8. Pharmacologic Approaches to Glycemic Treatment

American Diabetes Association

Diabetes Care 2017;40(Suppl. 1):S64–S74 | DOI: 10.2337/dc17-S011

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

- Most people with type 1 diabetes should be treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion. **A**
- Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**
- Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. **E**
- Individuals with type 1 diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access to this therapy after they turn 65 years of age. **E**

Insulin Therapy

Insulin is the mainstay of therapy for individuals with type 1 diabetes. Generally, the starting insulin dose is based on weight, with doses ranging from 0.4 to 1.0 units/kg/day of total insulin with higher amounts required during puberty. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in patients who are metabolically stable, with higher weight-based dosing required immediately following presentation with ketoacidosis (1), and provides detailed information on intensification of therapy to meet individualized needs. The American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" additionally provides a thorough overview of type 1 diabetes treatment and associated recommendations (2).

Education regarding matching prandial insulin dosing to carbohydrate intake, premeal glucose levels, and anticipated activity should be considered, and selected individuals who have mastered carbohydrate counting should be educated on fat and protein gram estimation (3–5). Although most studies of multiple daily injections (MDI) versus continuous subcutaneous insulin infusion (CSII) have been small and of short duration, a systematic review and meta-analysis concluded that there are minimal differences between the two forms of intensive insulin therapy in A1C (combined mean between-group difference favoring insulin pump therapy −0.30% [95% CI −0.58 to −0.02]) and severe hypoglycemia rates in children and adults (6). A 3-month randomized trial in patients with type 1 diabetes with nocturnal hypoglycemia reported that sensor-augmented insulin pump therapy with the threshold suspend feature reduced nocturnal hypoglycemia without increasing glycated hemoglobin levels (7). Intensive management using CSII and continuous glucose monitoring (CGM) should be encouraged in selected patients when there is active patient/family participation (8–10).

The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive therapy with MDI or CSII delivered by multidisciplinary teams of physicians, nurses, dietitians, and behavioral scientists improved glycemia and resulted in better long-term outcomes (11–13). The study was carried out with short-acting and intermediate-acting human insulins. Despite better microvascular, macrovascular, and all-cause mortality outcomes, intensive therapy was associated with a high rate of severe hypoglycemia (61 episodes per 100 patient-years of therapy). Since the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs are associated with less hypoglycemia in type 1 diabetes, while matching the A1C lowering of human insulins (14,15).

Suggested citation: American Diabetes Association. Pharmacologic approaches to glycemic treatment. Sec. 8. In Standards of Medical Care in Diabetes—2017. *Diabetes Care 2017; 40(Suppl. 1):S64–S74*

Rapid-acting inhaled insulin used before meals in type 1 diabetes was shown to be noninferior when compared with aspart insulin for A1C lowering, with less hypoglycemia observed with inhaled insulin therapy (16). However, the mean reduction in A1C was greater with aspart (−0.21% vs. −0.40%, satisfying the noninferiority margin of 0.4%), and more patients in the insulin aspart group achieved A1C goals of ≤7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol). Because inhaled insulin cartridges are only available in 4, 8, and 12 unit doses, people with type 1 diabetes may have limited dosing increments to fine-tune prandial insulin doses when using this therapy.

Postprandial glucose excursions may be better controlled by adjusting the timing of prandial (bolus) insulin dose administration. The optimal time to administer prandial insulin varies, based on the type of insulin used (regular, rapid-acting analog, inhaled, etc.), the measured blood glucose level, timing of meals, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized.

Pramlintide

Pramlintide, an amylin analog, is an agent that delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. It is U.S. Food and Drug Administration (FDA)–approved for use in adults with type 1 diabetes. It has been shown to induce weight loss and lower insulin doses. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia.

Pancreas and Islet Transplantation

Pancreas and islet transplantation have been shown to normalize glucose levels but require lifelong immunosuppression to prevent graft rejection and recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (17). Islet transplantation remains investigational. Autoislet transplantation may be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis.

Investigational Agents

Metformin

Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/obese patients with poorly controlled type 1 diabetes. In a meta-analysis, metformin in type 1 diabetes was found to reduce insulin requirements (6.6 units/day, $P < 0.001$) and led to small reductions in weight and total and LDL cholesterol but not to improved glycemic control (absolute A1C reduction 0.11%, $P = 0.42$) (18). Metformin is not FDA-approved for use in patients with type 1 diabetes.

Incretin-Based Therapies

Due to their potential protection of β-cell mass and suppression of glucagon release, glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors are being studied in patients with type 1 diabetes but are not currently FDA-approved for use in patients with type 1 diabetes.

Sodium–Glucose Cotransporter 2 Inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in type 2 diabetes. There are three FDA-approved agents for patients with type 2 diabetes, but none are FDA-approved for the treatment of patients with type 1 diabetes (2). The FDA issued a warning about the risk of ketoacidosis occurring in the absence of significant hyperglycemia (euglycemic diabetic ketoacidosis) in patients with type 1 and type 2 diabetes treated with SGLT2 inhibitors. Symptoms of ketoacidosis include dyspnea, nausea, vomiting, and abdominal pain. Patients should be instructed to stop taking SGLT2 inhibitors and seek medical attention immediately if they have symptoms or signs of ketoacidosis (19).

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **A**
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. **B**
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C ≥10% (86 mmol/mol) and/or blood glucose levels ≥300 mg/dL (16.7 mmol/L). **E**
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin. **A**
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences. **E**
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. **B**
- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. **B**

The use of metformin as first-line therapy was supported by findings from a large meta-analysis, with selection of second-line therapies based on patient-specific considerations (20). An ADA/European Association for the Study of Diabetes position statement (21) recommended a patient-centered approach, including assessment of efficacy, hypoglycemia risk, impact on weight, side effects, costs, and patient preferences. Renal effects may also be considered when selecting glucose-lowering medications for individual patients. Lifestyle modifications that improve health

(see Section 4 "Lifestyle Management") should be emphasized along with any pharmacologic therapy.

Initial Therapy

Metformin monotherapy should be started at diagnosis of type 2 diabetes unless there are contraindications. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (22). Metformin may be safely used in patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m^2 (23), and the U.S. label for metformin was recently revised to reflect its safety in patients with eGFR ≥30 mL/min/1.73 m^2 (24). Patients should be advised to stop the medication in cases of nausea, vomiting, or dehydration. Metformin is associated with vitamin B12 deficiency, with a recent report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting that periodic testing of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy (25).

In patients with metformin contraindications or intolerance, consider an initial drug from another class depicted in **Fig. 8.1** under "Dual Therapy" and proceed accordingly. When A1C is ≥9% (75 mmol/mol), consider initiating dual combination therapy (**Fig. 8.1**) to more expeditiously achieve the target A1C level. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms are present or any catabolic features (weight loss, ketosis) are present. Consider initiating combination insulin injectable therapy (**Fig. 8.2**) when blood glucose is ≥300 mg/dL (16.7 mmol/L) or A1C is ≥10% (86 mmol/mol) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia). As the patient's glucose toxicity resolves, the regimen may, potentially, be simplified.

Combination Therapy

Although there are numerous trials comparing dual therapy with metformin alone,

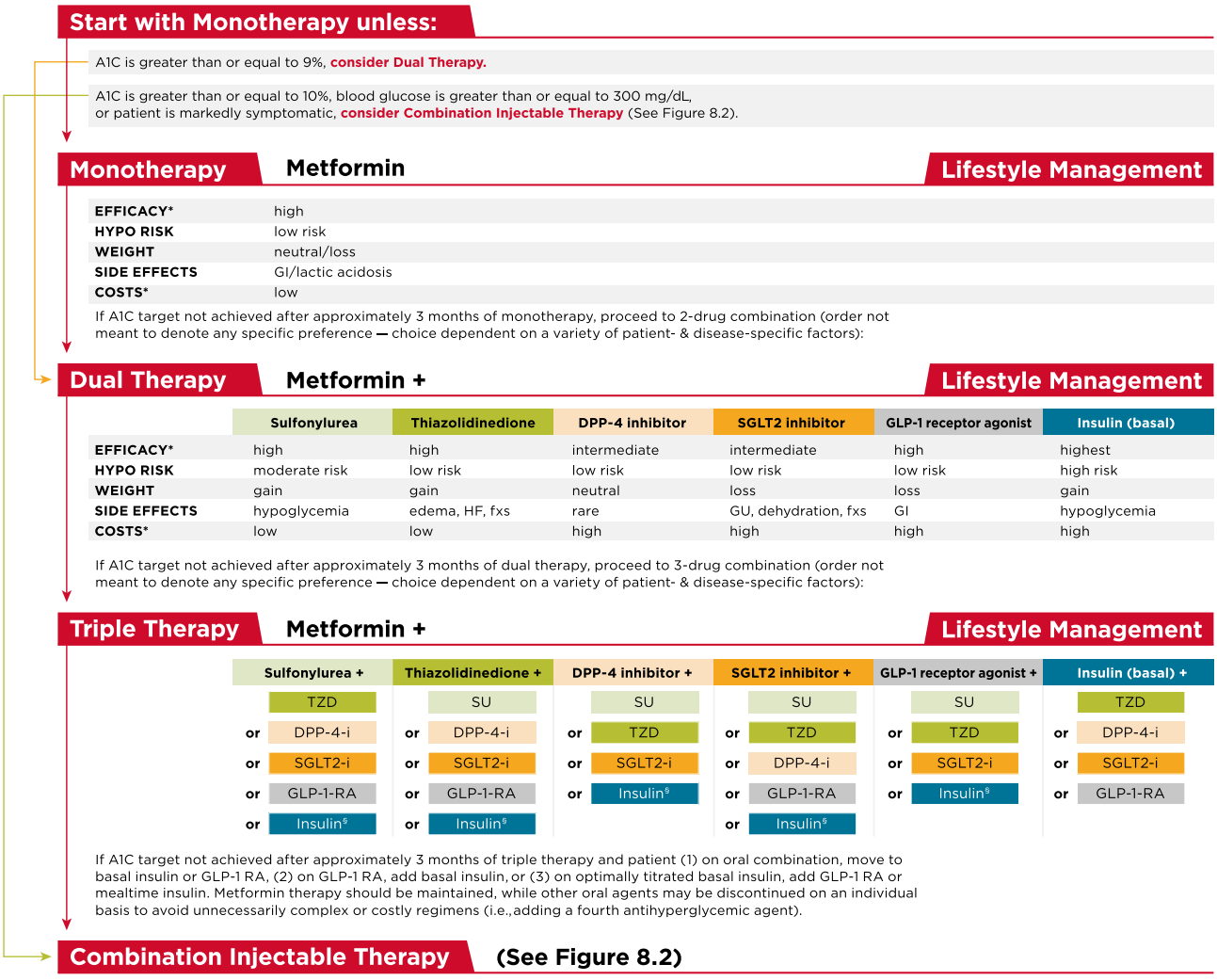

Figure 8.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations. The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. *See ref. 21 for description of efficacy and cost categorization. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (21).

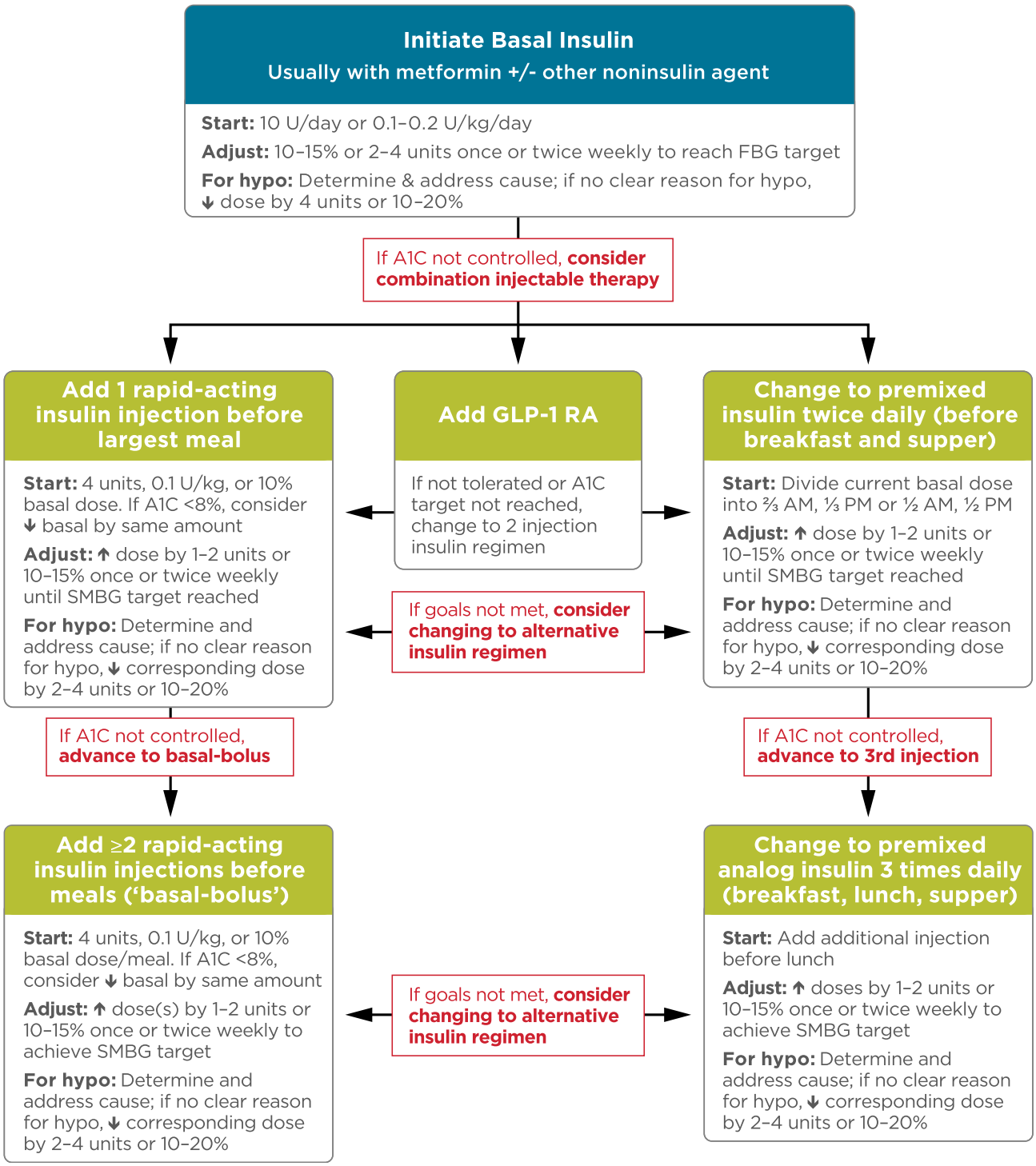

Figure 8.2—Combination injectable therapy for type 2 diabetes. FBG, fasting blood glucose; GLP-1 RA, GLP-1 receptor agonist; hypo, hypoglycemia. Adapted with permission from Inzucchi et al. (21).

few directly compare drugs as add-on therapy. A comparative effectiveness meta-analysis (23) suggests that each new class of noninsulin agents added to initial therapy generally lowers A1C approximately 0.9–1.1%. If the A1C target is not achieved after approximately 3 months, consider a combination of metformin and one of the six available treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin (**Fig. 8.1**). If A1C target is still not achieved after ~3 months of dual therapy, proceed to three-drug combination (**Fig. 8.1**). Again, if A1C target is not achieved after ~3 months of triple therapy, proceed to combination injectable therapy (**Fig. 8.2**).

Drug choice is based on patient preferences (26), as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially

Table 8.1—Properties of available glucose-lowering agents in the U.S. that may guide individualized treatment choices in patients with type 2 diabetes (21)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • Rare hypoglycemia • ↓ CVD events (UKPDS) • Relatively higher A1C efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Contraindications: eGFR <30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd generation • Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Relatively higher A1C efficacy	• Hypoglycemia • ↑ Weight	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• Rare hypoglycemia • Relatively higher A1C efficacy • Durability • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone) • ↓ Risk of stroke and MI in patients without diabetes and with *insulin resistance* and history of recent stroke or TIA (IRIS study [42], pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• Rare hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events in prediabetes (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• Rare hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ↑ Heart failure hospitalizations (saxagliptin; ? alogliptin)	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• Rare hypoglycemia • ↓ LDL-C	• Modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High

Continued on p. S69

Table 8.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• Rare hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• Rare hypoglycemia • ↓ Weight • ↓ Blood pressure • Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• Rare hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors • Associated with lower CVD event rate and mortality in patients with CVD (liraglutide LEADER) (30)	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • Training requirements • Patient and provider reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	High#

Continued on p. S70

Table 8.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
	• Basal insulin analogs - Glargine - Detemir - Degludec • Premixed insulin products - NPH/Regular 70/30 —70/30 aspart mix —75/25 lispro mix —50/50 lispro mix					

CVD, cardiovascular disease; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (29); GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; IRIS, Insulin Resistance Intervention After Stroke Trial; LDL-C, LDL cholesterol; PPAR-γ, peroxisome proliferator–activated receptor γ; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events (43); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (44); TIA, transient ischemic attack; TZD, thiazolidinedione; UKPDS, UK Prospective Diabetes Study (45,46). Cycloset trial of quick-release bromocriptine (47). *Cost is based on lowest-priced member of the class (21). ‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study. §Not licensed in Europe for type 2 diabetes. #Cost is highly dependent on type/brand (analogs > human insulins) and dosage. Adapted with permission from Inzucchi et al. (21).

hypoglycemia. **Table 8.1** lists drugs commonly used in the U.S. Cost-effectiveness models have suggested that some of the newer agents may be of relatively lower clinical utility based on high cost and moderate glycemic effect (27). **Table 8.2** provides cost information for currently approved noninsulin therapies. *Of note, prices listed are average wholesale prices (AWP) and do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the patient. While there are alternative means to estimate medication prices, AWP was utilized to provide a comparison of list prices with the primary goal of highlighting the importance of cost considerations when prescribing antihyperglycemic treatments*. The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) will compare four drug classes (sulfonylurea, DPP-4 inhibitor, GLP-1 receptor agonist, and basal insulin) when added to metformin therapy over 4 years on glycemic control and other medical, psychosocial, and health economic outcomes (28).

Rapid-acting secretagogues (meglitinides) may be used instead of sulfonylureas in patients with sulfa allergies, irregular meal schedules, or those who develop late postprandial hypoglycemia when taking a sulfonylurea. Other drugs not shown in **Fig. 8.1** (e.g., inhaled insulin, α-glucosidase inhibitors, colesevelam, bromocriptine, and pramlintide) may be tried in specific situations but are not often used due to modest efficacy in type 2 diabetes, the frequency of administration, the potential for drug interactions, and/or side effects.

Cardiovascular Outcome Trials

Several recently published cardiovascular outcome trials (CVOTs) have provided data on patients with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease. The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, a SGLT2 inhibitor, versus placebo and standard care, on cardiovascular outcomes in patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99%

Table 8.2—Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S. (48)

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($5, $94)	2,000 mg
		850 mg (IR)	$108 ($5, $108)	2,550 mg
		1,000 mg (IR)	$86 ($4, $87)	2,000 mg
		500 mg (ER)	$90 ($82, $6,672)	2,000 mg
		750 mg (ER)	$72 ($65, $92)	1,500 mg
		1,000 mg (ER)	$1,028 ($1,010, $7,213)	2,000 mg
Sulfonylureas (2nd Gen)	• Glyburide	5 mg	$94 ($64, $103)	20 mg
		6 mg (micronized)	$50 ($48, $71)	12 mg (micronized)
	• Glipizide	10 mg (IR)	$74 ($67, $97)	40 mg (IR)
		10 mg (XL)	$97	20 mg (XL)
	• Glimepiride	4 mg	$74 ($71, $198)	8 mg
Meglitinides (glinides)	• Repaglinide	2 mg	$799 ($163, $878)	16 mg
	• Nateglinide	120 mg	$156	360 mg
TZDs	• Pioglitazone	45 mg	$349 ($348, $349)	45 mg
	• Rosiglitazone	4 mg	$355	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$104 ($104, 105)	300 mg
	• Miglitol	100 mg	$241	300 mg
DPP-4 inhibitors	• Sitagliptin	100 mg	$436	100 mg
	• Saxagliptin	5 mg	$436	5 mg
	• Linagliptin	5 mg	$428	5 mg
	• Alogliptin	25 mg	$436	25 mg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$679	3.75 g
		1.875 g suspension	$1,357	3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	$719	4.8 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$470	300 mg
	• Dapagliflozin	10 mg	$470	10 mg
	• Empagliflozin	25 mg	$470	25 mg
GLP-1 receptor agonists	• Exenatide	10 μg pen	$729	20 μg
	• Exenatide (extended-release)	2 mg powder for suspension or pen	$692	2 mg**
	• Liraglutide	18 mg/3 mL pen	$831	1.8 mg
	• Albiglutide	50 mg pen	$527	50 mg**
	• Dulaglutide	1.5/0.5 mL pen	$690	1.5 mg**
Amylin mimetics	• Pramlintide	120 μg pen	$2,124	120 μg/injection††

ER and XL, extended release; IR, immediate release; TZD, thiazolidinedione. †Calculated for 30 day supply (AWP unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP listed alone when only one product and/or price. *Utilized to calculate median AWP (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP calculated based on 120 μg three times daily.

had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%) (29). The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors will have the same effect in high-risk patients and whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results: A Long Term Evaluation (LEADER) trial was a randomized double-blind trial that assessed the effect of liraglutide, a GLP-1 receptor agonist, versus placebo and standard care, on cardiovascular outcomes in patients with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease. Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease inclusive of a prior myocardial infarction (MI), prior stroke or transient ischemic attack, prior revascularization procedure, or ≥50% stenosis of coronary, carotid, or lower-extremity arteries. LEADER showed that the composite primary outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) after a median follow-up of 3.8 years (30). Whether other GLP-1 receptor agonists will have the same effect in high-risk patients or if this drug class will have similar effects in lower-risk patients with diabetes remains unknown.

CVOT data for the DPP-4 inhibitors sitagliptin (31), saxagliptin (32), and alogliptin (33) have also been reported, with no significant difference in rates of major cardiovascular events noted between treatment and placebo groups in any of these trials.

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients. *Providers*

should avoid using insulin as a threat or describing it as a sign of personal failure or punishment.

Equipping patients with an algorithm for self-titration of insulin doses based on self-monitoring of blood glucose (SMBG) improves glycemic control in patients with type 2 diabetes initiating insulin (34). Comprehensive education regarding SMBG, diet, and the avoidance of and appropriate treatment of hypoglycemia are critically important in any patient using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 units per day or 0.1–0.2 units/kg/day, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and sometimes one additional noninsulin agent. While there is evidence for reduced risk of hypoglycemia with newer, longer-acting basal insulin analogs, people with type 2 diabetes without a history of hypoglycemia may use NPH insulin safely and at much lower cost (27,35). **Table 8.3** provides average wholesale price information (cost per 1,000 units) for currently available insulin products in the U.S. There have been substantial increases in the price of insulin over the past decade and the cost-effectiveness of different antihyperglycemic agents is an important consideration when selecting therapies (36). A follow-on U-100 (100 units/mL) glargine product (basaglar) is now available in the U.S. This product was approved through an abbreviated FDA approval pathway based, in part, on the FDA's finding of safety and effectiveness for the reference U-100 glargine product.

Bolus Insulin

Many individuals with type 2 diabetes may require mealtime bolus insulin dosing in addition to basal insulin. Rapid-acting analogs are preferred due to their prompt onset of action after dosing. The recommended starting dose of mealtime insulin is 4 units, 0.1 U/kg, or 10% of the basal dose. If A1C is <8% (64 mmol/mol) when starting mealtime bolus insulin, consideration should be given to decreasing the basal insulin dose.

Premixed Insulin

Premixed insulin products contain both a basal and prandial component, allowing coverage of both basal and prandial needs with a single injection. NPH/Regular 70/30 insulin, for example, is composed of 70% NPH insulin and 30% regular insulin. The use of premixed insulin products has its advantages and disadvantages, as discussed below in COMBINATION INJECTABLE THERAPY.

Concentrated Insulin Products

Several concentrated insulin preparations are currently available. U-500 regular insulin, by definition, is five times as concentrated as U-100 regular insulin and has a delayed onset and longer duration of

Table 8.3—Median cost of insulins in the U.S. calculated as average wholesale price per 1,000 units of specified dosage form/product (48)

Insulins	Compounds	Dosage form/product	Median AWP package price (min, max)*
Rapid-acting analogs			
	• Lispro	U-100 vial	$306
		U-100 3 mL cartridges	$306 ($306, $379)
		U-100 prefilled pen; U-200 prefilled pen	$394
	• Aspart	U-100 vial	$306
		U-100 3 mL cartridges	$380
		U-100 prefilled pen	$395
	• Glulisine	U-100 vial	$283
		U-100 prefilled pen	$365
	• Inhaled insulin	Inhalation cartridges	$557 ($453, $754)
Short-acting			
	• Human Regular	U-100 vial	$165
Intermediate-acting			
	• Human NPH	U-100 vial	$165
		U-100 prefilled pen	$350
Concentrated Human Regular insulin			
	• U-500 Human Regular insulin	U-500 vial	$165
		U-500 prefilled pen	$213
Basal analogs			
	• Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	$298
	• Detemir	U-100 vial; U-100 prefilled pen	$323
	• Degludec	U-100 prefilled pen; U-200 prefilled pen	$355
Premixed products			
	• NPH/Regular 70/30	U-100 vial	$165
		U-100 prefilled pen	$350
	• Lispro 50/50	U-100 vial	$317
		U-100 prefilled pen	$394
	• Lispro 75/25	U-100 vial	$317
		U-100 prefilled pen	$394
	• Aspart 70/30	U-100 vial	$318
		U-100 prefilled pen	$395

AWP listed alone when only one product and/or price.

action than U-100 regular, posessing both prandial and basal properties. U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations, have longer durations of action, and allow higher doses of basal insulin administration per volume used. The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL). These concentrated preparations may be more comfortable for the patient and may improve adherence for patients with insulin resistance who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials (a dedicated syringe was FDA approved in July 2016), other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Inhaled Insulin

Inhaled insulin is available for prandial use with a more limited dosing range. It is contraindicated in patients with chronic lung disease such as asthma and chronic obstructive pulmonary disease and is not recommended in patients who smoke or who recently stopped smoking. It requires spirometry (FEV_1) testing to identify potential lung disease in all patients prior to and after starting therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day) and A1C remains above target, consider advancing to combination injectable therapy (**Fig. 8.2**). When initiating combination injectable therapy, metformin therapy should be maintained while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent). In general, GLP-1 receptor agonists should not be discontinued with the initiation of basal insulin. Sulfonylureas, DPP-4 inhibitors, and GLP-1 receptor agonists are typically stopped once more complex insulin regimens beyond basal are used. In patients with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once an insulin regimen is initiated, dose titration is important with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control).

Studies have demonstrated the noninferiority of basal insulin plus a single injection of rapid-acting insulin at the largest meal relative to basal insulin plus a GLP-1 receptor agonist relative to two daily injections of premixed insulins (**Fig. 8.2**). Basal insulin plus GLP-1 receptor agonists are associated with less hypoglycemia and with weight loss instead of weight gain but may be less tolerable and have a greater cost (37,38). In November 2016, the FDA approved two different once-daily combination products containing basal insulin plus a GLP-1 receptor agonist: insulin glargine plus lixisenatide and insulin degludec plus liraglutide. Other options for treatment intensification include adding a single injection of rapid-acting insulin analog (lispro, aspart, or glulisine) before the largest meal or stopping the basal insulin and initiating a premixed (or biphasic) insulin (NPH/Regular 70/30, 70/30 aspart mix, 75/25 or 50/50 lispro mix) twice daily, usually before breakfast and before dinner. Each approach has its advantages and disadvantages. For example, providers may wish to consider regimen flexibility when devising a plan for the initiation and adjustment of insulin therapy in people with type 2 diabetes, with rapid-acting insulin offering greater flexibility in terms of meal planning than premixed insulin. If one regimen is not effective (i.e., basal insulin + GLP-1 receptor agonist), consider switching to another regimen to achieve A1C targets (i.e., basal insulin + single injection of rapid-acting insulin or premixed insulin twice daily) (39,40). Regular human insulin and human NPH/Regular premixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogs and premixed insulin analogs, respectively, but their pharmacodynamic profiles may make them less optimal.

Figure 8.2 outlines these options, as well as recommendations for further intensification, if needed, to achieve glycemic goals. If a patient is still above the A1C target on premixed insulin twice daily, consider switching to premixed analog insulin three times daily (70/30 aspart mix, 75/25 or 50/50 lispro mix). In general, three times daily premixed analog insulins have been found to be noninferior to basal-bolus regimens with similar rates of hypoglycemia (41). If a patient is still above the A1C target on basal insulin + single injection of rapid-acting insulin before the largest meal, advance to a basal-bolus regimen with ≥2 injections of rapid-acting insulin before meals. Consider switching patients from one regimen to another (i.e., premixed analog insulin three times daily to basal-bolus regimen or vice-versa) if A1C targets are not being met and/or depending on other patient considerations (39,40).

References

1. American Diabetes Association, JDRF. *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook*. Peters AL, Laffel L, Eds. Alexandria, VA, American Diabetes Association, 2013
2. Chiang JL, Kirkman MS, Laffel LMB, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2034–2054
3. Wolpert HA, Atakov-Castillo A, Smith SA, Steil GM. Dietary fat acutely increases glucose concentrations and insulin requirements in patients with type 1 diabetes: implications for carbohydrate-based bolus dose calculation and intensive diabetes management. Diabetes Care 2013;36:810–816
4. Bell KJ, Toschi E, Steil GM, Wolpert HA. Optimized mealtime insulin dosing for fat and protein in type 1 diabetes: application of a model-based approach to derive insulin doses for open-loop diabetes management. Diabetes Care 2016;39:1631–1634
5. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. Diabetes Care 2015;38:1008–1015
6. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336–347
7. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
8. Wood JR, Miller KM, Maahs DM, et al.; T1D Exchange Clinic Network. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. Diabetes Care 2013;36:2035–2037
9. Kmietowicz Z Insulin pumps improve control and reduce complications in children with type 1 diabetes. BMJ 2013;347:f5154
10. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013;368:824–833
11. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986

12. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
13. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383
14. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254–2264
15. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005;28:950–955
16. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC, Bregman DB; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 2015;38:2266–2273
17. American Diabetes Association. Pancreas and islet transplantation in type 1 diabetes. Diabetes Care 2006;29:935
18. Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: a systematic review of efficacy. Diabetologia 2010;53:809–820
19. –U.S. Food and Drug Administration. SGLT2 Inhibitors: Drug Safety Communication - Labels to Include Warnings About Too Much Acid in the Blood and Serious Urinary Tract Infections [Internet]. Available from http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm475553.htm. Accessed 3 October 2016
20. Palmer SC, Mavridis D, Nicolucci A, 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;316:313–324
21. Inzucchi SE, Bergenstal RM, Buse JB, 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;38:140–149
22. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
23. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–613
24. U.S. Food and Drug Administration. Metformin-containing Drugs: Drug Safety Communication - Revised Warnings for Certain Patients With Reduced Kidney Function [Internet]. Available from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494829.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed 3 October 2016
25. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016;101:1754–1761
26. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med 2014;174:1227–1234
27. Institute for Clinical and Economic Review. Controversies in the Management of Patients with Type 2 Diabetes [Internet]. Available from http://icer-review.org/wp-content/uploads/2015/03/CEPAC-T2D-Final-Report-December-22.pdf. Accessed 17 November 2016
28. Nathan DM, Buse JB, Kahn SE, et al.; GRADE Study Research Group. Rationale and design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2013;36:2254–2261
29. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
30. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
31. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242
32. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326
33. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335
34. Blonde L, Merilainen M, Karwe V, Raskin P; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. Diabetes Obes Metab 2009;11:623–631
35. Tricco AC, Ashoor HM, Soobiah C, et al. Safety, effectiveness, and cost of long-acting versus intermediate-acting insulin for type 1 diabetes: protocol for a systematic review and network meta-analysis. Syst Rev 2013;2:73
36. Hua X, Carvalho N, Tew M, Huang ES, Herman WH, Clarke P. Expenditures and prices of antihyperglycemic medications in the United States: 2002-2013. JAMA 2016;315:1400–1402
37. Diamant M, Nauck MA, Shaginian R, et al.; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014;37:2763–2773
38. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 2014;384:2228–2234
39. Dieuzeide G, Chuang L-M, Almaghamsi A, Zilov A, Chen J-W, Lavalle-González FJ. Safety and effectiveness of biphasic insulin aspart 30 in people with type 2 diabetes switching from basal-bolus insulin regimens in the A1chieve study. Prim Care Diabetes 2014;8:111–117
40. Mathieu C, Storms F, Tits J, Veneman TF, Colin IM. Switching from premixed insulin to basal-bolus insulin glargine plus rapid-acting insulin: the ATLANTIC study. Acta Clin Belg 2013;68:28–33
41. Giugliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Endocrine 2016;51:417–428
42. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321–1331
43. Dormandy JA, Charbonnel B, Eckland DJA, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
44. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002;359:2072–2077
45. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
46. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865
47. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care 2010;33:1503–1508
48. Truven Health Analytics. Red Book: A Comprehensive, Consistent Drug Pricing Resource [Internet], 2016. Available from http://micromedix.com/products/product-suites/clinical-knowledge/redbook. Accessed 29 July 2016