR	500/50, 1000/50, 500/150, 1000/150 mg ER tabs	1000/100-1000/300 mg once/d[6,33]	391.70
Metformin/dapagliflozin[2] – *Xigduo XR* (AstraZeneca)	500/5, 1000/5, 500/10, 1000/10 mg ER tabs	500/5-1000/10 mg PO once/d[6,21]	391.70
Metformin/empagliflozin[2] – *Synjardy* (Boehringer Ingelheim/Lilly)	500/5, 1000/5, 500/12.5, 1000/12.5 mg tabs	500/5-1000/12.5 mg PO bid[3,22]	391.70
Glimepiride/pioglitazone – *Duetact* (Takeda)	2/30, 4/30 mg tabs	2/30-4/30 mg PO once/d[6,25]	576.50
Alogliptin/pioglitazone – generic	12.5/15, 12.5/30, 12.5/45,	25/15-25/45 mg PO once/d[25,34]	195.00
Oseni (Takeda)	25/15, 25/30, 25/45 mg tabs		363.40
Empagliflozin/linagliptin – *Glyxambi* (BI)	10/5, 25/5 mg tabs	10/5-25/5 mg PO once/d[6,22]	508.30
Long-Acting Insulin/GLP-1 Receptor Agonist Combinations			
Insulin degludec/liraglutide – *Xultophy* 100/3.6 (Novo Nordisk)	3 mL prefilled pen[35]	16-50 units SC once/d	190.60[38]
Insulin glargine/lixisenatide – *Soliqua* 100/33 (Sanofi)	3 mL prefilled pen[36]	15-60 units SC once/d[37]	127.00[38]

24. A starting dose of 0.5 mg tid with meals is recommended for patients with a CrCl 20-40 mL/min.
25. 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.
26. The initial dose of pioglitazone is 15 mg once daily in patients with NYHA class I or II heart failure.
27. 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.
28. Not recommended for patients with a serum creatinine >2 mg/dL.
29. Contraindicated in women who are breastfeeding.
30. Should be taken within 2 hours of waking in the morning.
31. Dose for patients with type 2 diabetes. Should be taken immediately before meals that contain ≥30 g of carbohydrate. Insulin dose should be reduced by 50%.
32. Patients who need 2000 mg/day of metformin should take two 1000/2.5 mg tablets once daily.
33. Maximum daily dose is 2000/300 mg in patients with an eGFR ≥60 mL/min/1.73 m². Patients with an eGFR 45 to <60 mL/min/1.73 m² should not receive more than 50 mg of canagliflozin bid.
34. Limit the initial dose of pioglitazone to 15 mg once daily in patients with NYHA class I or II heart failure. Reduce the alogliptin dose to 12.5 mg/d in patients with a CrCl of 30-59 mL/min.
35. Contains 100 units/mL of insulin degludec and 3.6 mg/mL of liraglutide.
36. Contains 100 units/mL of insulin glargine and 33 mcg/mL of lixisenatide.
37. Within one hour before first meal of the day.
38. Cost of one 3-mL pen.
39. Price from the manufacturer (May 2017).

Table 3. Some Insulin Products

	Some Available Formulations[1]	Onset	Peak	Duration	Cost[2]
Rapid-Acting		10-30 min	30 min-3 hrs	3-5 hrs	
Insulin aspart – *Novolog* (Novo Nordisk)	10 mL vial; 3 mL cartridge; 3 mL *FlexPen*				$255.40
Insulin glulisine – *Apidra* (Sanofi)	10 mL vial; 3 mL *Solostar* pen				255.10
Insulin lispro – *Humalog* (Lilly)	3, 10 mL vials; 3 mL *KwikPen*[3]				254.80
Insulin inhalation powder – *Afrezza* (Mannkind)	4, 8 unit cartridges[4]	10-30 min	12-15 min	~3 hrs	278.60[5]
Regular Insulin		30-60 min	2.5-5 hrs	4-12 hrs	
Humulin R (Lilly)	3, 10 mL vials[6]				137.90
Novolin R (Novo Nordisk)	10 mL vial				137.70
Intermediate-Acting		1-2 hrs	4-8 hrs	16-24+ hrs	
NPH – *Humulin N* (Lilly)	3, 10 mL vials; 3 mL *KwikPen*				137.90
Novolin N (Novo Nordisk)	10 mL vial				137.70
Long-Acting					
Insulin detemir – *Levemir* (Novo Nordisk)	10 mL vial; 3 mL *FlexTouch* pen	1-4 hrs	relatively flat	12-20 hrs	269.00
Insulin glargine – *Lantus* (Sanofi)	10 mL vial; 3 mL *SoloStar* pen	1-4 hrs	no peak	22-26 hrs	248.50
Toujeo (Sanofi)	1.5 mL *SoloStar* pen[7]	1-6 hrs	no peak	24-36 hrs	111.80
Basaglar[8] (Lilly/Boehringer Ingelheim)	3 mL *KwikPen*	1-4 hrs	no peak	~24 hrs[9]	63.40
Insulin degludec – *Tresiba* (Novo Nordisk)	3 mL *FlexTouch* pen[3]	1-9 hrs	no peak	>42 hrs	88.80
Premixed					
Humalog Mix 50/50 (Lilly) (50% insulin lispro protamine susp and 50% insulin lispro)	3 mL *KwikPen*	15-30 min	50 min-5 hrs	14-24 hrs	98.40
Humalog Mix 75/25 (Lilly) (75% insulin lispro protamine susp and 25% insulin lispro)	3 mL *KwikPen*	15-30 min	1-6.5 hrs	14-24 hrs	98.40
Humulin 70/30 (Lilly) (70% insulin aspart protamine susp and 30% insulin aspart)	10 mL vial; 3 mL *KwikPen*	30-60 min	2-12 hrs	18-24 hrs	137.90
Novolin 70/30 (Novo Nordisk) (70% NPH, human insulin isophane susp and 30% regular human insulin)	10 mL vial	30-60 min	2-12 hrs	18-24 hrs	137.70
Novolog Mix 70/30 (Novo Nordisk) (70% insulin aspart protamine susp and 30% insulin aspart)	10 mL vial; 3 mL *FlexPen*	10-20 min	1-4 hrs	18-24 hrs	264.90
Long-Acting Insulin/GLP-1 Receptor Agonist Combinations					
Insulin degludec/liraglutide – *Xultophy* 100/3.6 (Novo Nordisk)	3 mL prefilled pen[10]	1-9 hrs[11]	no peak	See footnote 12	190.60
Insulin glargine/lixisenatide – *Soliqua* 100/33 (Sanofi)	3 mL prefilled pen[13]	1-4 hrs[11]	no peak	See footnote 12	127.00

susp = suspension
1. Available in a concentration of 100 units/mL.
2. Approximate WAC for one 10-mL vial of the lowest strength or one 3-mL pen if vial not available. 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. December 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.
3. Also available in a concentration of 200 units/mL.
4. Administered via inhaler.
5. Cost for one package containing 60 8-unit and 30 4-unit cartridges of *Afrezza* and two inhalers.
6. Also available in a concentration of 500 units/mL.
7. *Toujeo* contains 300 units/mL compared to 100 units/mL in *Lantus* and *Basaglar*.
8. Basaglar is a "follow on" insulin glargine product similar to *Lantus*.
9. H Linnebjerg et al. Diabetes Obes Metab 2016 Aug 3 (epub).
10. Contains 100 units/mL of insulin degludec and 3.6 mg/mL of liraglutide.
11. Onset of insulin component only.
12. Refer to individual components alone.
13. Contains 100 units/mL of insulin glargine and 33 mcg/mL of lixisenatide.

compared to placebo.[27] There was a nonsignificant trend towards more hospitalizations for heart failure in patients taking alogliptin, compared to those taking placebo.[28] In 14,671 patients with type 2 diabetes and established cardiovascular disease, addition of **sitagliptin** to standard therapy did not increase the risk of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) or hospitalization for heart failure, compared to placebo.[29] A meta-analysis of these three trials concluded that use of DPP-4 inhibitors did not significantly increase the

risk of hospitalization for heart failure.[30] A pooled analysis of 19 trials including 9459 patients found that **linagliptin** did not increase the composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina, compared to placebo or active comparators.[31]

In a case-control analysis of 29,741 patients with diabetes who were hospitalized for heart failure, there was no increase in hospitalization rates with use of either DPP-4 inhibitors or GLP-1 receptor agonists, compared to use of other oral antidiabetic medications, among those with or without a history of heart failure.[32]

Pancreatitis – Incretin-based drugs (GLP-1 receptor agonists and DPP-4 inhibitors) have been associated with acute pancreatitis.[21] After adjustment for confounding variables, a population-based case-control study of 12,868 patients with acute pancreatitis and 128,680 matched controls concluded that use of incretin-based drugs did not appear to be associated with an increased risk of acute pancreatitis.[33] 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.[34]

SGLT2 INHIBITORS — SGLT2 (sodium-glucose co-transporter 2), a membrane protein expressed in the kidney, transports filtered glucose from the proximal renal tubule into tubular epithelial cells. The SGLT2 inhibitors **canagliflozin** *(Invokana),*[35] **dapagliflozin** *(Farxiga),*[36] and **empagliflozin** *(Jardiance)*[37] decrease renal glucose reabsorption and increase urinary glucose excretion, reducing fasting and prandial blood glucose levels, and achieving a 0.5-1% reduction in A1C when used as monotherapy or in addition to other drugs. Other beneficial effects include a 3-6 mm Hg reduction in systolic blood pressure and weight loss of about 0.1-4 kg.

In a randomized double-blind trial in 7020 patients with type 2 diabetes and established cardiovascular disease, addition of empagliflozin to standard care reduced the incidence of pooled cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), as well as hospitalizations for heart failure, cardiovascular death, and death from any cause, compared to addition of placebo.[38] Based on the results of this study, the FDA has approved use of empagliflozin to reduce the risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease. Empagliflozin has also reduced the risk of nephropathy compared to placebo.[39,40]

Since SGLT2 inhibitors increase sodium excretion, they can cause hypovolemia and dehydration; acute renal injury can occur.

MEGLITINIDES — Repaglinide (*Prandin*, and generics) and **nateglinide** (*Starlix*, and generics), 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.[41] 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 cause hypoglycemia and they have not been shown to reduce microvascular or macrovascular complications.

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 these agents outweigh their risks (weight gain, heart failure, anemia, increased fracture risk) remains unclear. They are FDA-approved for use as monotherapy or in combination with metformin, a sulfonylurea, or (only pioglitazone) insulin.

Cardiovascular Risk – Both pioglitazone and rosiglitazone have been associated with an increased risk of heart failure.[42] A meta-analysis found an increased risk of myocardial infarction with rosiglitazone,[43] but in an independent re-evaluation of data from 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.[44] Restrictions placed on rosiglitazone in 2010 because of concerns about its cardiovascular safety have been lifted.[45]

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.

PRAMLINTIDE — The amylinomimetic agent pramlintide *(Symlin)* acts by slowing gastric emptying, increasing satiety, and suppressing postprandial plasma glucagon and hepatic glucose production. It is injected subcutaneously before meals and is approved for use in patients with type 2 diabetes on prandial insulin.[46] It reduces A1C by 0.5%. The dose of short-acting insulins, including premixed insulins, should be reduced by 50% when pramlintide is started, and frequent (including postprandial) glucose monitoring is recommended. To avoid hypoglycemia, pramlintide should not be given before meals that contain <30 g of carbohydrate.

COLESEVELAM — A bile-acid sequestrant used to lower LDL cholesterol, colesevelam *(Welchol)* is also FDA-approved as an adjunct to diet and exercise for treatment of type 2 diabetes.[47] Its mechanism of action remains unclear. It reduces A1C by 0.5%. Colesevelam is not recommended for use as monotherapy.

BROMOCRIPTINE — An immediate-release formulation of the ergot-derived dopamine agonist bromocriptine mesylate *(Cycloset)* is minimally effective in decreasing A1C (0.5%) in patients with type 2 diabetes,[48] but it may reduce the risk of cardiovascular events. In a randomized, placebo-controlled 52-week trial in 3070 patients with type 2 diabetes, addition of *Cycloset* reduced the risk of the composite end point of myocardial infarction, stroke, and hospitalization for unstable angina, heart failure, or revascularization surgery.[49]

REGULAR AND RAPID-ACTING INSULINS — Rapid-acting insulin analogs have a faster onset and shorter duration of action than regular insulin and are generally administered with or just before a meal. In general, **insulin aspart** *(Novolog)*, **insulin glulisine** *(Apidra)*, and **insulin lispro** *(Humalog)* are slightly more effective than regular insulin in decreasing A1C, with less hypoglycemia.[50]

Inhaled Insulin – *Afrezza* is an inhaled, rapid-acting, dry powder formulation of recombinant human insulin FDA-approved for use as a prandial insulin in adults with type 2 diabetes. Compared to insulin lispro, *Afrezza* has an earlier maximum effect (50 vs 120 minutes) and shorter duration of action (~3 vs ~4 hours). In one 24-week study, addition of *Afrezza* to metformin (alone or with other oral agents) was more effective in lowering A1C than addition of placebo (additional 0.4% reduction).[51] Cough has been the most common reason for discontinuation of the drug, and hypoglycemia can occur.

LONGER-ACTING INSULINS — NPH, an intermediate-acting insulin, can be used in combination with regular and rapid-acting insulins. It has a 16- to >24-hour duration of action with a peak effect at 4 to 8 hours. Alternatively, patients can use premixed combinations, which simplify administration of insulin, but dose titration is more difficult and hypoglycemia may be more frequent than with individual insulins.

Insulin glargine *(Lantus, Basaglar, Toujeo)*, a recombinant DNA analog of human insulin, forms microprecipitates in subcutaneous tissue, prolonging its duration of action. Insulin glargine has less peak-to-trough variation and causes less nocturnal hypoglycemia than NPH insulin. *Basaglar* is a "follow-on" insulin glargine product similar to *Lantus*; both contain 100 units/mL.[52] *Toujeo* is a concentrated formulation of insulin glargine (300 units/mL) that is absorbed more slowly from the subcutaneous depot, resulting in more even activity throughout the dosing period and a longer duration of action. A randomized trial of insulin glargine 300 units/mL versus glargine 100 units/mL in patients with type 2 diabetes using basal and prandial insulin found comparable reductions in A1C; rates of nocturnal hypoglycemia were lower with glargine 300 units/mL.[53] Initial recommendations for switching from glargine 100 units/mL to glargine 300 units/mL are for a 1:1 transition by units, but patients may ultimately require about 10-15% more basal insulin per day.[54]

Insulin detemir *(Levemir)* has both delayed absorption from subcutaneous tissue and, due to reversible binding to albumin, delayed clearance from the circulation. Like insulin glargine, insulin detemir causes less nocturnal hypoglycemia than NPH. Since its effectiveness appears to decrease after 12 hours, insulin detemir is more effective when used twice daily.[55]

Insulin degludec *(Tresiba)*, a recombinant insulin analog that forms multihexamers in subcutaneous tissue, has delayed absorption and elimination that prolongs its duration of action to >42 hours. Compared to other long-acting insulins, it causes similar reductions in A1C with similar rates of hypoglycemia and, in some studies, causes less nocturnal hypoglycemia, especially when compared to insulin glargine.[56-58] In a randomized trial in 7637 patients, insulin degludec was noninferior to insulin glargine for the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes at high risk of cardiovascular events, and was associated with a significantly lower risk of hypoglycemia.[59]

Adverse Effects – All insulins, including long-acting and inhaled formulations, can cause hypoglycemia and weight gain. Inhaled insulin can cause bronchospasm, cough, and reductions in forced expiratory volume in one second (FEV1); it is not recommended for patients with chronic lung disease or active smokers. Until more long-term safety data become available, injectable prandial insulin is preferred over inhaled insulin. Some observational studies have found an increased risk of cancer, in particular breast cancer, in patients using insulin glargine, but a randomized controlled trial in >12,000 patients found no increase in cancer compared to standard-of-care diabetes therapy.[60]

LONG-ACTING INSULIN/GLP-1 RECEPTOR AGONIST COMBINATIONS — *Xultophy*, a combination of insulin degludec and liraglutide, and *Soliqua*, a combination of insulin glargine and lixisenatide, have been approved for patients with type 2 diabetes who are inadequately controlled on basal insulin, or on liraglutide or lixisenatide, respectively. *Xultophy* reduced A1C more than its individual components when added to either metformin, pioglitazone, or a sulfonylurea.[61,62] When added to metformin, *Soliqua* reduced A1C significantly more than insulin glargine alone (1.1% vs 0.6%).[63]

ADDITION OF INSULIN — When insulin is added to oral agents, it is usually given either as a single dose in the evening or at bedtime. In general, 10 units (or 0.2-0.5 units/kg) of NPH, insulin detemir, or insulin glargine at bedtime can be added initially. The dose can then be increased to achieve fasting plasma glucose concentrations between 70-130 mg/dL. Given the increased risk of hypoglycemia and reduced dosing flexibility, premixed insulin combinations are not recommended for insulin-naive patients.

A premixed insulin (30% rapid-acting insulin aspart/70% intermediate-acting protaminated insulin aspart) given twice daily, prandial insulin aspart given before meals three times daily, and basal insulin detemir given at bedtime or twice daily have been compared for initial insulin therapy in patients with type 2 diabetes and suboptimal glycemic control (mean A1C 8.5%) while taking metformin and a sulfonylurea. All regimens achieved similar A1C levels (6.8-7.1%), with the most weight gain and hypoglycemia occurring in the prandial group and the least in the basal group.[64]

PREGNANCY — Insulin is the drug of choice for treatment of pregestational type 2 diabetes that is not adequately controlled with diet, exercise, and metformin.[65]

1. American Diabetes Association. Professional practice committee for the standards of medical care in diabetes – 2016. Diabetes Care 2016; 39(Suppl 1).
2. SE Inzucchi et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38:140.
3. AJ Garber et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2016 executive summary. Endocr Pract 2016; 22:84.
4. Look AHEAD Research Group et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369:145.
5. A Qaseem et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017 January 3 (epub).
6. E Ferrannini. The target of metformin in type 2 diabetes. N Engl J Med 2014; 371:1547.
7. JB Buse et al. The primary glucose-lowering effect of metformin resides in the gut, not the circulation: results from short-term pharmacokinetic and 12-week dose-ranging studies. Diabetes Care 2016; 39:198.
8. SC Palmer et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes. a meta-analysis. JAMA 2016; 316:313.
9. RR Holman et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577.
10. SE Inzucchi et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA 2014; 312:2668.
11. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Available at: www.fda.gov/drugs/drugsafety/ucm493244.htm. Accessed January 5, 2017.
12 Y Li et al. Sulfonylurea use and incident cardiovascular disease among patients with type 2 diabetes: prospective cohort study among women. Diabetes Care 2014; 37:3106.
13. D Varvaki Rados et al. The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials. PLoS Med 2016; 13:e1001992.
14. Exenatide (Byetta) for type 2 diabetes. Med Lett Drugs Ther 2005; 47:45.
15. Extended-release exenatide (Bydureon) for type 2 diabetes. Med Lett Drugs Ther 2012; 54:21.
16. SP Marso et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375:311.
17. Two new GLP-1 receptor agonists for diabetes. Med Lett Drugs Ther 2014; 56:109.
18. F Zaccardi et al. Benefits and harms of once-weekly glucagon-like peptide-1 receptor agonist treatments: a systematic review and network meta-analysis. Ann Intern Med 2016; 164:102.
19. Lixisenatide (Adlyxin) and insulin glargine/lixisenatide (Soliqua) for type 2 diabetes. Med Lett Drugs Ther (in press).
20. MA Pfeffer et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015; 373:2247.
21. PC Butler et al. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? Diabetes Care 2013; 36:2118.
22. Alogliptin (Nesina) for type 2 diabetes. Med Lett Drugs Ther 2013; 55:41.
23. Linagliptin (Tradjenta) – a new DPP-4 inhibitor for type 2 diabetes. Med Lett Drugs Ther 2011; 53:49.

24. Saxagliptin (Onglyza) for type 2 diabetes. Med Lett Drugs Ther 2009; 51:85.
25. Sitagliptin (Januvia) for type 2 diabetes. Med Lett Drugs Ther 2007; 49:1.
26. BM Scirica et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369:1317.
27. WB White et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013; 369:1327.
28. VP Sanon et al. Play of chance versus concerns regarding dipeptidyl peptidase-4 inhibitors: heart failure and diabetes. Clin Diabetes 2014; 32:121.
29. JB Green et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015; 373:232.
30. KB Filion and S Suissa. DPP-4 inhibitors and heart failure: some reassurance, some uncertainty. Diabetes Care 2016; 39:735.
31. J Rosenstock et al. Cardiovascular safety of linagliptin in type 2 diabetes: a comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events. Cardiovasc Diabetol 2015; 14:57.
32. KB Filion et al. A multicenter observational study of incretin-based drugs and heart failure. N Engl J Med 2016: 374:1145.
33. RW Thomsen et al. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. Diabetes Care 2015; 38:1089.
34. AG Egan et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. N Engl J Med 2014; 370:794.
35. Canagliflozin (Invokana) for type 2 diabetes. Med Lett Drugs Ther 2013; 55:37.
36. Dapagliflozin (Farxiga) for type 2 diabetes. Med Lett Drugs Ther 2014; 56:13.
37. Empagliflozin (Jardiance) for diabetes. Med Lett Drugs Ther 2014; 56:99.
38. B Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117.
39. C Wanner et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016; 375:323.
40. SGLT2 inhibitors and renal function. Med Lett Drugs Ther 2016; 58:91.
41. DM Nathan. Diabetes: advances in diagnosis and treatment. JAMA 2015; 314:1052.
42. AV Hernandez et al. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011; 11:115.
43. SE Nissen and K Wolski. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356:2457.
44. KW Mahaffey et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J 2013; 166:240.
45. In brief: Rosiglitazone (Avandia) unbound. Med Lett Drugs Ther 2014; 56:12.
46. Pramlintide (Symlin) for diabetes. Med Lett Drugs Ther 2005; 47:43.
47. In brief: a new indication for colesevelam (Welchol). Med Lett Drugs Ther 2008; 50:33.
48. Bromocriptine (Cycloset) for type 2 diabetes. Med Lett Drugs Ther 2010; 52:97.
49. JM Gaziano et al. Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in type 2 diabetes subjects. J Am Heart Assoc 2012; 1:e002279.
50. Rapid-acting insulin analogues. Med Lett Drugs Ther 2009; 51:98.
51. An inhaled insulin (Afrezza). Med Lett Drugs Ther 2015; 57:34.
52. Another insulin glargine (Basaglar) for diabetes. Med Lett Drugs Ther 2017; 59:3.
53. MC Riddle et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab 2015; 17:835.
54. Concentrate insulin glargine (Toujeo) for diabetes. Med Lett Drugs Ther 2015; 57:69.
55. Insulin detemir (Levemir), a new long-acting insulin. Med Lett Drugs Ther 2006; 48:54.
56. P Hollander et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. Diabetes Obes Metab 2015; 17:202.
57. B Zinman et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012; 35:2464.
58. Insulin degludec (Tresiba) – a new long-acting insulin for diabetes. Med Lett Drugs Ther 2015; 57:163.
59. SP Marso et al. Design of DEVOTE (trial comparing cardiovascular safety of insulin degludec vs insulin glargine in patients with type 2 diabetes at high risk of cardiovascular events) - DEVOTE 1. Am Heart J 2016; 179:175.
60. ORIGIN Trial Investigators et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012; 367:319.
61. HW Rodbard et al. Safety and efficacy of insulin degludec/liraglutide (IDegLira) added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naive people with type 2 diabetes: the DUAL IV trial. Diabet Med 2016 Sep 2 (epub).
62. VR Aroda et al. Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 Study). Diabetes Obes Metab 2016; 18:663.
63. VR Aroda et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. Diabetes Care 2016; 39:1972.
64. RR Holman et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009; 361:1736.
65. American Diabetes Association. Professional practice committee for the standards of medical care in diabetes - 2016. Management of diabetes in pregnancy. Diabetes Care 2016; 39(Suppl 1): S94.

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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 program, the participant will be able to:

1. 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.
2. Determine the most appropriate therapy given the clinical presentation of an individual patient with type 2 diabetes.

Privacy and Confidentiality: The Medical Letter guarantees our firm commitment to your privacy. We do not sell any of your information. Secure server software (SSL) is used for commerce transactions through VeriSign, Inc. No credit card information is stored.

IT Requirements: Windows 7/8/10, Mac OS X+; current versions of Microsoft IE/Edge, Mozilla Firefox, Google Chrome, Safari, or any other compatible Web browser. High-speed connection.

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

Questions start on next page

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Issue 1512 Questions

(Correspond to questions #11-20 in Comprehensive Exam #76, available July 2017)

Drugs for Type 2 Diabetes

1. The target of drug therapy for type 2 diabetes is generally an A1C of less than:
   a. 6.8%
   b. 7.0%
   c. 7.2%
   d. 7.4%

2. Metformin:
   a. reduces A1C by 1-1.5%
   b. may decrease both micro- and macrovascular complications of diabetes
   c. does not cause weight gain
   d. all of the above

3. Sulfonylureas:
   a. reduce A1C by 1-1.5%
   b. increase the risk of stroke
   c. do not cause weight gain or hypoglycemia
   d. all of the above

4. GLP-1 receptor agonists:
   a. reduce A1C by 0.5%
   b. cause more weight gain than insulin
   c. have been shown to increase the risk of myocardial infarction
   d. must be injected

5. DPP-4 inhibitors:
   a. are taken orally
   b. do not cause weight gain
   c. produce small reductions in A1C
   d. all of the above

6. Which of the following can cause hypovolemia, dehydration, and acute renal injury?
   a. sulfonylureas
   b. DPP-4 inhibitors
   c. SGLT2 inhibitors
   d. GLP-1 receptor agonists

7. A 68-year-old woman with a BMI of 36, systolic hypertension, and type 2 diabetes has not achieved an A1C <8% on maximum doses of metformin and exenatide. You are considering whether to start her on insulin or a SGLT2 inhibitor. Factors that you might consider could include which of the following?
   a. SGLT2 inhibitors cause weight loss
   b. SGLT2 inhibitors reduce systolic blood pressure
   c. empagliflozin has been found to reduce the risk of cardiovascular events
   d. all of the above

8. Compared to NPH insulin, the main advantage of the recombinant insulin analogs glargine, detemir, and degludec is that they:
   a. do not cause weight gain
   b. cause less nocturnal hypoglycemia
   c. have a more rapid peak effect
   d. all of the above

9. A 58-year-old man with type 2 diabetes had a myocardial infarction 12 years ago and is concerned about the effect of diabetes treatment on his heart disease. You could tell him that a number of the drugs used to treat diabetes have been associated with a lower risk of cardiovascular events. These include:
   a. metformin
   b. empagliflozin
   c. liraglutide
   d. all of the above

10. The inhaled formulation of insulin *(Afrezza)*:
    a. has an earlier maximum effect than injected insulin lispro
    b. has a longer duration of action than injected insulin lispro
    c. does not cause hypoglycemia
    d. all of the above

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