8. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*

American Diabetes Association

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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 with type 1 diabetes 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 (2).

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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 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). The U.S. Food and Drug Administration (FDA) has also approved the first hybrid closed-loop system pump. The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (8,9).

Intensive management using CSII and continuous glucose monitoring should be encouraged in selected patients when there is active patient/family participation (10–12).

The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive therapy with multiple daily injections or CSII delivered by multidisciplinary teams of physicians, nurses, dietitians, and behavioral scientists improved glycemia and resulted in better long-term outcomes (13–15). 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, less weight gain, and lower A1C than human insulins in people with type 1 diabetes (16–18). Longer-acting basal analogs (U-300 glargine or degludec) may additionally convey a lower hypoglycemia risk compared with U-100 glargine in patients with type 1 diabetes (19,20).

Rapid-acting inhaled insulin used before meals in patients with type 1 diabetes was shown to be noninferior when compared with aspart insulin for A1C lowering, with less hypoglycemia observed with inhaled insulin therapy (21). 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 $\leq$7.0% (53 mmol/mol) and $\leq$6.5% (48 mmol/mol). Because inhaled insulin cartridges are only available in 4-, 8-, and 12-unit doses, limited dosing increments to fine-tune prandial insulin doses in type 1 diabetes are a potential limitation.

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.), 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 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.

Investigational Agents

Metformin

Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in patients with type 1 diabetes. In one study, metformin 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%, $P = 0.42$) (22). A randomized clinical trial similarly found that, among overweight adolescents with type 1 diabetes, the addition of metformin to insulin did not improve glycemic control and increased risk for gastrointestinal adverse events after 6 months compared with placebo (23). The Reducing With Metformin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) trial investigated the addition of metformin therapy to titrated insulin therapy in adults with type 1 diabetes at increased risk for cardiovascular disease and found that metformin did not significantly improve glycemic control beyond the first 3 months of treatment and that progression of atherosclerosis (measured by carotid artery intima-media thickness) was not significantly reduced, although other cardiovascular risk factors such as body weight and LDL cholesterol improved (24). 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 (25) and dipeptidyl peptidase 4 (DPP-4) inhibitors (26) 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). SGLT2 inhibitors may have glycemic benefits in patients with type 1 or type 2 diabetes on insulin therapy (27). 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 or 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 (28).

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Pancreas and islet transplantation have been shown to normalize glucose levels

but require life-long 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 (29).

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**
- Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥9% (75 mmol/mol). **E**
- In patients without atherosclerotic cardiovascular disease, if monotherapy or dual therapy does not achieve or maintain the A1C goal over 3 months, add an additional antihyperglycemic agent based on drug-specific and patient factors (**Table 8.1**). **A**
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, history of atherosclerotic cardiovascular disease, impact on weight, potential side effects, renal effects, delivery method (oral versus subcutaneous), cost, and patient preferences. **E**
- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors (**Table 8.1**). **A***
- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, after lifestyle management and metformin, the antihyperglycemic agent canagliflozin may be considered to reduce major adverse cardiovascular events, based on drug-specific and patient factors (**Table 8.1**). **C***
- Continuous reevaluation of the medication regimen and adjustment as needed to incorporate patient factors (**Table 8.1**) and regimen complexity is recommended. **E**
- For patients with type 2 diabetes who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed. **B**
- Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated. **A**

See Section 12 for recommendations specific for children and adolescents with type 2 diabetes. 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 (30). An ADA/European Association for the Study of Diabetes position statement "Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach" (31) 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 (32). Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality (33). Metformin may be safely used in patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m^2, and the FDA recently revised the label for metformin to reflect its safety in patients with eGFR ≥30 mL/min/1.73 m^2 (34). 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 (35).

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 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, few directly compare drugs as add-on therapy. A comparative effectiveness meta-analysis (36) suggests that each new class of noninsulin agents added to initial therapy generally lowers A1C approximately 0.7–1.0%. If the A1C target is not achieved after approximately 3 months and patient *does not* have atherosclerotic cardiovascular disease (ASCVD), consider a combination of metformin and any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, DPP-4

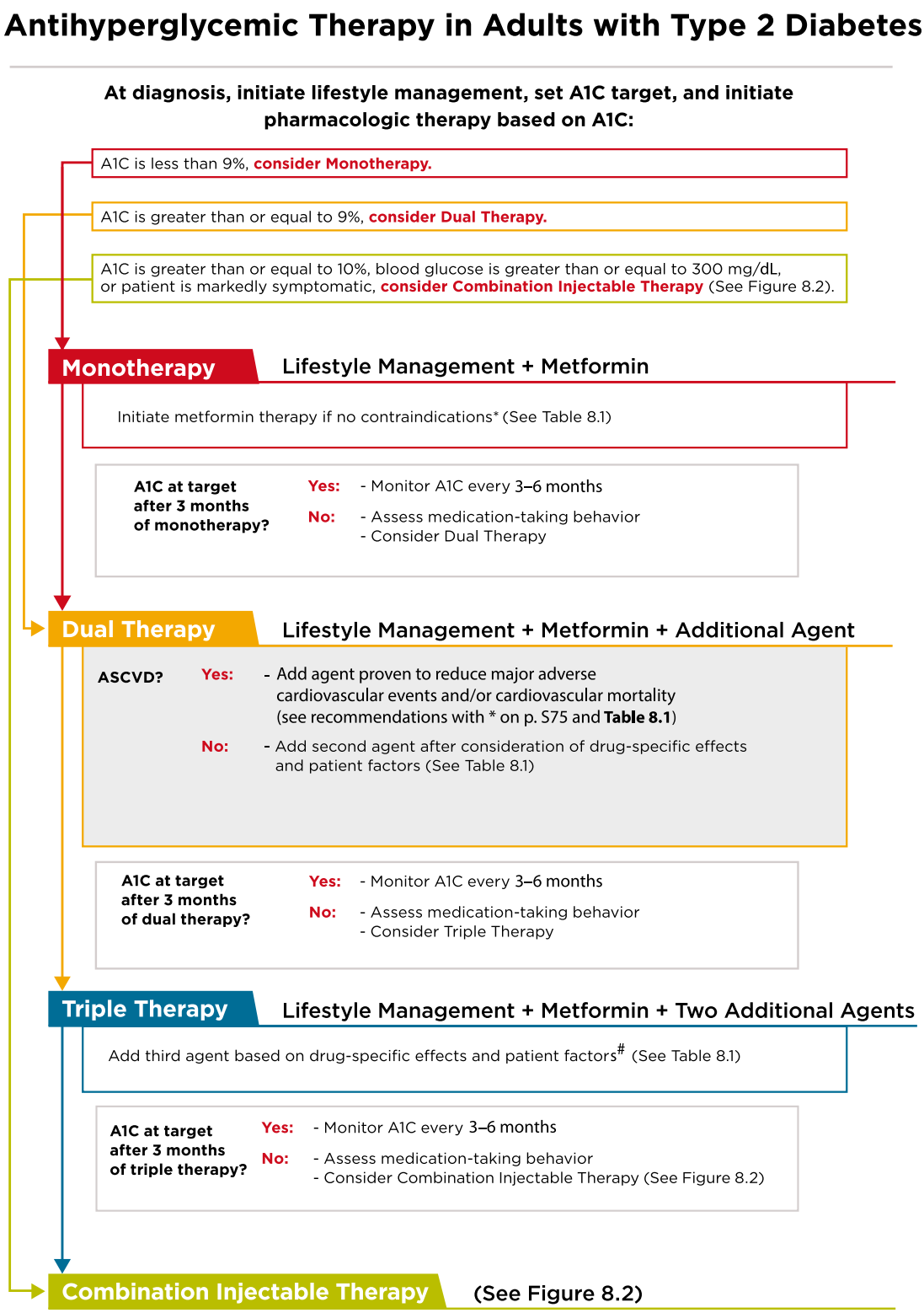

Figure 8.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations. *If patient does not tolerate or has contraindications to metformin, consider agents from another class in Table 8.1. #GLP-1 receptor agonists and DPP-4 inhibitors should not be prescribed in combination. If a patient with ASCVD is not yet on an agent with evidence of cardiovascular risk reduction, consider adding.

inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin (**Fig. 8.1**); the choice of which agent to add is based on drug-specific effects and patient factors (**Table 8.1**). For patients with ASCVD, add a second agent with evidence of cardiovascular risk reduction after consideration of drug-specific and patient factors (see p. S77 CARDIOVASCULAR OUTCOMES TRIALS). If A1C target is still not achieved after ~3 months of dual therapy, proceed to a 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

Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
					ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin		High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors		Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs		High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors		Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	**Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

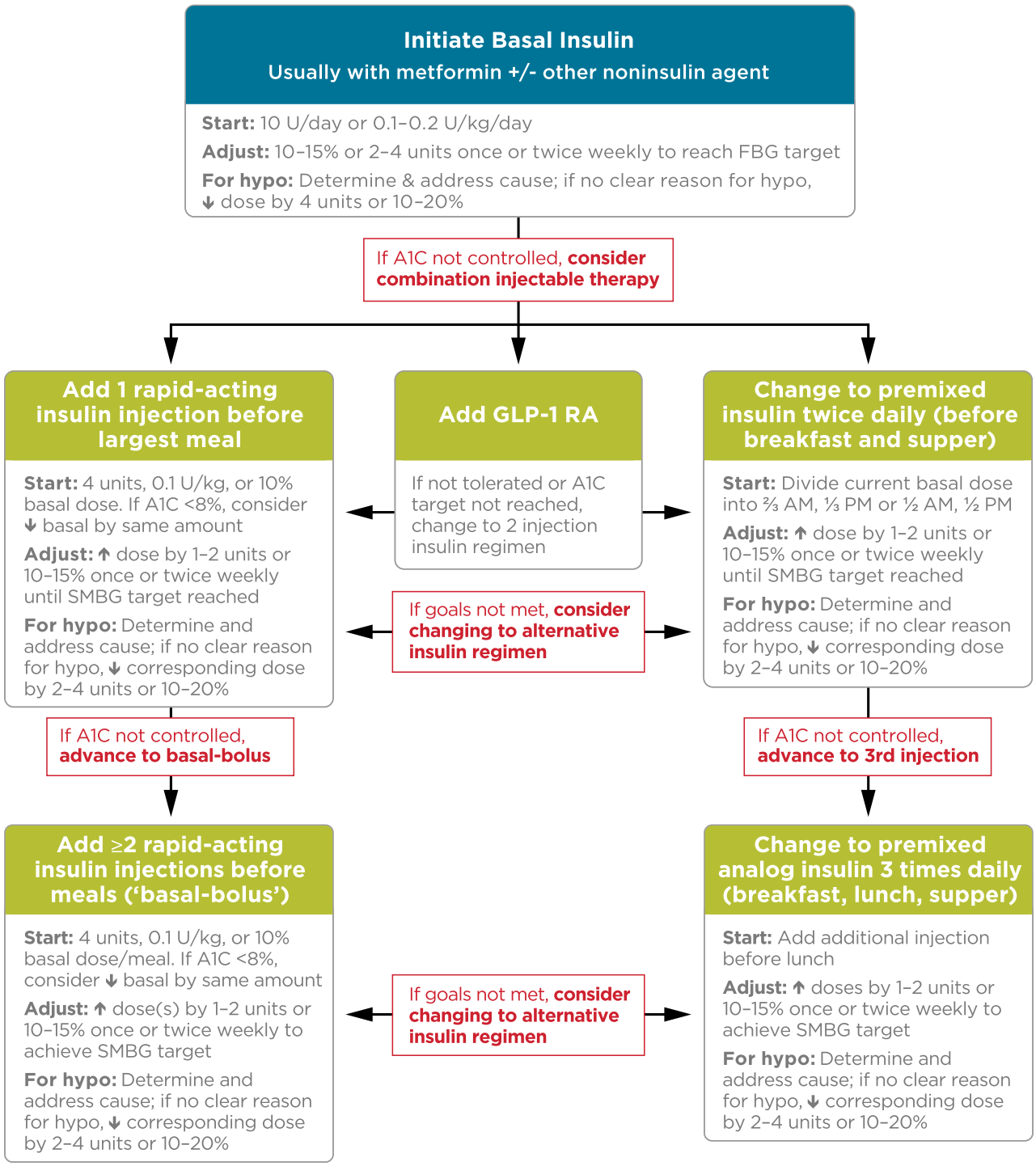

Figure 8.2—Combination injectable therapy for type 2 diabetes. FBG, fasting blood glucose; hypo, hypoglycemia. Adapted with permission from Inzucchi et al. (31).

patient preferences (37), as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. If not already included in the treatment regimen, addition of an agent with evidence of cardiovascular risk reduction should be considered in patients with ASCVD beyond dual therapy, with continuous reevaluation of patient factors to guide treatment (**Table 8.1**).

Table 8.2 lists drugs commonly used in the U.S. Cost-effectiveness models of the newer agents based on clinical utility and glycemic effect have been reported (38). **Table 8.3** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (39) and National Average Drug Acquisition Costs (NADAC) (40) 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 and NADAC

Table 8.2—Pharmacology of available glucose-lowering agents in the U.S. for the treatment of type 2 diabetes

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Renal dosing recommendations (63–66)*
Biguanides	• Metformin	Activates AMP kinase (? other)	↓ Hepatic glucose production	• No dose adjustment if eGFR >45; do not initiate OR assess risk/benefit if currently on metformin if eGFR 30–45; discontinue if eGFR <30
Sulfonylureas (2nd generation)	• Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	↑ Insulin secretion	• Avoid use in patients with renal impairment • Initiate conservatively at 2.5 mg daily to avoid hypoglycemia • Initiate conservatively at 1 mg daily to avoid hypoglycemia
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	↑ Insulin secretion	• Initiate conservatively at 0.5 mg with meals if eGFR <30 • Initiate conservatively at 60 mg with meals if eGFR <30
Thiazolidinediones	• Pioglitazone • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	↑ Insulin sensitivity	• No dose adjustment required • No dose adjustment required
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	Slows intestinal carbohydrate digestion/absorption	• Avoid if eGFR <30 • Avoid if eGFR <25
DPP-4 inhibitors	• Sitagliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	↑ Insulin secretion (glucose dependent); ↓ Glucagon secretion (glucose dependent)	• 100 mg daily if eGFR >50; 50 mg daily if eGFR 30–50; 25 mg daily if eGFR <30
	• Saxagliptin			• 5 mg daily if eGFR >50; 2.5 mg daily if eGFR ≤50
	• Linagliptin			• No dose adjustment required
	• Alogliptin			• 25 mg daily if eGFR >60; 12.5 mg daily if eGFR 30–60; 6.25 mg daily if eGFR <30
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	? ↓ Hepatic glucose production; ? ↑ Incretin levels	• No specific dose adjustment recommended by manufacturer
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	Modulates hypothalamic regulation of metabolism; ↑ Insulin sensitivity	• No specific dose adjustment recommended by manufacturer
SGLT2 inhibitors	• Canagliflozin	Inhibits SGLT2 in the proximal nephron	Blocks glucose reabsorption by the kidney, increasing glucosuria	• No dose adjustment required if eGFR ≥60; 100 mg daily if eGFR 45–59; avoid use and discontinue in patients with eGFR persistently <45
	• Dapagliflozin			• Avoid initiating if eGFR <60; not recommended with eGFR 30–60; contraindicated with eGFR <30
	• Empagliflozin			• Contraindicated with eGFR <30
GLP-1 receptor agonists	• Exenatide • Exenatide extended release	Activates GLP-1 receptors	↑ Insulin secretion (glucose dependent)	• Not recommended with eGFR <30 • Not recommended with eGFR <30

Continued on p. S80

Table 8.2—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Renal dosing recommendations (63–66)*
	• Liraglutide		↓ Glucagon secretion (glucose dependent); Slows gastric emptying; ↑ Satiety	• No specific dose adjustment recommended by the manufacturer; limited experience in patients with severe renal impairment
	• Albiglutide			• No dose adjustment required for eGFR 15–89 per manufacturer; limited experience in patients with severe renal impairment
	• Lixisenatide			• No dose adjustment required for eGFR 60–89; no dose adjustment required for eGFR 30–59, but patients should be monitored for adverse effects and changes in kidney function; clinical experience is limited with eGFR 15–29; patients should be monitored for adverse effects and changes in kidney function; avoid if eGFR <15
	• Dulaglutide			• No specific dose adjustment recommended by the manufacturer; limited experience in patients with severe renal impairment
Amylin mimetics	• Pramlintide§	Activates amylin receptors	↓ Glucagon secretion; Slows gastric emptying; ↑ Satiety	• No specific dose adjustment recommended by manufacturer
Insulins	• Rapid-acting analogs Lispro Aspart Glulisine Inhaled insulin • Short-acting analogs Human Regular • Intermediate-acting analogs Human NPH • 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	Activates insulin receptors	↑ Glucose disposal; ↓ Hepatic glucose production; Suppresses ketogenesis	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response

*eGFR is given in mL/min/1.73 m^2. §Not licensed in Europe for type 2 diabetes. GIP, glucose-dependent insulinotropic peptide; PPAR-γ, peroxisome proliferator–activated receptor γ.

Table 8.3—Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($4, $93)	$2	2,000 mg
		850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		500 mg (ER)	$89 ($82, $6,671)	$5 ($5, $3,630)	2,000 mg
		750 mg (ER)	$72 ($65, $92)	$5	1,500 mg
		1,000 mg (ER)	$1,028 ($1,028, $7,214)	$539 ($539, $5,189)	2,000 mg
Sulfonylureas (2nd generation)	• Glyburide	5 mg	$93 ($63, $103)	$17	20 mg
		6 mg (micronized)	$50 ($48, $71)	$12	12 mg (micronized)
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$4	40 mg (IR)
		10 mg (XL)	$48	$16	20 mg (XL)
	• Glimepiride	4 mg	$71 ($71, $198)	$7	8 mg
Meglitinides (glinides)	• Repaglinide	2 mg	$659 ($122, $673)	$40	16 mg
	• Nateglinide	120 mg	$155	$56	360 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$5	45 mg
	• Rosiglitazone	4 mg	$387	$314	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$104 ($104, $106)	$25	300 mg
	• Miglitol	100 mg	$241	N/A††	300 mg
DPP-4 inhibitors	• Sitagliptin	100 mg	$477	$382	100 mg
	• Saxagliptin	5 mg	$462	$370	5 mg
	• Linagliptin	5 mg	$457	$367	5 mg
	• Alogliptin	25 mg	$449	$357	25 mg
Bile acid sequestrants	• Colesevelam	625 mg tabs	$713	$570	3.75 g
		1.875 g suspension	$1,426	$572	3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	$784	$629	4.8 mg
SGLT2 inhibitors	• Canagliflozin	300 mg	$512	$411	300 mg
	• Dapagliflozin	10 mg	$517	$413	10 mg
	• Empagliflozin	25 mg	$517	$415	25 mg
GLP-1 receptor agonists	• Exenatide	10 μg pen	$802	$642	20 μg
	• Lixisenatide	20 μg pen	$669	N/A††	20 μg
	• Liraglutide	18 mg/3 mL pen	$968	$775	1.8 mg
	• Exenatide (extended release)	2 mg powder for suspension or pen	$747	$600	2 mg**
	• Albiglutide	50 mg pen	$626	$500	50 mg**
	• Dulaglutide	1.5/0.5 mL pen	$811	$648	1.5 mg**
Amylin mimetics	• Pramlintide	120 μg pen	$2,336	N/A††	120 μg/injection†††

ER and XL, extended release; IR, immediate release. †Calculated for 30-day supply (AWP or NADAC unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. ††Not applicable; data not available. **Administered once weekly. †††AWP and NADAC calculated based on 120 μg three times daily.

were utilized to provide two separate measures to allow for a comparison of drug 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 (41).

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

Cardiovascular Outcomes Trials

There are now three large randomized controlled trials reporting statistically significant reductions in cardiovascular events for two SGLT2 inhibitors (empagliflozin and canagliflozin) and one GLP-1 receptor agonist (liraglutide) where the majority, if not all patients, in the trial had ASCVD. The empagliflozin and liraglutide trials demonstrated significant reductions in cardiovascular death. Exenatide once-weekly did not have statistically significant reductions in major adverse cardiovascular events or cardiovascular mortality but did have a significant reduction in all-cause mortality. In contrast, other GLP-1 receptor agonists have not shown similar reductions in cardiovascular events (**Table 9.4**). Whether the benefits of GLP-1 receptor agonists are a class effect remains to be definitively established. See ANTIHYPERGLYCEMIC THERAPIES AND CARDIOVASCULAR OUTCOMES in Section 9 "Cardiovascular Disease and Risk Management" and **Table 9.4** for a detailed description of these cardiovascular

Table 8.4—Median cost of insulin products in the U.S. calculated as AWP (39) and NADAC (40) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting analogs	• Lispro	U-100 vial;	$330	$264
		U-100 3 mL cartridges;	$408	$326
		U-100 prefilled pen; U-200 prefilled pen	$424	$339
	• Aspart	U-100 vial;	$331	$265
		U-100 3 mL cartridges;	$410	$330
		U-100 prefilled pen	$426	$341
	• Glulisine	U-100 vial;	$306	$245
		U-100 prefilled pen	$394	$315
	• Inhaled insulin	Inhalation cartridges	$725 ($544, $911)	N/A†
Short-acting analogs	• Human Regular	U-100 vial	$165 ($165, $178)	$135 ($135, $145)
Intermediate-acting analogs	• Human NPH	U-100 vial;	$165 ($165, $178)	$135 ($135, $145)
		U-100 prefilled pen	$377	$305
Concentrated Human Regular insulin	• U-500 Human Regular insulin	U-500 vial;	$178	$143
		U-500 prefilled pen	$230	$184
Basal analogs	• Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	$298	$239 ($239, $241)
	• Glargine biosimilar	U-100 prefilled pen	$253	$203
	• Detemir	U-100 vial; U-100 prefilled pen	$323	$259
	• Degludec	U-100 prefilled pen; U-200 prefilled pen	$355	$285
Premixed insulin products	• NPH/Regular 70/30	U-100 vial;	$165 ($165, $178)	$134 ($134, $146)
		U-100 prefilled pen	$377	$305
	• Lispro 50/50	U-100 vial;	$342	$278
		U-100 prefilled pen	$424	$339
	• Lispro 75/25	U-100 vial;	$342	$273
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial;	$343	$275
		U-100 prefilled pen	$426	$341
Premixed insulin/GLP-1 receptor agonist products	• Degludec/Liraglutide	100/3.6 prefilled pen	$763	N/A†
	• Glargine/Lixisenatide	100/33 prefilled pen	$508	$404

*AWP or NADAC calculated as in **Table 8.3**; median listed alone when only one product and/or price. †Not applicable; data not available.

outcomes trials. Additional large randomized trials of other agents in these classes are ongoing.

Of note, these studies examined the drugs in combination with metformin (**Table 9.4**) in the great majority of patients for whom metformin was not contraindicated or not tolerated. For patients with type 2 diabetes who have ASCVD, on lifestyle and metformin therapy, it is recommended to incorporate an agent with strong evidence for cardiovascular risk reduction especially those with proven benefit on both major adverse cardiovascular events and cardiovascular death after consideration of drug-specific patient factors (**Table 8.1**). See **Fig. 8.1** for additional recommendations on antihyperglycemic treatment in adults with type 2 diabetes.

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 improves glycemic control in patients with type 2 diabetes initiating insulin (42). Comprehensive education regarding self-monitoring of blood glucose, 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. When basal insulin is added to antihyperglycemic agents in patients with type 2 diabetes, long-acting basal analogs (U-100 glargine or detemir) can be used instead of NPH to reduce the risk of symptomatic and nocturnal hypoglycemia (43–48). Longer-acting basal analogs (U-300 glargine or degludec) may additionally convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral antihyperglycemic agents (49–55). While there is evidence for reduced hypoglycemia with newer, longer-acting basal insulin analogs, people without a history of hypoglycemia are at decreased risk and could potentially be switched to human insulin safely. Thus, due to high costs of analog insulins, use of human insulin may be a practical option for some patients, and clinicians should be familiar with its use (56). **Table 8.4** provides AWP (39) and NADAC (40) information (cost per 1,000 units) for currently available insulin and insulin combination 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 in a patient-centered approach to care, along with

efficacy, hypoglycemia risk, weight, and other patient and drug-specific factors (**Table 8.1**) (57).

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. In September 2017, the FDA approved a new faster-acting formulation of insulin aspart. The recommended starting dose of mealtime insulin is 4 units, 0.1 units/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 action than U-100 regular, possessing both prandial and basal properties. U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine. 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 (58,59). In November 2016, the FDA approved two different once-daily fixed-dual 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 plus GLP-1 receptor agonist), consider switching to another regimen to achieve A1C targets (i.e., basal insulin plus single injection of rapid-acting insulin or premixed insulin twice daily) (60,61). 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.

Fig. 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 (62). If a patient is still above the A1C target on basal insulin plus 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 (60,61). Metformin should be continued in patients on combination injectable insulin therapy, if not contraindicated and if tolerated, for further glycemic benefits.

References

1. Peters AL, Laffel L, Eds. *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook.* Alexandria, VA, American Diabetes Association, 2013

2. Chiang JL, Kirkman MS, Laffel LMB, Peters AL; Type 1 Diabetes Sourcebook Authors. 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. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408
9. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155–163
10. 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
11. Kmietowicz Z. Insulin pumps improve control and reduce complications in children with type 1 diabetes. BMJ 2013;347:f5154
12. 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
13. Nathan DM, Genuth S, Lachin J, et al.; 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
14. 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
15. 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
16. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ 2014;349:g5459
17. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442–449
18. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254–2264
19. Lane W, Bailey TS, Gerety G, et al.; SWITCH 1. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 Randomized Clinical Trial. JAMA 2017;318:33–44
20. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care 2015;38:2217–2225
21. 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
22. 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
23. Libman IM, Miller KM, DiMeglio LA, et al.; T1D Exchange Clinic Network Metformin RCT Study Group. Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial. JAMA 2015;314:2241–2250
24. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:597–609
25. Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2016;4:221–232
26. Guo H, Fang C, Huang Y, Pei Y, Chen L, Hu J. The efficacy and safety of DPP4 inhibitors in patients with type 1 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2016;121:184–191
27. Yang Y, Chen S, Pan H, et al. Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes: systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96:e6944
28. 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], 2015. Available from http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm475553.htm. Accessed 3 October 2016
29. Robertson RP, Davis C, Larsen J, Stratta R, Sutherland DER; American Diabetes Association. Pancreas and islet transplantation in type 1 diabetes. Diabetes Care 2006;29:935
30. 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
31. 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
32. 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
33. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751
34. U.S. Food and Drug Administration. Metformin-containing drugs: drug safety communication - revised warnings for certain patients with reduced kidney function [Internet], 2016. Available from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494829.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed 3 October 2016
35. 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
36. 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
37. 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
38. Institute for Clinical and Economic Review. Controversies in the management of patients with type 2 diabetes [Internet], 2014. Available from https://icer-review.org/wp-content/uploads/2015/03/CEPAC-T2D-Final-Report-December-22.pdf. Accessed 2 November 2017
39. Truven Health Analytics. Red Book: A Comprehensive, Consistent Drug Pricing Resource [Internet], 2016. Available from: http://www.micromedexsolutions.com/micromedex2/librarian. Accessed 18 July 2017
40. Centers for Medicare & Medicaid Services. Pharmacy pricing: national average drug acquisition cost [Internet], 2017. Available from https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html. Accessed 19 July 2017
41. 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
42. 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
43. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180:385–397
44. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;2:CD005613
45. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2008;81:184–189
46. Owens DR, Traylor L, Mullins P, Landgraf W. Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy. Diabetes Res Clin Pract 2017;124(Suppl. C):57–65
47. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086
48. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006;29:1269–1274
49. Bolli GB, Riddle MC, Bergenstal RM, et al.; EDITION 3 Study Investigators. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 2015;17:386–394
50. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). Diabetes Obes Metab 2016;18:366–374
51. Yki-Järvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. Diabetes Obes Metab 2015; 17:1142–1149
52. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017;377:723–732
53. Rodbard HW, Cariou B, Zinman B, et al.; BEGIN Once Long trial investigators. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. Diabet Med 2013;30: 1298–1304
54. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 Randomized Clinical Trial. JAMA 2017;318:45–56
55. Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. 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;35:2464–2471
56. Lipska KJ, Hirsch IB, Riddle MC. Human insulin for type 2 diabetes: an effective, less-expensive option. JAMA 2017;318:23–24
57. 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
58. 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
59. 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
60. 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
61. 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
62. 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
63. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
64. Neumiller JJ, Alicic RZ, Tuttle KR. Therapeutic considerations for antihyperglycemic agents in diabetic kidney disease. J Am Soc Nephrol 2017;28: 2263–2274
65. U.S. Food and Drug Administration. Cycloset [bromocriptine] prescribing information [Internet], 2017. [Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020866s006s007lbl.pdf. Accessed 22 September 2017
66. U.S. Food and Drug Administration. Welchol [Colesevelam] prescribing information [Internet], 2014. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022362s007lbl.pdf. Accessed 22 September 2017