Because endogenous insulin secretion continues and is capable of providing some coverage of mealtime caloric intake, insulin is usually initiated in a single dose of long-acting insulin (0.3–0.4 U/kg per day), given in the evening (NPH) or just before bedtime (NPH, glargine, detemir). Because fasting hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM, bedtime insulin is more effective in clinical trials than a single dose of morning insulin. Glargine given at bedtime has less nocturnal hypoglycemia than NPH insulin. Some physicians prefer a relatively low, fixed starting dose of long-acting insulin (5–15 units) or a weight-based dose (0.2 units/kg). The insulin dose may then be adjusted in 10% increments as dictated by SMBG results. Both morning and bedtime long-acting insulin may be used in combination with oral glucose-lowering agents. Initially, basal insulin may be sufficient, but often prandial insulin coverage with multiple insulin injections is needed as diabetes progresses (see insulin regimens used for type 1 DM). Other insulin formulations that have a combination of short-acting and long-acting insulin (Table 418-4) are sometimes used in patients with type 2 DM because of convenience but do not allow independent adjustment of short-acting and long-acting insulin dose and often do not achieve the same degree of glycemic control as basal/bolus regimens. In selected patients with type 2 DM, insulin-infusion devices may be considered.

CHOICE OF INITIAL GLUCOSE-LOWERING AGENT The level of hyperglycemia and the patient's individualized goal (see "Establishment of Target Level of Glycemic Control") should influence the initial choice of therapy. Assuming that maximal benefit of MNT and increased physical activity has been realized, patients with mild to moderate hyperglycemia (FPG <11.1–13.9 mmol/L [200–250 mg/dL]) often respond well to a single, oral glucose-lowering agent. Patients with more severe hyperglycemia (FPG >13.9 mmol/L [250 mg/dL]) may respond partially but are unlikely to achieve normoglycemia with oral monotherapy. A stepwise approach that starts with a single agent and adds a second agent to achieve the glycemic target can be used (see "Combination therapy with glucose-lowering agents," below). Insulin can be used as initial therapy in individuals with severe hyperglycemia (FPG <13.9–16.7 mmol/L [250–300 mg/dL]) or in those who are symptomatic from the hyperglycemia. This approach is based on the rationale that more rapid glycemic control will reduce "glucose toxicity" to the islet cells, improve endogenous insulin secretion, and possibly allow oral glucose-lowering agents to be more effective. If this occurs, the insulin may be discontinued.

Insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, GLP-1 receptor agonists, DPP-IV inhibitors, SLGT2 inhibitors, and insulin are approved for monotherapy of type 2 DM. Although each class of oral glucose-lowering agents has advantages and disadvantages (Table 418-5), certain generalizations apply: (1) insulin secretagogues, biguanides, GLP-1 receptor agonists, and thiazolidinediones improve glycemic control to a similar degree (1–2% reduction in HbA_{1c}) and are more effective than α-glucosidase inhibitors, DPP-IV inhibitors, and SLGT2 inhibitors; (2) assuming a similar degree of glycemic improvement, no clinical advantage to one class of drugs has been demonstrated; any therapy that improves glycemic control is likely beneficial; (3) insulin secretagogues, GLP-1 receptor agonists, DPP-IV inhibitors, α-glucosidase inhibitors, and SLGT2 inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides and thiazolidinediones are delayed by weeks; (4) not all agents are effective in all individuals with type 2 DM; (5) biguanides, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-IV inhibitors, thiazolidinediones, and SLGT2 inhibitors do not directly cause hypoglycemia; (6) most individuals will eventually require treatment with more than one class of oral glucose-lowering agents or insulin, reflecting the progressive nature of type 2 DM; and (7) durability of glycemic control is slightly less for glyburide compared to metformin or rosiglitazone.

Considerable clinical experience exists with metformin and sulfonylureas because they have been available for several decades. It is assumed that the α-glucosidase inhibitors, GLP-1 agonists, DPP-IV inhibitors, thiazolidinediones, and SLGT2 inhibitors will reduce

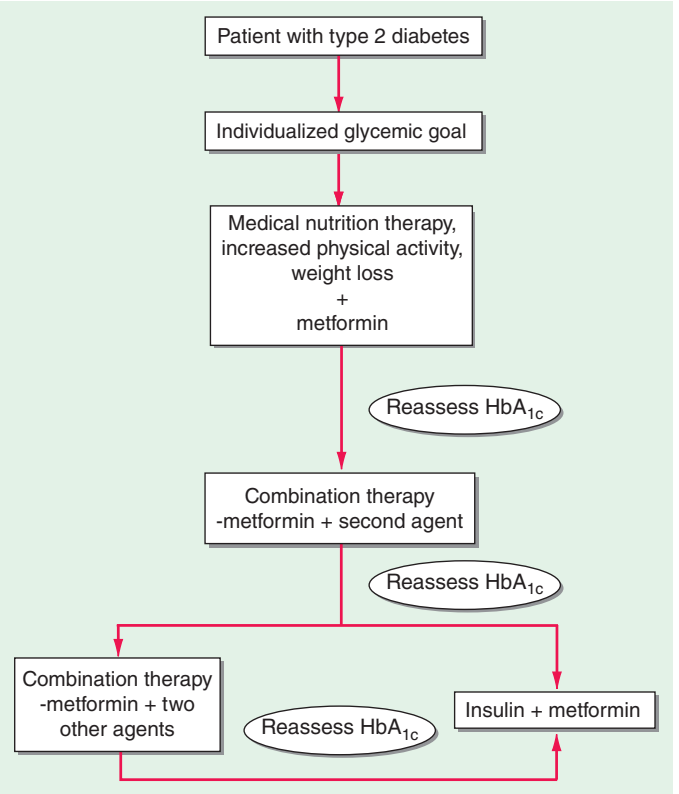

FIGURE 418-3 Glycemic management of type 2 diabetes. See text for discussion of treatment of severe hyperglycemia or symptomatic hyperglycemia. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, SLGT2 inhibitors, and insulin. HbA_{1c}, hemoglobin HbA_{1c}.

DM-related complications by improving glycemic control, but long-term data are not yet available. The thiazolidinediones are theoretically attractive because they target a fundamental abnormality in type 2 DM, namely insulin resistance. However, all of these agents are currently more costly than metformin and sulfonylureas.

Treatment algorithms by several professional societies (ADA/European Association for the Study of Diabetes [EASD], IDF, AACE) suggest metformin as initial therapy because of its efficacy, known side effect profile, and low cost (Fig. 418-3). Metformin's advantages are that it promotes mild weight loss, lowers insulin levels, and improves the lipid profile slightly. Based on SMBG results and the HbA_{1c}, the dose of metformin should be increased until the glycemic target is achieved or maximum dose is reached. If metformin is not tolerated, then initial therapy with an insulin secretagogue or DPP-IV inhibitor is reasonable.

COMBINATION THERAPY WITH GLUCOSE-LOWERING AGENTS A number of combinations of therapeutic agents are successful in type 2 DM (metformin + second oral agent, metformin + GLP-1 receptor agonist, or metformin + insulin), and the dosing of agents in combination is the same as when the agents are used alone. Because mechanisms of action of the first and second agents should be different, the effect on glycemic control is usually additive. There are little data to support the choice of one combination over another combination. Medication costs vary considerably (Table 418-5), and this often factors into medication choice. Several fixed-dose combinations of oral agents are available, but evidence that they are superior to titration of single agent to a maximum dose and then addition of a second agent is lacking. If adequate control is not achieved with the combination of two agents (based on reassessment of the HbA_{1c} every 3 months), a third oral agent or basal insulin should be added (Fig. 418-3). Treatment approaches vary considerably from country to country. For example, α-glucosidase inhibitors are used commonly in South Asian patients