7. Approaches to Glycemic Treatment

American Diabetes Association

Diabetes Care 2015;38(Suppl. 1):S41–S48 | DOI: 10.2337/dc15-S010

PHARMACOLOGICAL THERAPY FOR TYPE 1 DIABETES

Recommendations

- Most people with type 1 diabetes should be treated with multiple-dose insulin (MDI) injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII). **A**
- Most people with type 1 diabetes should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. **E**
- Most people with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. **A**

Insulin Therapy

There are excellent reviews to guide the initiation and management of insulin therapy to achieve desired glycemic goals (1,2,3). Although most studies of MDI versus pump therapy have been small and of short duration, a systematic review and meta-analysis concluded that there were no systematic differences in A1C or severe hypoglycemia rates in children and adults between the two forms of intensive insulin therapy (4). A large randomized trial in type 1 diabetic patients with nocturnal hypoglycemia reported that sensor-augmented insulin pump therapy with the threshold suspend feature reduced nocturnal hypoglycemia, without increasing glycated hemoglobin values (5). Overall, intensive management through pump therapy/continuous glucose monitoring and active patient/family participation should be strongly encouraged (6–8). For selected individuals who have mastered carbohydrate counting, education on the impact of protein and fat on glycemic excursions can be incorporated into diabetes management (9).

The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive insulin therapy (three or more injections per day of insulin) or CSII (insulin pump therapy) was a key part of improved glycemia and better outcomes (10,11). The study was carried out with short- and intermediate-acting human insulins. Despite better microvascular 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 (1,12).

Recommended therapy for type 1 diabetes consists of the following:

1. Use MDI 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 an elevated risk of hypoglycemia), use insulin analogs.
4. For patients with frequent nocturnal 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

Suggested citation: American Diabetes Association. Approaches to glycemic treatment. Sec. 7. In Standards of Medical Care in Diabetes—2015. *Diabetes Care 2015;38(Suppl. 1):S41–S48*

Administration (FDA)-approved therapy for use in type 1 diabetes. It has been shown to induce weight loss and lower insulin dose; however, it is only indicated in adults. 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 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 U/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%, $P = 0.42$) (13).

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. Although there are two FDA-approved agents for use in patients with type 2 diabetes, there are insufficient data to recommend clinical use in type 1 diabetes at this time (14).

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**
- In patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C, consider initiating insulin therapy (with or without additional agents). **E**
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or basal insulin. **A**
- A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences. **E**
- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. **B**

An updated American Diabetes Association/European Association for the Study of Diabetes position statement (15) evaluated the data and developed recommendations, including advantages and disadvantages, for antihyperglycemic agents for type 2 diabetic patients. 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 4. Foundations of Care) should be emphasized along with any pharmacological therapy.

Initial Therapy

Most patients should begin with lifestyle changes (lifestyle counseling, weight-loss education, exercise, etc.). When lifestyle efforts alone have not achieved or maintained 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 (16). 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.

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 (17) 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**.

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, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin (**Fig. 7.1**). Drug choice is based on patient preferences 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.

Rapid-acting secretagogues (meglitinides) may be used instead of sulfonylureas in patients with irregular meal schedules or 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 $\geq$9% to more expeditiously achieve the target A1C level. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms are present or any catabolic features (weight loss, ketosis) are in evidence. Consider initiating combination insulin injectable therapy when blood glucose is $\geq$300–350 mg/dL (16.7–19.4 mmol/L) and/or A1C is $\geq$10–12%. As the patient's glucose toxicity resolves, the regimen can, potentially, be subsequently simplified.

Insulin Therapy

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. Providers should avoid using insulin as a threat or describing it as a failure

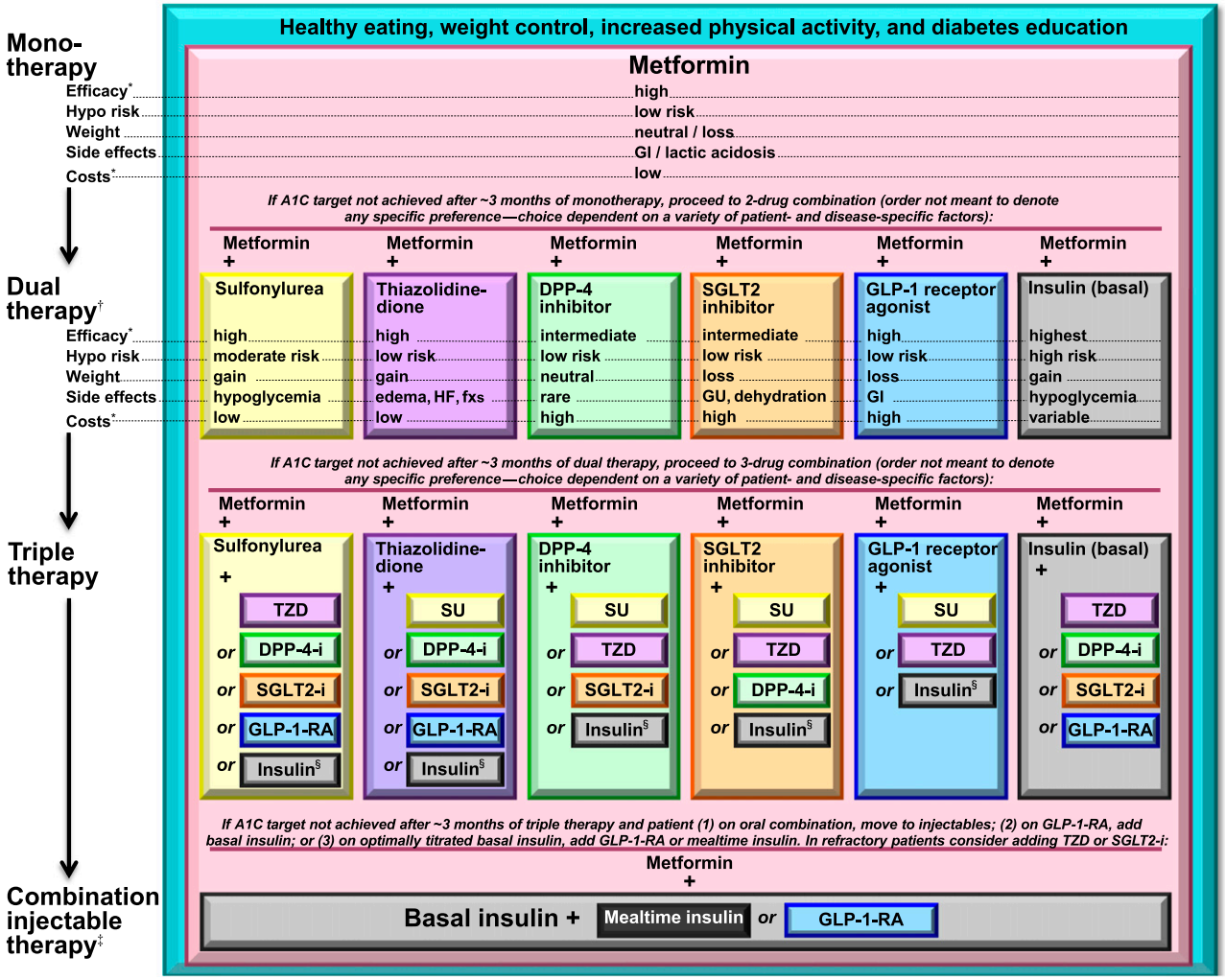

Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (15). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic 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. 15 for description of efficacy categorization. †Consider starting at this stage when A1C is ≥9%. ‡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%, 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. (15).

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 type 2 diabetic patients initiating insulin (18).

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 U or 0.1–0.2 U/kg, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and possibly one additional noninsulin agent. 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 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 analog (70/30 aspart mix, 75/25 or 50/50 lispro mix), could also be considered. 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 for the coverage of postprandial glucose excursions. A less commonly used and more costly alternative to "basal–bolus" therapy with multiple daily injections is CSII (insulin pump). 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.

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 (15)

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) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.	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 • ? Blunts myocardial ischemic preconditioning • Low durability	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	• ↑ Insulin secretion	• ↓Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • ? Blunts myocardial ischemic preconditioning • 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	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

Continued on p. S45

Table 7.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin‡ • Empagliflozin	Inhibits SGLT2 in the proximal nephron	• Blocks glucose reabsorption by the kidney, increasing glucosuria	• No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of T2DM	• Genitourinary infections • Polyuria • Volume depletion/hypotension/ dizziness • ↑ LDL-C • ↑ Creatinine (transient)	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 • 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 • Other	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Mitogenic effects • Injectable • Patient reluctance • Training requirements	Variable#

CKD, chronic kidney disease; CVD, cardiovascular disease; 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 (30); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (31); TZD, thiazolidinedione; T2DM, type 2 diabetes mellitus; UKPDS, UK Prospective Diabetes Study (32,33). Cycloset trial of quick-release bromocriptine (34). *Cost is based on lowest-priced member of the class (see ref. 15). †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. (15).

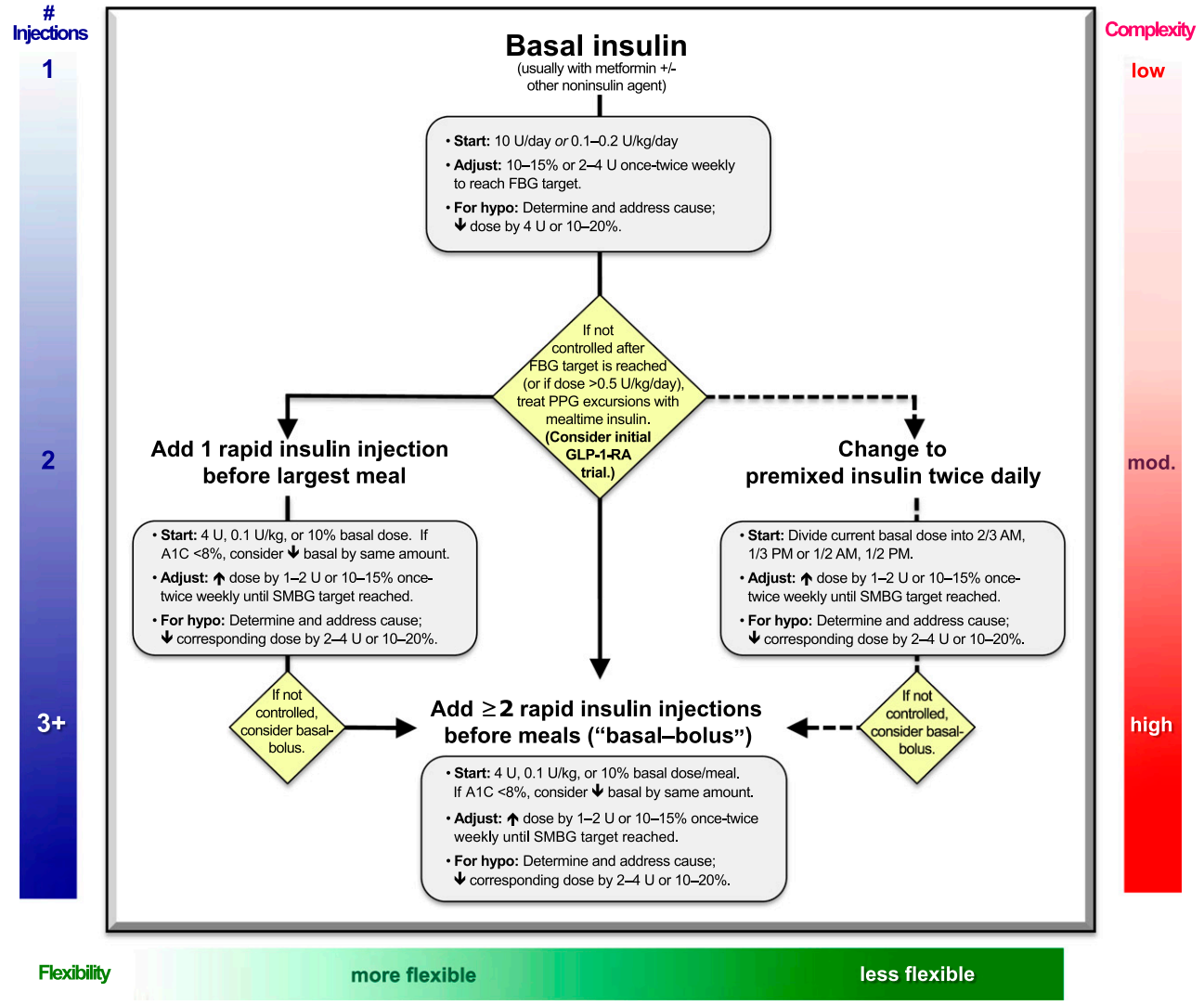

Figure 7.2—Approach to starting and adjusting insulin in type 2 diabetes (15). FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo, hypoglycemia; mod., moderate; PPG, postprandial glucose; #, number. Adapted with permission from Inzucchi et al. (15).

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

Recommendations

- Bariatric surgery may be considered for adults with BMI >35 kg/m^2 and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. **B**
- Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring. **B**
- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m^2, there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m^2. **E**

Bariatric and metabolic surgeries, either gastric banding or procedures that involve resecting, bypassing, or transposing sections of the stomach and small intestine, can be effective weight-loss treatments for severe obesity when performed as part of a comprehensive weight-management program with lifelong lifestyle support

and medical monitoring. National guidelines support consideration for bariatric surgery for people with type 2 diabetes with BMI >35 kg/m^2.

Advantages

Treatment with bariatric surgery has been shown to achieve near- or complete normalization of glycemia 2 years following surgery in 72% of patients (compared with 16% in a matched control group treated with lifestyle and pharmacological interventions) (19). A study evaluated the long-term (3-year) outcomes of surgical intervention (Roux-en-Y gastric bypass or sleeve gastrectomy) and intensive medical therapy (quarterly visits, pharmacological therapy, SMBG, diabetes education, lifestyle counseling, and encouragement to participate in Weight Watchers) compared with just intensive medical therapy on achieving a target A1C ≤6% among obese patients with uncontrolled type 2 diabetes (mean A1C 9.3%). This A1C target was achieved by 38% ($P < 0.001$) in the gastric bypass group, 24% ($P = 0.01$) in the sleeve gastrectomy group, and 5% in those receiving medical therapy (20). Diabetes remission rates tend to be higher with procedures that bypass portions of the small intestine and lower with procedures that only restrict the stomach.

Younger age, shorter duration of type 2 diabetes, lower A1C, higher serum insulin levels, and nonuse of insulin have all been associated with higher remission rates after bariatric surgery (21).

Although bariatric surgery has been shown to improve the metabolic profiles of morbidly obese patients with type 1 diabetes, the role of bariatric surgery in such patients will require larger and longer studies (22).

Disadvantages

Bariatric surgery is costly and has associated risks. Morbidity and mortality rates directly related to the surgery have decreased considerably in recent years, with 30-day mortality rates now 0.28%, similar to those for laparoscopic cholecystectomy (23). Outcomes vary depending on the procedure and the experience of the surgeon and center. Longer-term concerns include vitamin and mineral deficiencies, osteoporosis, and rare but often severe hypoglycemia from insulin hypersecretion. Cohort studies attempting to match surgical and nonsurgical subjects suggest that the procedure may reduce longer-term mortality rates (19). In contrast, a propensity score-adjusted analysis of older, severely obese patients in Veterans Affairs Medical Centers found that bariatric surgery was not associated with decreased mortality compared with usual care (mean follow-up 6.7 years) (24). Retrospective analyses and modeling studies suggest that bariatric surgery may be cost-effective for patients with type 2 diabetes, but the results are largely dependent on assumptions about the long-term effectiveness and safety of the procedures (25–27). Understanding the long-term benefits and risks of bariatric surgery in individuals with type 2 diabetes, especially those who are not severely obese, will require well-designed clinical trials, with optimal medical therapy as the comparator (28). Unfortunately, such studies may not be feasible (29).

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