



9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019

American Diabetes Association

Diabetes Care 2019;42(Suppl. 1):S90–S102 | <https://doi.org/10.2337/dc19-S009>

The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations, please refer to the Standards of Care Introduction. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

- 9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**
- 9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**
- 9.3 Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. **E**
- 9.4 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

Because the hallmark of type 1 diabetes is absent or near-absent β -cell function, insulin treatment is essential for individuals with type 1 diabetes. Insufficient provision of insulin causes not only hyperglycemia but also systematic metabolic disturbances like hypertriglyceridemia and ketoacidosis, as well as tissue catabolism. Over the past three decades, evidence has accumulated supporting multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump as providing the best combination of effectiveness and safety for people with type 1 diabetes.

Generally, insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and medical illness. The American Diabetes Association/JDRF

Suggested citation: American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2019. Diabetes Care 2019;42(Suppl. 1):S90–S102

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

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 half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption (1); this guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association position statement “Type 1 Diabetes Management Through the Life Span” provides a thorough overview of type 1 diabetes treatment (2).

Physiologic insulin secretion varies with glycemia, meal size, and tissue demands for glucose. To approach this variability in people using insulin treatment, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education of patients on how to adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be considered. Newly available information suggests that individuals in whom carbohydrate counting is effective can incorporate estimates of meal fat and protein content into their prandial dosing for added benefit (3–5).

Most studies comparing multiple daily injections with continuous subcutaneous insulin infusion (CSII) have been relatively small and of short duration. However, a recent systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C (–0.30% [95% CI –0.58 to –0.02]) and for reducing severe hypoglycemia rates in children and adults (6). There is no consensus to guide choosing which form of insulin administration is best for a given patient, and research to guide this decision making is needed (7). The arrival of continuous glucose monitors to clinical practice has proven beneficial in specific circumstances. Reduction of nocturnal hypoglycemia in people with type 1 diabetes using insulin pumps with glucose sensors is improved by automatic suspension of insulin delivery at a preset glucose level (7–9). The U.S. Food and Drug Administration (FDA) has also approved the first hybrid closed-loop pump system. The safety and efficacy of hybrid closed-loop systems has been supported in

the literature in adolescents and adults with type 1 diabetes (10,11). Intensive diabetes management using CSII and continuous glucose monitoring should be considered in selected patients. See Section 7 “Diabetes Technology” for a full discussion of insulin delivery devices.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or CSII reduced A1C and was associated with improved long-term outcomes (12–14). 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 higher rate of severe hypoglycemia (61 episodes per 100 patient-years of therapy). Since the DCCT, 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 (15–17). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine in patients with type 1 diabetes (18,19). Rapid-acting inhaled insulin to be used before meals is now available and may reduce rates of hypoglycemia in patients with type 1 diabetes (20).

Postprandial glucose excursions may be better controlled by adjusting the timing of prandial 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.

Insulin Injection Technique

Ensuring that patients and/or caregivers understand correct insulin injection technique is important to optimize glucose control and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the right way. Recommendations have been published elsewhere outlining best practices for insulin injection (21). Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other

complications, and avoidance of intramuscular (IM) insulin delivery.

Exogenous-delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm (21). Because insulin absorption from IM sites differs according to the activity of the muscle, inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose, with IM injection being associated with frequent and unexplained hypoglycemia in several reports (21–23). Risk for IM insulin delivery is increased in younger and lean patients when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles (24). Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared to longer needles (25,26), including a study performed in obese adults (27). Injection site rotation is additionally necessary to avoid lipohypertrophy and lipoatrophy (21). Lipohypertrophy can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes (28). Patients and/or caregivers should receive education about proper injection site rotation and to recognize and avoid areas of lipohypertrophy (21). As noted in **Table 4.1**, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of injection device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. As referenced above, there are now numerous evidence-based insulin delivery recommendations that have been published. Proper insulin injection technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β -cell peptide amylin and is approved for use in adults with type 1 diabetes. Results from randomized controlled studies show variable reductions of A1C (0–0.3%) and body weight

(1–2 kg) with addition of pramlintide to insulin (29,30). Similarly, results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin to adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C (31,32). The addition of the glucagon-like peptide 1 (GLP-1) receptor agonists liraglutide and exenatide to insulin therapy caused small (0.2%) reductions in A1C compared with insulin alone in people with type 1 diabetes and also reduced body weight by ~3 kg (33). Similarly, the addition of a sodium–glucose cotransporter 2 (SGLT2) inhibitor to insulin therapy has been associated with improvements in A1C and body weight when compared with insulin alone (34–36); however, SGLT2 inhibitor use is also associated with more adverse events including ketoacidosis. The dual SGLT1/2 inhibitor sotagliflozin is currently under consideration by the FDA and, if approved, would be the first adjunctive oral therapy in type 1 diabetes.

The risks and benefits of adjunctive agents beyond pramlintide in type 1 diabetes continue to be evaluated through the regulatory process; however, at this time, these adjunctive agents are not approved in the context of type 1 diabetes (37).

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Pancreas and islet transplantation normalizes glucose levels but requires 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 (38).

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

Recommendations

9.5 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **A**

9.6 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **A**

9.7 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**

9.8 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥ 300 mg/dL [16.7 mmol/L]) are very high. **E**

9.9 Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C $\geq 1.5\%$ (12.5 mmol/mol) above their glycemic target. **E**

9.10 A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. **E**

9.11 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium–glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit (**Table 9.1**) are recommended as part of the antihyperglycemic regimen. **A**

9.12 Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium–glucose cotransporter 2 inhibitors are preferred. **C**

9.13 For patients with type 2 diabetes and chronic kidney disease,

consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. **C**

9.14 In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. **B**

9.15 Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. **B**



9.16 The medication regimen should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate new patient factors (**Table 9.1**). **E**

The American Diabetes Association/European Association for the Study of Diabetes consensus report “Management of Hyperglycemia in Type 2 Diabetes, 2018” (39) recommends a patient-centered approach to choosing appropriate pharmacologic treatment of blood glucose (**Fig. 9.1**). This includes consideration of efficacy and key patient factors: 1) important comorbidities such as atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and heart failure (HF), 2) hypoglycemia risk, 3) effects on body weight, 4) side effects, 5) cost, and 6) patient preferences. Lifestyle modifications that improve health (see Section 5 “Lifestyle Management”) should be emphasized along with any pharmacologic therapy. See Sections 12 and 13 for recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively.

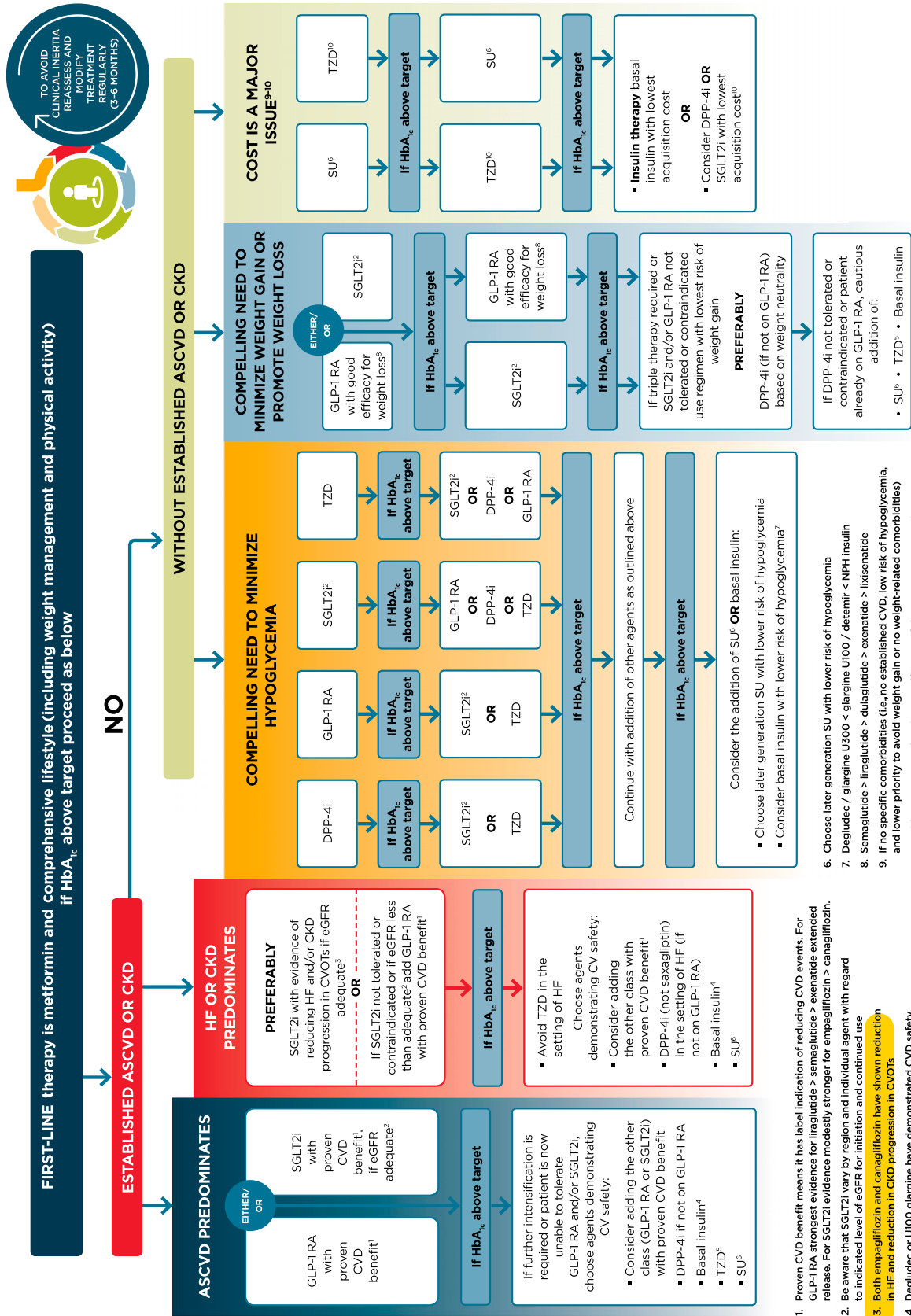
Initial Therapy

Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for most patients this will be monotherapy in combination with lifestyle modifications. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (40). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release

Table 9.1 Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

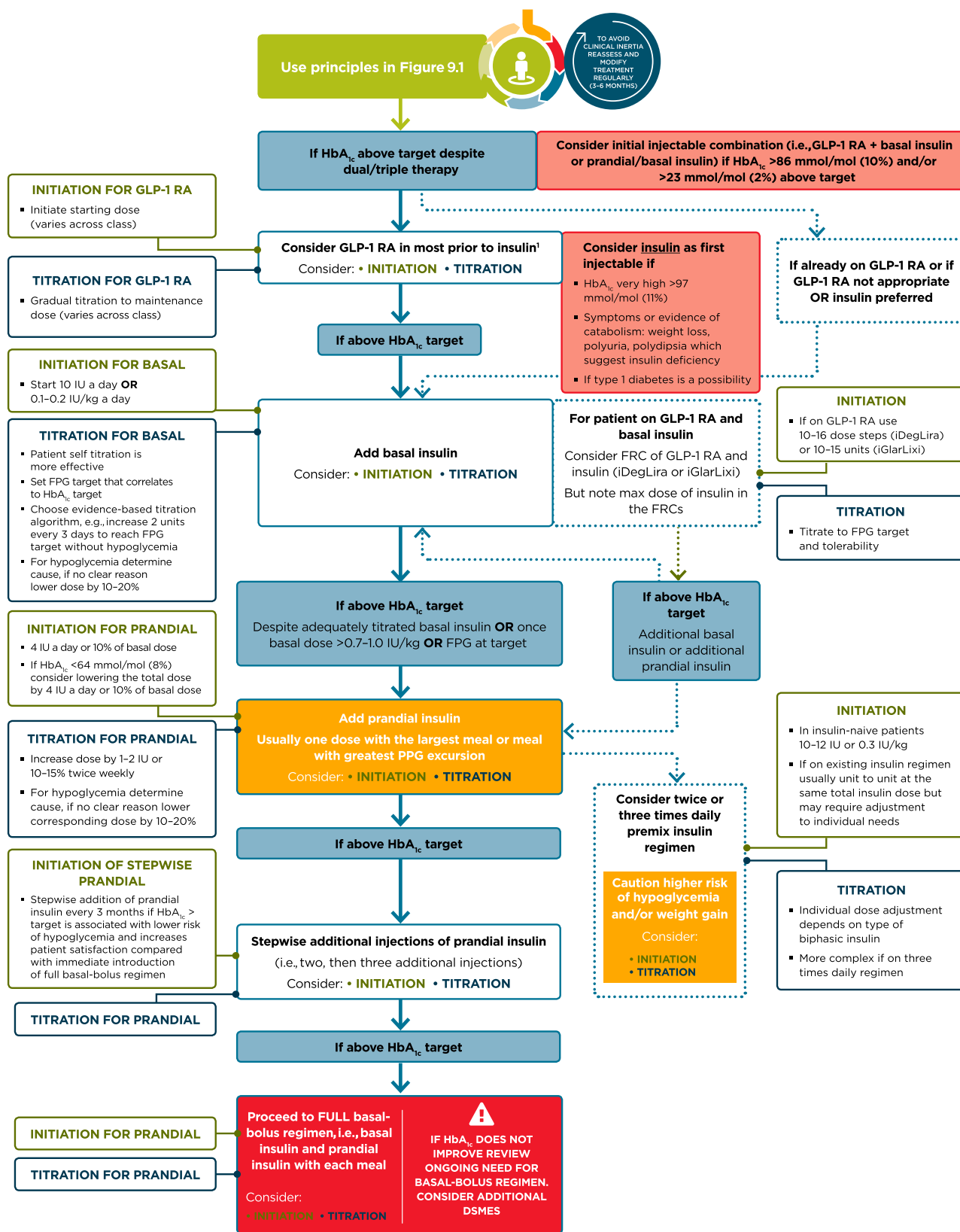
Medication	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations	
				ASCVD	CHF			Progression of CKD	Dosing/use considerations*		
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	Progression of CKD	<ul style="list-style-type: none"> • Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency 	
SGLT2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	 Dapagliflozin, ertugliflozin	High	Oral	 Dapagliflozin, ertugliflozin	<ul style="list-style-type: none"> • Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) 	<ul style="list-style-type: none"> • 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 • Risk of Fournier's gangrene 	
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide	Neutral	High	SQ	Benefit: liraglutide	Benefit: liraglutide	<ul style="list-style-type: none"> • Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Renal dose adjustment required (saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for liraglutin 	<ul style="list-style-type: none"> • Potential risk of acute pancreatitis • Joint pain 	
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	<ul style="list-style-type: none"> • No dose adjustment required • Generally not recommended in renal impairment due to fluid retention 	<ul style="list-style-type: none"> • 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	Neutral	<ul style="list-style-type: none"> • FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide) 	
Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	Neutral	<ul style="list-style-type: none"> • Lower insulin doses required with a decrease in eGFR; titrate per clinical response 	
							Human Insulin Analogs				SQ

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium-glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
 2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
 3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
 4. Degludec or U100 glargine have demonstrated CVD safety
 5. Low dose may be better tolerated though less well studied for CVD effects

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Fig. 4.1. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies et al. (39).



1. When selecting GLP-1 RA, consider: patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

Figure 9.2—Intensifying to injectable therapies. For appropriate context, see Fig. 4.1. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (39).

Table 9.2—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)	\$4 (\$4, \$1,267)	2,000 mg	
		750 mg (ER)	\$72 (\$65, \$92)	\$4	1,500 mg	
		1,000 mg (ER)	\$1,028 (\$1,028, \$7,214)	\$311 (\$311, \$1,321)	2,000 mg	
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	\$71 (\$71, \$198)	\$4	8 mg	
		10 mg (IR)	\$75 (\$67, \$97)	\$5	40 mg (IR)	
	• Glipizide	10 mg (XL)	\$48	\$15	20 mg (XL)	
		• Glyburide	6 mg (micronized)	\$50 (\$48, \$71)	\$10	12 mg (micronized)
	5 mg		\$93 (\$63, \$103)	\$13	20 mg	
Thiazolidinediones	• Pioglitazone	45 mg	\$348 (\$283, \$349)	\$4	45 mg	
		4 mg	\$407	\$329	8 mg	
α-Glucosidase inhibitors	• Acarbose	100 mg	\$106 (\$104, \$106)	\$23	300 mg	
		100 mg	\$241	\$311	300 mg	
Meglitinides (glinides)	• Nateglinide	120 mg	\$155	\$46	360 mg	
		• Repaglinide	2 mg	\$878 (\$162, \$898)	\$48	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	\$234	\$170	25 mg	
		• Saxagliptin	5 mg	\$490 (\$462, \$490)	\$392	5 mg
		• Linagliptin	5 mg	\$494	\$395	5 mg
		• Sitagliptin	100 mg	\$516	\$413	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	\$322	\$257	15 mg	
		• Dapagliflozin	10 mg	\$557	\$446	10 mg
		• Canagliflozin	300 mg	\$558	\$446	300 mg
		• Empagliflozin	25 mg	\$558	\$448	25 mg
GLP-1 receptor agonists	• Exenatide (extended release)	2 mg powder for suspension or pen	\$792	\$634	2 mg**	
		• Exenatide	10 µg pen	\$850	\$680	20 µg
		• Dulaglutide	1.5/0.5 mL pen	\$876	\$702	1.5 mg**
		• Semaglutide	1 mg pen	\$875	\$704	1 mg**
		• Liraglutide	18 mg/3 mL pen	\$1,044	\$835	1.8 mg
Bile acid sequestrants	• Colesevelam	625 mg tabs	\$712 (\$674, \$712)	\$354	3.75 g	
		3.75 g suspension	\$674	\$598	3.75 g	
Dopamine-2 agonists	• Bromocriptine	0.8 mg	\$855	\$685	4.8 mg	
Amylin mimetics	• Pramlintide	120 µg pen	\$2,547	\$2,036	120 µg/injection+++	

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1, glucagon-like peptide 1; IR, immediate release; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium-glucose cotransporter 2. [†]Calculated for 30-day supply (AWP [44] or NADAC [45] 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. **Administered once weekly. +++AWP and NADAC calculated based on 120 µg three times daily.

form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality (41); there is little systematic data available for other oral agents as initial therapy of type 2 diabetes. The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea. The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be safely

used in patients with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in patients with eGFR ≥30 mL/min/1.73 m² (42). A recent randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (43). This is compatible with a recent report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (44).

In patients with contraindications or intolerance of metformin, initial therapy should be based on patient factors;

consider a drug from another class depicted in Fig. 9.1. When A1C is ≥1.5% (12.5 mmol/mol) above glycemic target (see Section 6 “Glycemic Targets” for more information on selecting appropriate targets), many patients will require dual combination therapy to achieve their target A1C level (45). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. Consider initiating insulin therapy when blood glucose is ≥300 mg/dL (16.7 mmol/L) or A1C is ≥10% (86 mmol/

Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (44) and NADAC (45) 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 biosimilar	U-100 vial	\$280	\$226	
		U-100 prefilled pen	\$361	\$289	
	• Glulisine	U-100 vial	\$324	\$260	
		U-100 prefilled pen	\$417	\$334	
	• Lispro	U-100 vial	\$330	\$264	
		U-100 3 mL cartridges	\$408	\$326	
		U-100 prefilled pen; U-200 prefilled pen	\$424	\$340	
	• Aspart	U-100 vial	\$347	\$278	
		U-100 3 mL cartridges	\$430	\$343	
		U-100 prefilled pen	\$447	\$358	
• Inhaled insulin	Inhalation cartridges	\$993	\$606		
Short-acting	• Human Regular	U-100 vial	\$165 (\$165, \$178)	\$135 (\$135, \$146)	
Intermediate-acting	• Human NPH	U-100 vial	\$165 (\$165, \$178)	\$135 (\$135, \$144)	
		U-100 prefilled pen	\$377	\$304	
Concentrated Human Regular insulin	• U-500 Human Regular insulin	U-500 vial	\$178	\$142	
		U-500 prefilled pen	\$230	\$184	
Basal analogs	• Glargine biosimilar	U-100 prefilled pen	\$261	\$209	
		• Glargine	U-100 vial; U-100 prefilled pen	\$323	\$259
			U-300 prefilled pen	\$331	\$266
	• Detemir	U-100 vial; U-100 prefilled pen	\$353	\$281	
		• Degludec	U-100 prefilled pen; U-200 prefilled pen	\$388	\$310
	Premixed insulin products	• NPH/Regular 70/30	U-100 vial	\$165 (\$165, \$178)	\$135 (\$135, \$144)
U-100 prefilled pen			\$377	\$306	
• Lispro 50/50		U-100 vial	\$342	\$274	
		U-100 prefilled pen	\$424	\$340	
• Lispro 75/25		U-100 vial	\$342	\$273	
		U-100 prefilled pen	\$424	\$340	
• Aspart 70/30		U-100 vial	\$360	\$288	
		U-100 prefilled pen	\$447	\$358	
Premixed insulin/GLP-1 receptor agonist products	• Degludec/Liraglutide	100/3.6 prefilled pen	\$793	\$638	
	• Glargine/Lixisenatide	100/33 prefilled pen	\$537	\$431	

AWP, average wholesale price; GLP-1, glucagon-like peptide 1; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in Table 9.2; median listed alone when only one product and/or price.

mol) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia), even at diagnosis or early in the course of treatment (Fig. 9.2). As glucose toxicity resolves, simplifying the regimen and/or changing to oral agents is often possible.

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 suggests that each new class of noninsulin agents added to initial therapy generally lowers A1C approximately 0.7–1.0% (46). If the A1C target is not achieved after approximately 3 months and the patient *does not* have ASCVD or CKD, consider a combination of metformin and any one of the

preferred six treatment options: sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin; the choice of which agent to add is based on drug-specific effects and patient factors (Fig. 9.1 and Table 9.1). For patients in whom ASCVD, HF, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated cardiovascular risk reduction, after consideration of drug-specific and patient factors (Table 9.1). For patients without established ASCVD or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence. Rather, drug choice is based on avoidance of side effects, particularly hypoglycemia and weight gain, cost, and patient preferences (47). Similar

considerations are applied in patients who require a third agent to achieve glycemic goals; there is also very little trial-based evidence to guide this choice. In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and patient burden (Table 9.1). In some instances, patients will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, intolerable side effects, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). See Section 12 “Older Adults” for a full discussion of treatment considerations in older adults.

Even though most patients prefer oral medications to drugs that need to be injected, the eventual need for the greater potency of injectable medications

is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent regimens is a well-established approach that is effective for many patients. In addition, recent evidence supports the utility of GLP-1 receptor agonists in patients not reaching glycemic targets with oral agent regimens. In trials comparing the addition of GLP-1 receptor agonists or insulin in patients needing further glucose lowering, the efficacy of the two treatments was similar (48–50). However, GLP-1 receptor agonists had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support a GLP-1 receptor agonist as the preferred option for patients requiring the potency of an injectable therapy for glucose control (Fig. 9.2). However, high costs and tolerability issues are important barriers to the use of GLP-1 receptor agonists.

Cost-effectiveness models of the newer agents based on clinical utility and glycemic effect have been reported (51). Table 9.2 provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (52) and National Average Drug Acquisition Costs (NADAC) (53) 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 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.

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in patients with type 2 diabetes treated with an SGLT2 inhibitor (empagliflozin, canagliflozin) or GLP-1 receptor agonist (liraglutide, semaglutide). In people with diabetes with established ASCVD, empagliflozin decreased a composite three-point major cardiovascular event (MACE) outcome and mortality compared with placebo (54). Similarly, canagliflozin reduced the occurrence

of MACE in a group of subjects with, or at high risk for, ASCVD (55). In both of these trials, SGLT2 inhibitors reduced hospitalization for HF (54,55); this was a secondary outcome of these studies and will require confirmation in more defined populations. In people with type 2 diabetes with ASCVD or increased risk for ASCVD, the addition of liraglutide decreased MACE and mortality (56), and the closely related GLP-1 receptor agonist semaglutide also had favorable effects on cardiovascular end points in high-risk subjects (57). In these cardiovascular outcomes trials, empagliflozin, canagliflozin, liraglutide, and semaglutide all had beneficial effects on composite indices of CKD (54–57). See ANTIHYPERGLYCEMIC THERAPIES AND CARDIOVASCULAR OUTCOMES in Section 10 “Cardiovascular Disease and Risk Management” and Table 10.4 for a detailed description of these cardiovascular outcomes trials, as well as a discussion of how HF may impact treatment choices. See Section 11 “Microvascular Complications and Foot Care” for a detailed discussion on how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

The subjects enrolled in the cardiovascular outcomes trials using empagliflozin, canagliflozin, liraglutide, and semaglutide had A1C $\geq 7\%$, and more than 70% were taking metformin at baseline. Moreover, the benefit of treatment was less evident in subjects with lower risk for ASCVD. Thus, extension of these results to practice is most appropriate for people with type 2 diabetes and established ASCVD who require additional glucose-lowering treatment beyond metformin and lifestyle management. For these patients, incorporating one of the SGLT2 inhibitors or GLP-1 receptor agonists that have been demonstrated to reduce cardiovascular events is recommended (Table 9.1).

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy (Fig. 9.2). See the section above, INSULIN INJECTION TECHNIQUE, for important guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients, and providers

should avoid using insulin as a threat or describing it as a sign of personal failure or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of oral agents should be emphasized. Educating and involving patients in insulin management is beneficial. Instruction of patients in self-titration of insulin doses based on self-monitoring of blood glucose improves glycemic control in patients with type 2 diabetes initiating insulin (58). Comprehensive education regarding self-monitoring of blood glucose, diet, and the avoidance 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 and can be added to metformin and other oral agents. Starting doses can be estimated based on body weight (e.g., 10 units a day or 0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production, with a goal of maintaining euglycemia overnight and between meals (59,60). Control of fasting glucose can be achieved with human NPH insulin or with the use of a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine or detemir) have been demonstrated to reduce the risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin (61–66), although these advantages are generally modest and may not persist (67). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral agents (68–74). Despite evidence for reduced hypoglycemia with newer, longer-acting basal insulin analogs in clinical trial settings, in practice they may not affect the development of hypoglycemia compared with NPH insulin (75).

The cost of insulin has been rising steadily, and at a pace several fold that of other medical expenditures, over the past decade (76). This expense contributes significant burden to the patient as insulin has become a growing “out-of-pocket” cost for people with diabetes, and direct patient costs

contribute to treatment nonadherence (76). Therefore, consideration of cost is an important component of effective management. For many patients with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), human insulin (NPH and Regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (77). **Table 9.3** provides AWP (52) and NADAC (53) information (cost per 1,000 units) for currently available insulin and insulin combination products in the U.S. As stated for **Table 9.2**, AWP and NADAC prices listed do not account for discounts, rebates, or other price adjustments that may affect the actual cost to the patient. For example, human regular insulin, NPH, and 70/30 NPH/Regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.3** at select pharmacies.

Prandial Insulin

Individuals with type 2 diabetes may require doses of insulin before meals in addition to basal insulin. The recommended starting dose of mealtime insulin is either 4 units or 10% of the basal dose at each meal. Titration is done based on home glucose monitoring or A1C. With significant additions to the prandial insulin dose, particularly with the evening meal, consideration should be given to decreasing the basal insulin dose. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in patients with type 2 diabetes have not reported important differences in A1C or hypoglycemia (78,79).

Premixed Insulin

Premixed insulin products contain both a basal and prandial component, allowing coverage of both basal and prandial needs with a single injection. The NPH/Regular premix 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 is, by definition, five times more concentrated than U-100 regular insulin. Regular U-500 has distinct

pharmacokinetics with delayed onset and longer duration of action, characteristics more like an intermediate-acting insulin. U-300 glargine and U-200 degludec are three and two times as concentrated, respectively, 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 but modestly lower efficacy per unit administered (80,81). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL). These concentrated preparations may be more convenient and comfortable for patients to inject and may improve adherence in those 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 limited dosing range; studies in people with type 1 diabetes suggest rapid pharmacokinetics (20). A pilot study found evidence that compared with injectable rapid-acting insulin, supplemental doses of inhaled insulin taken based on postprandial glucose levels may improve blood glucose management without additional hypoglycemia or weight gain, although results from a larger study are needed for confirmation (82).

Inhaled insulin 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. All patients require spirometry (FEV₁) testing to identify potential lung disease prior to and after starting inhaled insulin 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. 9.2**). This approach can use a GLP-1 receptor agonist added to basal insulin or multiple doses of insulin. The combination of basal insulin and GLP-1 receptor agonist has potent glucose-

lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens (83–85). Two different once-daily fixed-dual combination products containing basal insulin plus a GLP-1 receptor agonist are available: insulin glargine plus lixisenatide and insulin degludec plus liraglutide.

Intensification of insulin treatment can be done by adding doses of prandial to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a regimen with multiple prandial doses if necessary (86). Alternatively, in a patient on basal insulin in whom additional prandial coverage is desired, the regimen can be converted to two or three doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal/prandial regimens offer greater flexibility for patients who eat on irregular schedules. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately or as premixed NPH/Regular (70/30) formulations, are less costly alternatives to insulin analogs. **Figure 9.2** outlines these options, as well as recommendations for further intensification, if needed, to achieve glycemic goals.

When initiating combination injectable therapy, metformin therapy should be maintained while sulfonylureas and DPP-4 inhibitors are typically discontinued. In patients with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once a basal/bolus 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). As people with type 2 diabetes get older, it may become necessary to simplify complex insulin regimens because of a decline in self-management ability (see Section 12 “Older Adults”).

References

1. Peters A, 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. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. *J Diabetes Sci Technol* 2013;7:1567–1574
8. 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
9. Buckingham BA, Raghinaru D, Cameron F, et al.; In Home Closed Loop Study Group. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. *Diabetes Care* 2015;38:1197–1204
10. 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
11. 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
12. Cleary PA, Orchard TJ, Genuth S, et al.; DCCT/EDIC Research Group. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes* 2006;55:3556–3565
13. 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
14. 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
15. 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
16. 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
17. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003;289:2254–2264
18. Lane W, Bailey TS, Gerety G, et al.; Group Information; 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
19. 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
20. 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
21. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. *Mayo Clin Proc* 2016;91:1231–1255
22. Karges B, Boehm BO, Karges W. Early hypoglycaemia after accidental intramuscular injection of insulin glargine. *Diabet Med* 2005;22:1444–1445
23. Frid A, Gunnarsson R, Güntner P, Linde B. Effects of accidental intramuscular injection on insulin absorption in IDDM. *Diabetes Care* 1988;11:41–45
24. Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. *Curr Med Res Opin* 2010;26:1519–1530
25. Hirsch LJ, Gibney MA, Albanese J, et al. Comparative glycemic control, safety and patient ratings for a new 4 mm × 32G insulin pen needle in adults with diabetes. *Curr Med Res Opin* 2010;26:1531–1541
26. Miwa T, Itoh R, Kobayashi T, et al. Comparison of the effects of a new 32-gauge × 4-mm pen needle and a 32-gauge × 6-mm pen needle on glycemic control, safety, and patient ratings in Japanese adults with diabetes. *Diabetes Technol Ther* 2012;14:1084–1090
27. Bergenstal RM, Strack ES, Peremislav D, Gibney MA, Parvu V, Hirsch LJ. Safety and efficacy of insulin therapy delivered via a 4mm pen needle in obese patients with diabetes. *Mayo Clin Proc* 2015;90:329–338
28. Famulla S, Hövelmann U, Fischer A, et al. Insulin injection into lipohypertrophic tissue: blunted and more variable insulin absorption and action and impaired postprandial glucose control. *Diabetes Care* 2016;39:1486–1492
29. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004;21:1204–1212
30. Edelman S, Garg S, Frias J, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. *Diabetes Care* 2006;29:2189–2195
31. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Metab Res Rev* 2018;34:e2983
32. 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
33. Wang W, Liu H, Xiao S, Liu S, Li X, Yu P. Effects of insulin plus glucagon-like peptide-1 receptor agonists (GLP-1RAs) in treating type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Ther* 2017;8:727–738
34. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* 2015;38:2258–2265
35. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;5:864–876
36. Patoulias D, Imprialos K, Stavropoulos K, Athyros V, Doumas M. SGLT-2 inhibitors in type 1 diabetes mellitus: a comprehensive review of the literature. *Curr Clin Pharmacol*. 7 August 2018 [Epub ahead of print]. DOI: 10.2174/1574884713666180807150509
37. Lexicon Pharmaceuticals. FDA to review Zynquista™ (sotagliflozin) as potential treatment for type 1 diabetes [Internet], 2018. Available from <http://www.lexipharma.com/media-center/news/673-fda-to-review-zynquista-sotagliflozin-as-potential-treatment-for-type-1-diabetes>. Accessed 30 September 2018
38. 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
39. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–2701
40. 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
41. 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

42. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function [Internet]. Available from <http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm>. Accessed 14 October 2016
43. Out M, Kooy A, Leher P, Schalkwijk CA, Stehouwer CDA. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: post hoc analysis of a randomized controlled 4.3 year trial. *J Diabetes Complications* 2018;32:171–178
44. 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
45. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. *Int J Clin Pract* 2012;66:446–456
46. 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
47. 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
48. Singh S, Wright EE Jr, Kwan AYM, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab* 2017;19:228–238
49. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. *Diabetes Metab Syndr Obes* 2017;10:123–139
50. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes Metab* 2017;19:216–227
51. Institute for Clinical and Economic Review. Controversies in the management of patients with type 2 diabetes [Internet], December 2014. Available from <https://icer-review.org/wp-content/uploads/2015/03/CEPAC-T2D-Final-Report-December-22.pdf>. Accessed 9 November 2018
52. Truven Health Analytics. Micromedex 2.0 Introduction to RED BOOK Online [Internet], 2018. Available from http://www.micromedexolutions.com/micromedex2/4.34.0/WebHelp/RED_BOOK/Introduction_to_REDB_BOOK_Online.htm. Accessed 5 September 2018
53. Centers for Medicare & Medicaid Services. NADAC (national average drug acquisition cost), drug pricing and payment [Internet], 2018. Available from <https://data.medicare.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d>. Accessed 5 September 2018
54. 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
55. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657
56. 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
57. Marso SP, Bain SC, Consoi A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
58. 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
59. Porcellati F, Lucidi P, Cioli P, et al. Pharmacokinetics and pharmacodynamics of insulin glargine given in the evening as compared with in the morning in type 2 diabetes. *Diabetes Care* 2015;38:503–512
60. Wang Z, Hedrington MS, Gogitidze Joy N, et al. Dose-response effects of insulin glargine in type 2 diabetes. *Diabetes Care* 2010;33:1555–1560
61. 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
62. 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
63. 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
64. 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 100 U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy. *Diabetes Res Clin Pract* 2017;124(Suppl. C):57–65
65. 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
66. Hermansen K, Davies M, Dereziński T, Martínez 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-naïve people with type 2 diabetes. *Diabetes Care* 2006;29:1269–1274
67. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006;49:442–451
68. 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
69. 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
70. 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
71. Marso SP, McGuire DK, Zinman B, et al.; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 2017;377:723–732
72. Rodbard HW, Cariou B, Zinman B, et al.; BEGIN Once Long trial investigators. Comparison of insulin degludec with insulin glargine in insulin-naïve subjects with type 2 diabetes: a 2-year randomized, treat-to-target trial. *Diabet Med* 2013;30:1298–1304
73. 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
74. Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care* 2012;35:2464–2471
75. Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of initiation of basal insulin analogs vs neutral protamine Hagedorn insulin with hypoglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. *JAMA* 2018;320:53–62
76. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Insulin Access and Affordability Working Group: conclusions and recommendations. *Diabetes Care* 2018;41:1299–1311
77. Lipska KJ, Hirsch IB, Riddle MC. Human insulin for type 2 diabetes: an effective, less-expensive option. *JAMA* 2017;318:23–24
78. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. *Diabetes Obes Metab* 2009;11:53–59
79. Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. *J Diabetes* 2013;5:482–491
80. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab* 2015;17:835–842

81. Yki-Järvinen H, Bergenstal R, Ziemer M, et al.; EDITION 2 Study Investigators. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care* 2014;37:3235–3243
82. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. *Diabetes Technol Ther* 2018;20:639–647
83. 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
84. 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
85. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care* 2017;40:614–624
86. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DHW. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. *Lancet Diabetes Endocrinol* 2014;2:30–37