

thiazolidinediones, α -glucosidase inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin. HbA_{1c}, hemoglobin HbA_{1c}.

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, metformin + insulin, or combinations of a long-acting insulin and a GLP-1 receptor agonist. 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. Recent results from the NIH-funded Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) indicated that addition of liraglutide or basal insulin to metformin leads to better glycemic control than glimepiride or sitagliptin (SGLT2 inhibitors were not studied). Based on recent demonstrations of a beneficial cardiovascular effect in certain individuals with type 2 DM and CVD, or at high risk of CVD, a GLP-1 receptor agonist or a SGLT2 inhibitor should now be considered in these populations. Medication costs vary considerably (Table 404-5), 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 a 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, GLP-1 receptor agonist, or basal insulin should be added (Fig. 404-3). Treatment approaches vary considerably from country to country. For example, α -glucosidase inhibitors are used commonly in South Asian patients (Indian), but infrequently in the United States or Europe. Whether this reflects an underlying difference in the disease or physician preference is not clear.

Treatment with insulin often becomes necessary as type 2 DM enters the phase of relative insulin deficiency and is signaled by inadequate glycemic control with one or two oral glucose-lowering agents. Insulin alone or in combination should be used in patients who fail to reach glycemic targets. For example, a single dose of long-acting insulin at bedtime is often effective in combination with