consistent with the results observed in the randomized trials in the previous text. For example, in CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors), compared with a propensity-matched cohort of patients receiving other oral medications for T2D, those receiving SGLT2 inhibitors had a 51% lower associated risk of all-cause mortality (HR: 0.49; 95% CI: 0.41 to 0.57) and a 39% lower associated risk of hospitalization for HF (HR: 0.61; 95% CI: 0.51 to 0.73) (31). Comparable results were found in the even larger CVD-REAL 2 study, with a 49% lower risk of all-cause mortality, 36% lower risk of hospitalization for HF, and lower risks of MI and stroke (34). These observational data have important limitations and may overestimate the effectiveness of these medications, despite the use of sophisticated statistical techniques (43). Nonetheless, these observations from outside of the tightly controlled clinical trial setting provide support for the CV effects of this class of medications.

5.1.3. SGLT2 Inhibitors: Non-CV Benefits

Both empagliflozin and canagliflozin have favorable effects on kidney function (12,44,45). In the EMPA-REG OUTCOME study, empagliflozin slowed the progression of kidney disease, reducing incident or worsening nephropathy, which was defined as a progression to macroalbuminuria (HR: 0.61, 95% CI: 0.53 to 0.70). Mechanisms to explain these observations may include tubuloglomerular feedback, reduction in glomerular hypertension, containment of hyperfiltration injury, and effects on sodium-hydrogen exchange. In the CANVAS and CANVAS-R trials, progression of albuminuria occurred less frequently (HR: 0.73; 95% CI: 0.67 to 0.79) and regression of albuminuria occurred more frequently (HR: 1.70; 95% CI: 1.51 to 1.91) among those assigned to canagliflozin than among those assigned to placebo. A renal composite outcome in CANVAS of 40% reduction in estimated glomerular filtration rate (eGFR), renal replacement therapy, or renal death was improved by 40% in those assigned to active therapy (HR: 0.60; 95% CI: 0.47 to 0.77), although whether this effect was due to a benefit seen in 1, 2, or all 3 of the components of the composite endpoint has not yet been reported (12).

5.1.4. SGLT2 Inhibitors: Safety Concerns

The contraindications and safety concerns of SGLT2 inhibitors are included in **Table 4**.

An increased risk for genital mycotic infections (mostly candida vaginitis in women, balanitis in men) has been seen with SGLT2 inhibitors (12,29,46,47). These infections are not usually serious, tend to resolve with a brief course of antifungal agents, and rarely recur (12,29). Although there have been spontaneous postmarketing reports of pyelonephritis and urosepsis requiring hospitalization in patients receiving SGLT2 inhibitors, large clinical trials have shown no difference in the rates of any urinary tract infections or serious urinary tract infections between SGLT2 inhibitors and placebo. Rare postmarketing reports of necrotizing fasciitis of the perineum (12 cases over 5 years, with more than 1.7 million patients being prescribed SGLT2 inhibitors in 2017) have led the FDA to request a warning to SGLT2 inhibitor prescribing instructions; whether these infections are causally related to SGLT2 inhibitor use is unclear.

Case reports have pointed to an increased risk of diabetic ketoacidosis with SGLT2 inhibitors in the absence of significant hyperglycemia, often called “euglycemic diabetic ketoacidosis,” although moderate hyperglycemia is common. This risk has been shown to be very low in the large randomized controlled trials of patients with T2D, particularly in those not requiring insulin therapy (48). Patients with signs or symptoms of ketoacidosis, such as dyspnea, nausea, vomiting, and abdominal pain, should be instructed to discontinue SGLT2 inhibitors and seek immediate medical attention (29). Providers should be aware of precipitating factors and treatment strategies, which have been reviewed recently (49).

Canagliflozin has been associated with increased risk for lower limb amputation (6.3 vs. 3.4 amputations per 1,000 patient-years of observation after a median follow-up of 126 weeks; $p < 0.001$) (12,22) prompting the FDA to add a black box warning to the canagliflozin

TABLE 4 Contraindications and Cautions for SGLT2 Inhibitors

Contraindications	Cautions*
■ History of serious hypersensitivity reaction to drug ■ Severe renal impairment, ESRD, or dialysis†	■ May cause intravascular volume contraction, particularly in patients with renal impairment or low systolic blood pressure, those on diuretics, or the elderly ■ Increased incidence of bone fractures reported with canagliflozin ■ Hypoglycemia risk increased with insulin and insulin secretagogues (e.g., sulfonylureas); a lower dose of insulin or the insulin secretagogue may be required ■ Increased risk of mycotic genital infections. ■ Euglycemic ketoacidosis in vulnerable patients ■ History of prior amputation, severe peripheral vascular disease, neuropathy, or diabetic foot ulcers. This caution is for canagliflozin and ertugliflozin. No increased risk of amputation has been seen for empagliflozin or dapagliflozin to date. ■ History of osteoporosis. This caution is for canagliflozin.

*SGLT2 inhibitors are not for the treatment of type 1 diabetes.
†SGLT2 inhibitors have shown benefit for CV event reduction down to eGFR of 30 mL/min/m^2

ESRD = end-stage renal disease; SGLT2 = sodium-glucose cotransporter 2.