HF. Monitor patients for signs and symptoms.) The FDA also noted a trend toward increased hospitalization for CHF without increase in mortality with alogliptin and stated "There is limited experience with alogliptin therapy in patients with CHF of New York Heart Association (NYHA) functional classes III and IV. Alogliptin should therefore, be used with caution in these patients,"[1044,1047] Despite no evidence of increased risk in their CVOTs, the prescribing information for sitagliptin and linagliptin say because HF has been observed with other members of the DPP-4 inhibitor class, consider risks and benefits in patients who have known risk factors for HF. Monitor patients for signs and symptoms. The main adverse effects noted with DPP-4 inhibitors are a small increase in upper respiratory tract viral infections (rates of nasopharyngitis were 6.4% with a DPP-4 inhibitor vs 6.1% with comparators; risk ratio, 1.2; 95% CI, 1.0-1.4) and a rare hypersensitivity reaction.[1032] Severe and disabling arthralgia has been reported in individuals taking DPP-4 inhibitors.[1032]

SGLT2is are the newest class of oral antihyperglycemic agents approved for treatment of individuals with T2D. The glucosuric effect of these agents reduces both glycemia and weight in most persons. Most also experience decreases in systolic BP. Dehydration due to increased diuresis could lead to hypotension.[1048] Clinicians and persons with DM should be alert for the potential of postural hypotension, especially in older adults on loop diuretics. Although the antihyperglycemic effect can be diminished with decreasing eGFR, studies have shown that SGLT2is continue to exert their renal protective benefit for those with low eGFRs (eg, <45 mL/min/1.73 m^2).[423]

By increasing glycosuria, SGLT2is may increase the risk of fungal genital tract infection and much less frequently urinary tract infection. Risk of DKA is increased in persons using SGLT2is, especially in those being treated with insulin (especially if there has been a recent reduction in their insulin dose) and/or those with acute illnesses and prolonged fasting.[1049,1050] Small increases in LDL-C levels (4 to 8 mg/dL) occurred with canagliflozin, dapagliflozin, and empagliflozin in pivotal trials. Bone fracture has been described in post-marketing safety reporting.[1051] Multiple studies have shown renal and CV benefits of SGLT2is[239,424-426,444,1052-1054] (see also **Evidence Base 9: How should antihyperglycemic agents be prioritized in persons with T2D at high risk for or with established CVD?**). Empagliflozin and canagliflozin demonstrated reduction in MACE in CVOTs; empagliflozin also demonstrated decreased CV death and all-cause mortality. Empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin have shown a decrease in hospitalization for HF in their CVOTs. Dapagliflozin also has shown in people with HFrEF reduced risk of worsening HF or death from CV causes regardless of the presence or absence of DM.[457] Empagliflozin has also demonstrated reduction in composite of CV death or hospitalization for worsening HF in those with HFrEF with or without T2D.[470] More recently, empagliflozin was demonstrated to reduce the combined risk of CV death or hospitalization for HF in persons with HFpEF, regardless of the presence or absence of DM.[239,425,426,443] Dapagliflozin has now been shown to reduce the combined risk of worsening HF or CV death in patients with HF and a mildly reduced or preserved ejection fraction.[1054a] Dapagliflozin received an FDA indication to reduce the risk of CV death and hospitalization for HF in adults with and without DM with HFrEF (NYHA Class II-IV). Empagliflozin received an indication for those with and without DM to reduce the risk of CV death and hospitalization for HF in adults with HF (HFrEF or HFpEF).

Based on the CREDENCE trial,[423] the FDA has given canagliflozin an indication to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF in adults with T2D and diabetic nephropathy with albuminuria. Dapagliflozin based on the DAPA-CKD RCT[424] has received an FDA indication to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for HF in adults with CKD at risk of progression.

As a result of GLP-1 RA and SGLT2i studies above, independent of glycemic control or targets, individuals with T2D at significant risk for or with established ASCVD, HF, and/or CKD should be treated with a GLP-1 RA or SGLT2i with proven benefit for the individual's specific conditions.

Colesevelam, alpha-glucosidase inhibitors, and bromocriptine primarily affect PPG levels and are worth consideration in selected persons. Colesevelam carries a low risk of hypoglycemia and also reduces LDL-C, for which it was originally developed. It also modestly increases triglyceride levels, and its main adverse effect is constipation, but it is not systemically absorbed and therefore is not likely to have systemic adverse effects.[1055]

Alpha-glucosidase inhibitors also have a low risk for hypoglycemia, although persons may not tolerate the GI side effects (eg, bloating, flatulence, and diarrhea). These may be reduced by starting with a low dose and slowly titrating the dose as needed. Acarbose has been shown to lower A1C and cause weight loss.[1056,1057] Some clinical trials have suggested some CV benefit in persons with IGT or DM. However, in a large RCT[1058] of Chinese participants with coronary heart disease and IGT, acarbose did not reduce the risk of MACE, but did reduce the incidence of DM.[891,892]

The dopamine receptor agonist bromocriptine does not cause hypoglycemia. It can cause nausea and orthostasis and should not be used in persons taking antipsychotic drugs. Bromocriptine in one study with a small number of events was associated with reduced CV event rates.[1059]

Because many persons do not achieve adequate glycemic control with monotherapy or are at risk for early loss of efficacy with metformin or another monotherapy, combining antihyperglycemic agents is often appropriate.[1060] For some recently diagnosed individuals with T2D and more severe hyperglycemia, early combination pharmacotherapy should be considered, usually to include metformin plus another first-line agent that does not cause hypoglycemia, especially a GLP-1 RA or an SGLT2i, or DPP-4 inhibitor (see **R 12.2.6** and **R 12.2.7** and **R 9.1 to R 9.4** on CVD). In the VERIFY trial,[1040] initial combination therapy of metformin and the DPP-4 inhibitor vildagliptin was superior to sequential addition of medications in prolonging the occurrence of primary and secondary failure. For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual or possibly triple combination pharmacotherapy usually including metformin and considering basal insulin. If there are significant symptoms of hyperglycemia, especially including catabolism (eg, weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (300 mg/dL [16.7 mmol/L]), insulin is recommended. The Efficacy and Durability of Initial Combination Therapy study compared efficacy of initial metformin/pioglitazone/exenatide in new-onset T2D vs sequential addition of metformin followed by glipizide and insulin. The decrease in A1C from triple therapy was greater at 6 months than that of conventional therapy and the superiority was maintained at 3 years.[1061]

Metformin is quite effective when administered in combination with other agents, as long as one avoids its use in persons with CKD (eGFR <30 mL/min/1.73 m^2)[73] or GI intolerance. SUs, in contrast, may be problematic when used in combinations because they can cause hypoglycemia and may reduce, eliminate, or minimize the weight-loss benefit of drugs such as metformin, GLP-1 RAs, and SGLT2is.[993] See **R 12.2.4** and **Evidence Base 9: How should antihyperglycemic agents be prioritized in persons with T2D at high risk for or with established CVD?** for those with established or high risk for ASCVD, HF, and/or CKD for recommendations about antihyperglycemic medications that should be used often in combination with metformin. Even for those without these conditions