7. Approaches to Glycemic Treatment

American Diabetes Association

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PHARMACOLOGICAL THERAPY FOR TYPE 1 DIABETES

Recommendations

- Most people with type 1 diabetes should be treated with multiple-dose insulin injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. **A**
- Consider educating individuals with type 1 diabetes on matching prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. **E**
- Most individuals with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. **A**
- Individuals who have been successfully using continuous subcutaneous insulin infusion should have continued access after they turn 65 years of age. **E**

Insulin Therapy

Insulin is the mainstay of therapy for individuals with type 1 diabetes. There are excellent reviews to guide the initiation and management of insulin therapy to achieve desired glycemic goals (1). Although most studies of multiple-dose insulin versus pump therapy 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 (2). A large 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 values (3). Intensive management through pump therapy/continuous glucose monitoring and active patient/family participation should be strongly encouraged (4–6). Selected individuals who have mastered carbohydrate counting should be educated that fat increases glucose concentrations and insulin requirements (7).

The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive insulin therapy (three or more injections per day of insulin) or continuous subcutaneous insulin infusion (CSII) (insulin pump therapy) was a key part of improved glycemia and better outcomes (8,9). The study was carried out with short-acting and intermediate-acting human insulins. Despite better microvascular, macrovascular, and all-cause mortality outcomes, intensive insulin therapy was associated with a high rate of severe hypoglycemia (62 episodes per 100 patient-years of therapy). Since the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs are associated with less hypoglycemia in type 1 diabetes, while matching the A1C lowering of human insulins (10,11).

Rapid-acting inhaled insulin used before meals in type 1 diabetes leads to inferior A1C lowering when compared with aspart insulin, with less hypoglycemia across all A1C target categories (12).

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

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Recommended therapy for type 1 diabetes consists of the following:

1. Multiple-dose insulin injections (three to four injections per day of basal and prandial insulin) or CSII therapy.
2. Match prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated physical activity.
3. For most patients (especially those at elevated risk of hypoglycemia), use insulin analogs.
4. For patients with frequent nocturnal hypoglycemia, recurrent severe hypoglycemia, and/or hypoglycemia unawareness, a sensor-augmented low glucose threshold suspend pump may be considered.

Pramlintide

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

Pancreas and Islet Cell Transplantation

Pancreas and islet cell transplantation have been shown to normalize glucose levels but require lifelong immunosuppression to prevent graft rejection and recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite aggressive glycemic management (13). Islet cell transplantation remains investigational. Autoislet transplantation may be considered for patients requiring total pancreatectomy who meet eligibility criteria.

Investigational Agents

Metformin

Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/obese patients with poorly controlled type 1 diabetes. In a meta-analysis, metformin in type 1 diabetes was found to reduce insulin requirements (6.6 units/day, $P < 0.001$) and led to small reductions in weight and total and LDL cholesterol but not to improved glycemic control (absolute A1C reduction 0.11%, $P = 0.42$) (14).

Incretin-Based Therapies

Therapies approved for the treatment of type 2 diabetes are currently being evaluated in type 1 diabetes. Glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors are not currently FDA approved for those with type 1 diabetes but are being studied in this population.

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. There are three FDA-approved agents for use in patients with type 2 diabetes, but there are insufficient data to recommend treatment in type 1 diabetes (15). The FDA recently issued a warning about the risk of ketoacidosis with SGLT2 inhibitors in individuals with type 1 or type 2 diabetes. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and dyspnea. Urinary tract infections leading to urosepsis and pyelonephritis may also occur with SGLT2 inhibitors. Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have symptoms of ketoacidosis (16).

PHARMACOLOGICAL THERAPY FOR TYPE 2 DIABETES

Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. **A**
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C. **E**
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, then add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin. **A**
- A patient-centered approach should be used to guide the choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences. **E**
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed. **B**

An American Diabetes Association/European Association for the Study of Diabetes position statement (17) evaluated the data and developed recommendations, including advantages and disadvantages, for antihyperglycemic agents for patients with type 2 diabetes. A patient-centered approach is stressed, including patient preferences, cost, and potential side effects of each class, effects on body weight, and hypoglycemia risk. Lifestyle modifications that improve health (see Section 3 "Foundations of Care and Comprehensive Medical Evaluation") should be emphasized along with any pharmacological therapy.

Initial Therapy

Most patients should begin with lifestyle changes, which may include lifestyle counseling, setting a physical activity goal of 150 min/week minimum, and weight loss counseling to lose a minimum of 7% of body weight (for details on lifestyle therapy, see Section 6 "Obesity Management for the Treatment of Type 2 Diabetes"). When lifestyle efforts alone do not achieve or maintain glycemic goals, metformin monotherapy should be added at, or soon after, diagnosis, unless there are contraindications or intolerance. Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and may reduce risk of cardiovascular events and death (18). Accumulating observational data suggest that metformin may be safely continued down to glomerular filtration rate (GFR) of 45 mL/min/1.73 m^2 or even 30 mL/min/1.73 m^2 (19). If metformin is used in the lower GFR range, the dose should be reduced and patients should be advised to stop the medication for nausea, vomiting, and dehydration. In patients with metformin intolerance or contraindications, consider an initial drug from other classes depicted in **Fig. 7.1** under "Dual therapy" and proceed accordingly.

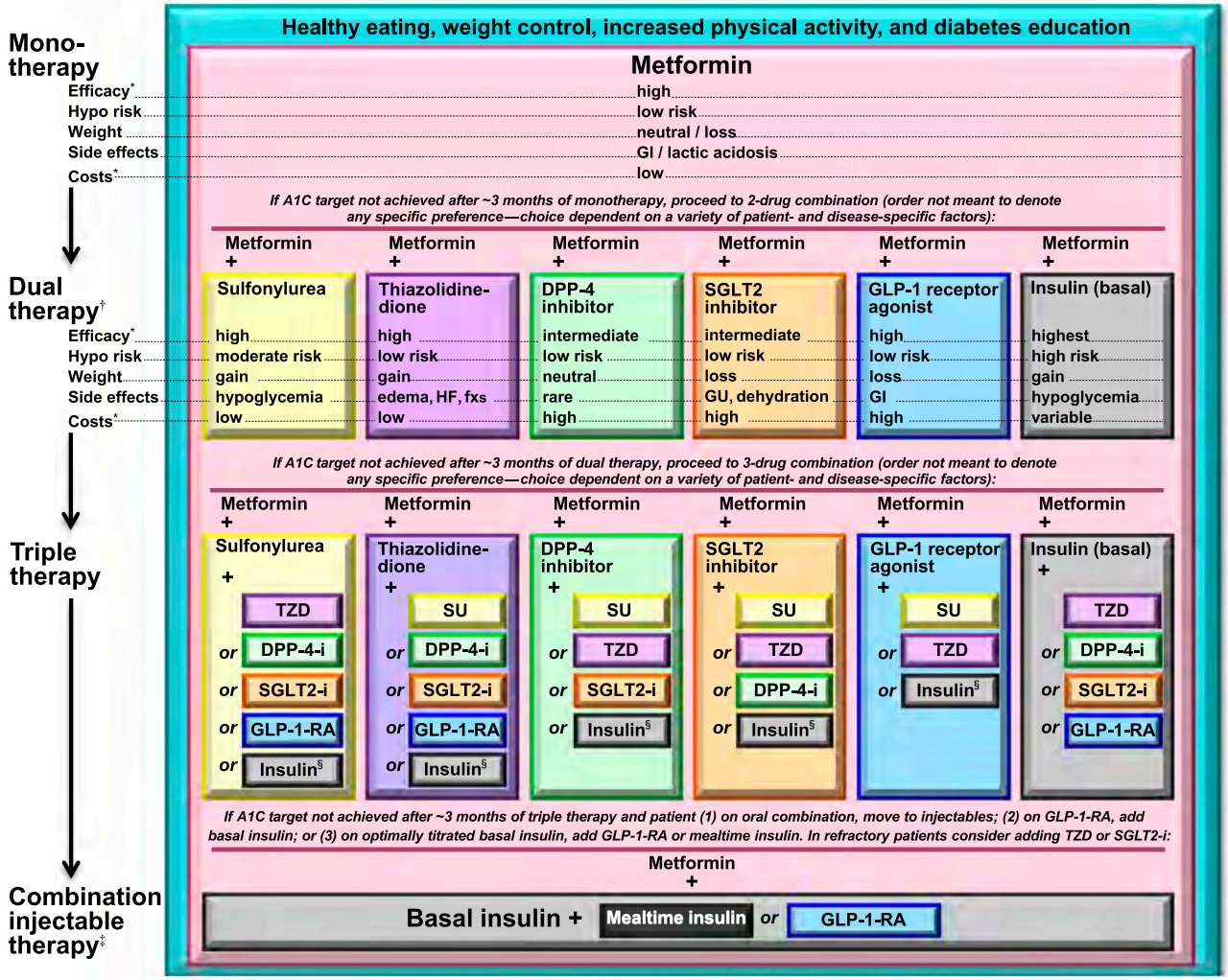

Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (17). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. *See ref. 17 for description of efficacy categorization. †Consider starting at this stage when A1C is ≥9% (75 mmol/mol). ‡Consider starting at this stage when blood glucose is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12% (86–108 mmol/mol), especially if symptomatic or catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (17).

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 (20) suggests that overall each new class of noninsulin agents added to initial therapy lowers A1C around 0.9–1.1%. A comprehensive listing, including the cost, is available in **Table 7.1.** The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) will compare the effect of four major drug classes (sulfonylurea, DPP-4 inhibitor, GLP-1 analog, and basal insulin) over 4 years on glycemic control and other medical, psychosocial, and health economic outcomes (21).

If the A1C target is not achieved after approximately 3 months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors (22), SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin (**Fig. 7.1**). Drug choice is based on patient preferences (23), as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. **Figure 7.1** emphasizes drugs commonly used in the U.S. and/or Europe. Cost-effectiveness models have suggested that some of the newer agents may be low-value based on high cost and moderate glycemic effect (24).

Rapid-acting secretagogues (meglitinides) may be used instead of sulfonylureas in patients with irregular meal schedules or those who develop late postprandial hypoglycemia on a sulfonylurea. Other drugs not shown in the figure (e.g., α-glucosidase inhibitors, colesevelam, bromocriptine, pramlintide) may be tried in specific situations, but are generally not favored due to modest efficacy, the frequency of administration, and/or side effects.

For all patients, consider initiating therapy with a dual combination when A1C is ≥9% (75 mmol/mol) to more

Table 7.1—Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes (17)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	• Metformin	Activates AMP-kinase (? other)	• ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Vitamin B_{12} deficiency • Contraindications: CKD, acidosis, hypoxia, dehydration, etc. • Lactic acidosis risk (rare)	Low
Sulfonylureas	2nd Generation • Glyburide/ glibenclamide • Glipizide • Gliclazide† • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • ↑ Weight	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↑ HDL-C • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive, pioglitazone)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • ? ↑ MI (meta-analyses, rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	• Slows intestinal carbohydrate digestion/absorption	• No hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Low to moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin† • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent)	• No hypoglycemia • Well tolerated	• Angioedema/urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ? ↑ Heart failure hospitalizations	High
Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Generally modest A1C efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High

Continued on p. S56

Table 7.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of type 2 diabetes • Associated with lower CVD event rate and mortality in patients with CVD (EMPA-REG OUTCOME)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/ dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide† • Dulaglutide	Activates GLP-1 receptors	• ↑ Insulin secretion (glucose dependent) • ↓ Glucagon secretion (glucose dependent) • Slows gastric emptying • ↑ Satiety	• No hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors	• Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High
Amylin mimetics	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Generally modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro - Aspart - Glulisine - Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH • Basal insulin analogs - Glargine - Detemir - Degludec† • Premixed (several types)	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Mitogenic effects • Training requirements • Patient reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	Moderate to high#

CKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (31); GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; MI, myocardial infarction; PPAR-γ, peroxisome proliferator–activated receptor γ; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events (32); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (33); TZD, thiazolidinedione; UKPDS, UK Prospective Diabetes Study (34,35). Cycloset trial of quick-release bromocriptine (36). *Cost is based on lowest-priced member of the class (see ref. 17). †Not licensed in the U.S. ‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study. §Not licensed in Europe for type 2 diabetes. #Cost is highly dependent on type/brand (analogs > human insulins) and dosage. Adapted with permission from Inzucchi et al. (17).

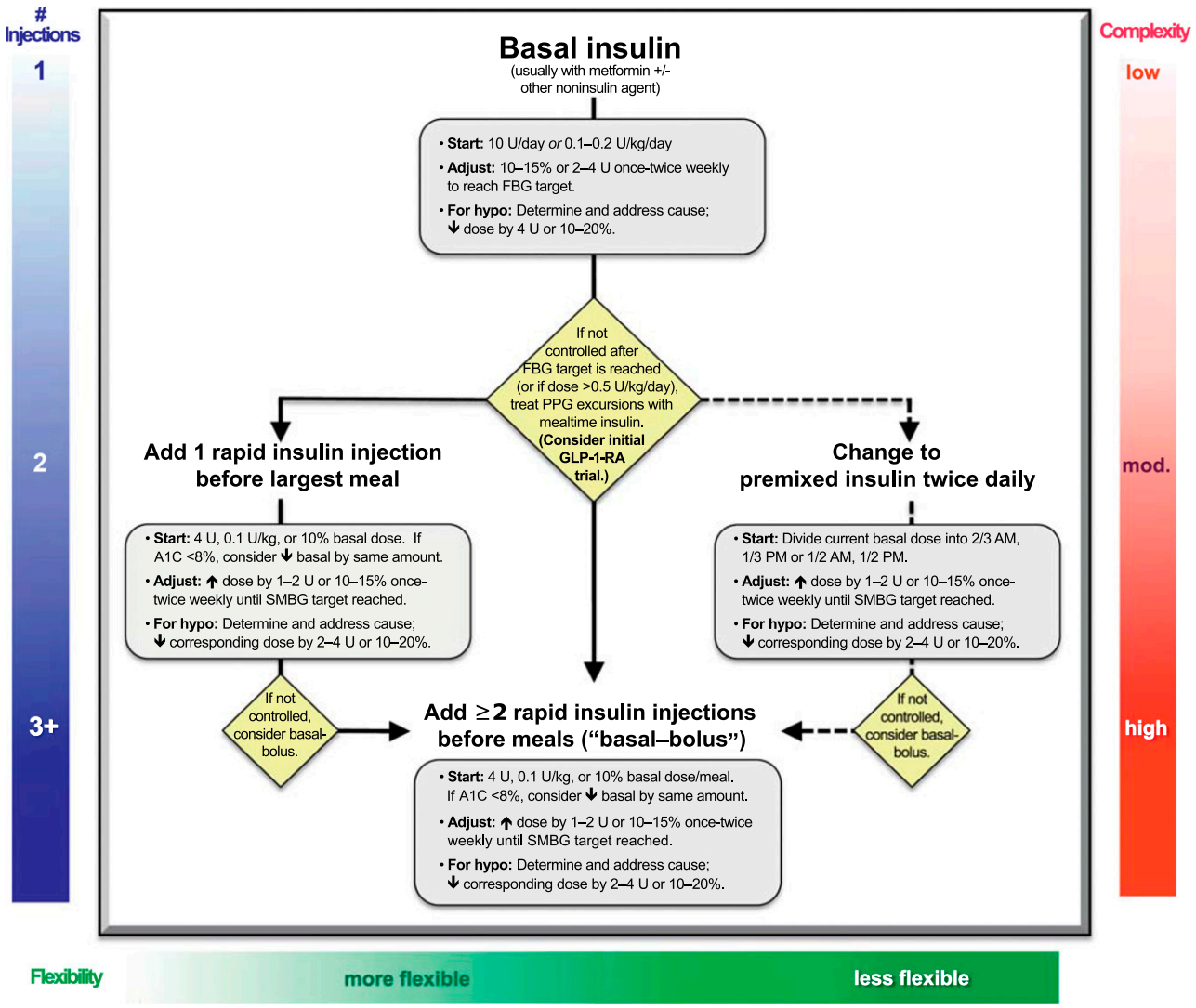

Figure 7.2—Approach to starting and adjusting insulin in type 2 diabetes (17). FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo, hypoglycemia; mod., moderate; PPG, postprandial glucose; #, number. Adapted with permission from Inzucchi et al. (17).

expeditiously achieve the target A1C level. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms are present or any catabolic features (weight loss, ketosis) are present. Consider initiating combination insulin injectable therapy when blood glucose is ≥300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥10–12% (86–108 mmol/mol). As the patient's glucose toxicity resolves, the regimen may, potentially, be simplified.

Insulin Therapy

Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C. Many patients with type 2 diabetes eventually require and benefit from insulin therapy. 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 (**Fig. 7.2**). The progressive nature of type 2 diabetes and its therapies should be regularly and objectively explained to patients. For patients with type 2 diabetes who are not achieving glycemic goals, providers should promptly initiate insulin therapy.

Providers should avoid using insulin as a threat or describing it as a failure or punishment. Equipping patients with an algorithm for self-titration of insulin doses based on self-monitoring of blood glucose (SMBG) improves glycemic control in patients with type 2 diabetes initiating insulin (25).

Basal Insulin

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 units or 0.1–0.2 units/kg, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and possibly one additional noninsulin agent. While there is evidence for reduced risk of hypoglycemia with newer, longer-acting, basal insulin analogs, people with type 2 diabetes without history of hypoglycemia or severe hypoglycemia may use NPH safely at much lower cost (24,26). Concentrated preparation of basal insulin such as U-500 regular is five times as potent per volume of insulin (i.e.,

0.01 mL ~5 units of U-100 regular) and has a delayed onset and longer duration of action than U-100 regular. U-300 glargine and U-200 degludec are three and two times, respectively, as potent per volume, have a longer duration of action, and may allow higher doses of insulin administration in smaller volumes. These concentrated preparations may be more comfortable for the patient and allow better absorption. However, they are more expensive, and accurate dosing may be more complicated.

If basal insulin has been titrated to an acceptable fasting blood glucose level, but A1C remains above target, consider advancing to combination injectable therapy (**Fig. 7.2**) to cover postprandial glucose excursions. Options include adding a GLP-1 receptor agonist (27) or mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (lispro, aspart, or glulisine) administered just before eating. A less studied alternative, transitioning from basal insulin to twice-daily premixed (or biphasic) insulin analogs (70/30 aspart mix, 75/25 or 50/50 lispro mix), could also be considered; pharmacodynamic profiles make them suboptimal to cover postprandial glucose excursions.

Bolus Insulin

Some individuals with type 2 diabetes may require bolus insulin dosing in addition to basal insulin. Rapid-acting analogs are preferred due to their prompt onset of action after dosing. The FDA recently approved a more concentrated formulation of rapid-acting insulin analog, U-200 (200 units/mL), dosed 15 min or immediately prior to a meal.

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 make them suboptimal to cover postprandial glucose excursions.

Continuous Subcutaneous Insulin Infusion

A less commonly used and more costly alternative to "basal–bolus" therapy with multiple daily injections is CSII (insulin pump) (28,29). In addition to the suggestions provided for determining the starting dose of mealtime insulin under a basal–bolus regimen, another method consists of adding up the total current insulin dose and then providing one-half of this amount as basal and one-half as mealtime insulin, the latter split evenly between three meals. It is critical that individuals who have been successfully using CSII should have continued access after they turn 65 years of age (30).

Inhaled Insulin

Inhaled insulin is now available for prandial use with a more limited dosing range and may require serial lung function testing prior to and after starting therapy.

Treatment Strategies

Figure 7.2 focuses solely on sequential insulin strategies, describing the number of injections and the relative complexity and flexibility of each stage. Once an insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the prevailing blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control).

Noninsulin agents may be continued, although 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 increasing insulin doses, adjunctive use of thiazolidinediones (usually pioglitazone) or SGLT2 inhibitors may be helpful in improving control and reducing the amount of insulin needed. Comprehensive education regarding SMBG, diet, exercise, and the avoidance of and response to hypoglycemia are critically important in any patient using insulin.

BARIATRIC SURGERY

Bariatric surgery also improves glycemic control in type 2 diabetes. Its effects are discussed in Section 6 "Obesity Management for the Treatment of Type 2 Diabetes."

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