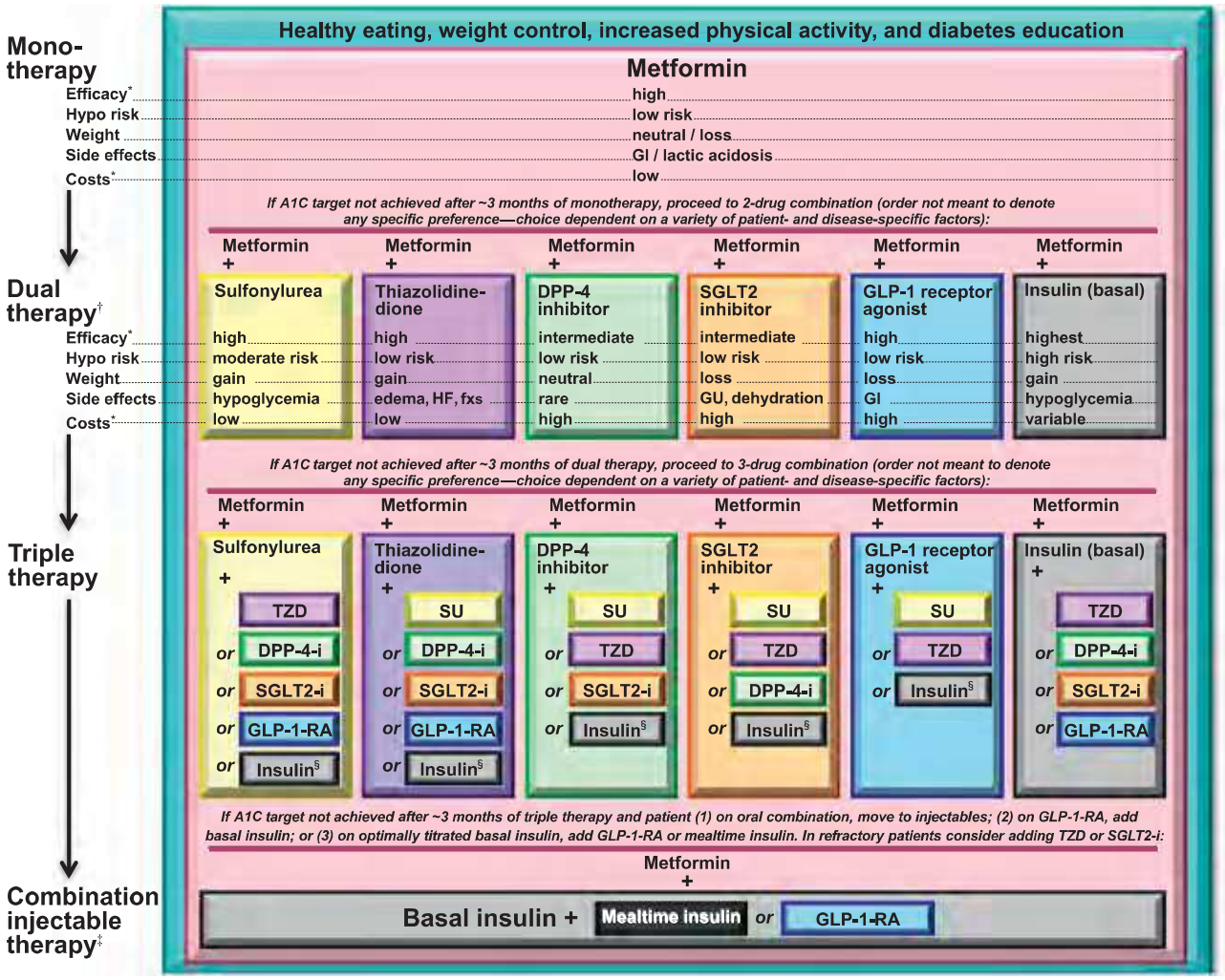

Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (17). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic 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

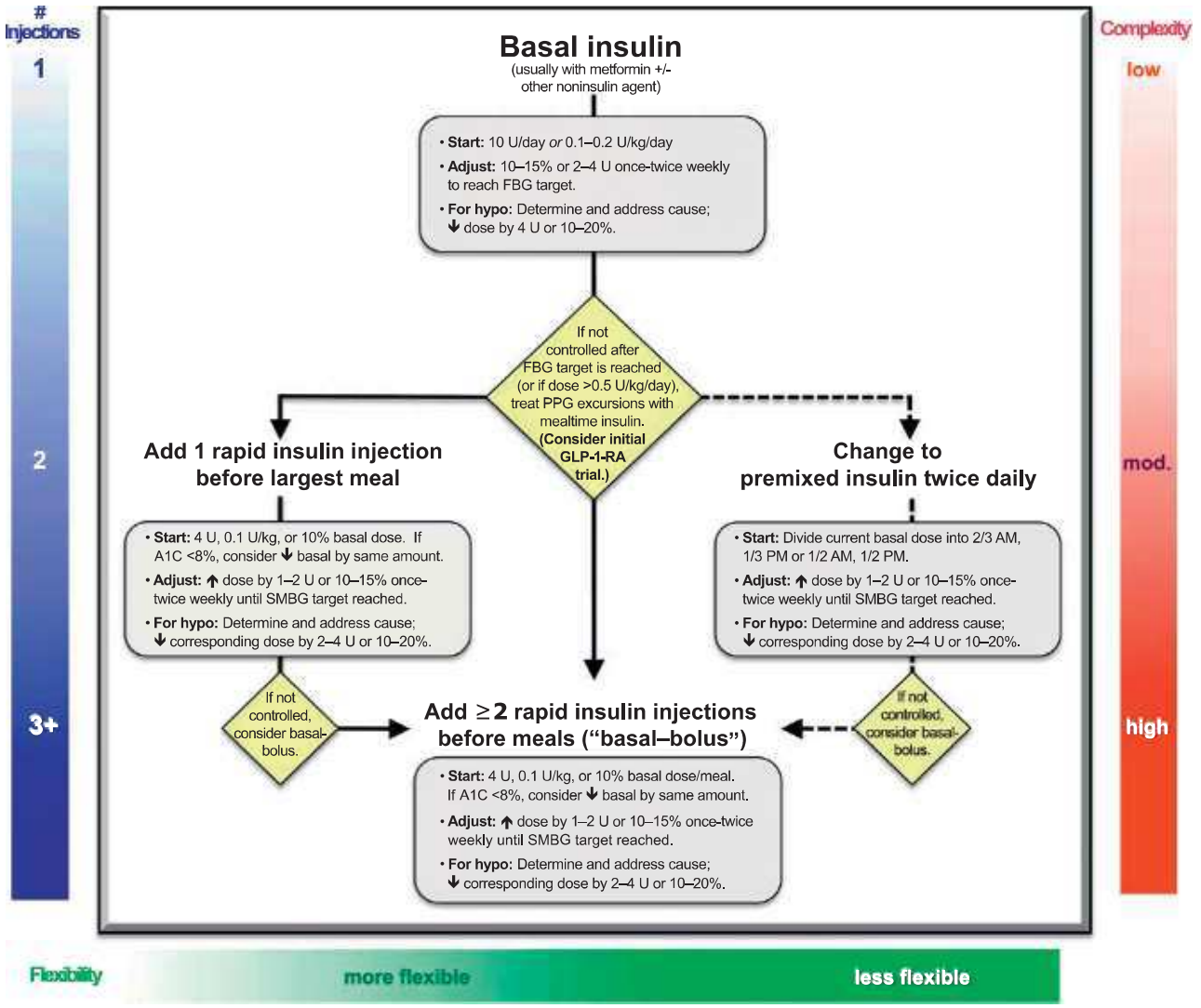

Figure 7.2—Approach to starting and adjusting insulin in type 2 diabetes (17). FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo, hypoglycemia; mod., moderate; PPG, postprandial glucose; #, number. Adapted with permission from Inzucchi et al. (17).

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 de vising 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.,