liraglutide or placebo (10). The 3-point MACE composite was reduced by 13% (HR: 0.87; 95% CI: 0.78 to 0.97; p = 0.01 for superiority) with liraglutide versus placebo. All components of the composite contributed to a reduction in 3-point MACE, and all-cause mortality was reduced by 15% (HR: 0.85; 95% CI: 0.74 to 0.97; p = 0.02). The reduction in all-cause mortality was driven by reduction in CV death. No reduction in HF events was noted in the LEADER trial (HR: 0.87; 95% CI: 0.73 to 1.05; p = 0.14). To date, liraglutide is the only GLP-1RA approved by the FDA to reduce the risk of MACE in adults with T2D and established CV disease (38).

The preapproval SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) enrolled 3,297 patients using the same trial inclusion criteria as LEADER and had the same primary composite endpoint (11). Although the study was not powered for superiority, semaglutide reduced 3-point MACE by 26% (HR: 0.74; 95% CI: 0.58 to 0.95), with a consistent magnitude and direction of effect for the key components of nonfatal stroke (HR: 0.61; 95% CI: 0.38 to 0.99) and nonfatal MI (HR: 0.74; 95% CI: 0.51 to 1.08). No reduction in all-cause mortality (HR: 1.05; 95% CI: 0.74 to 1.50) or CV mortality (HR: 0.98; 95% CI: 0.65 to 1.48) was observed. No reduction in HF events was seen. A planned cardiovascular outcomes trials will assess whether an oral version of semaglutide is superior to placebo for CV event reduction (NCT02692716).

The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial enrolled 14,752 subjects, approximately 70% of whom had established ASCVD, randomizing them to once-weekly exenatide versus usual care (58). Three-point MACE was directionally lower for exenatide compared with placebo, but this difference did not reach statistical significance (HR: 0.91, 95% CI: 0.83 to 1.00). All-cause mortality was lower in the once-weekly exenatide group (HR: 0.86, 95% CI: 0.77 to 0.97), and the direction and magnitude of effect of CV mortality was similar (HR: 0.88, 95% CI: 0.76 to 1.02). There was no difference in hospitalization for HF between exenatide and placebo. Lixisenatide, which was tested in 6,068 patients with acute coronary syndrome in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial, did not show evidence for a reduction in a 4-point MACE composite outcome (CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina), or in any components of that MACE composite, or hospitalization for HF. Two phase 2 trials have tested whether liraglutide can improve outcomes in heart failure. The FIGHT trial (Functional Impact of GLP-1 for Heart Failure Treatment, n = 300) and the LIVE trial (A Randomised, Double-blind, Placebo-controlled Study of the Effect of LIraglutide on Left VEntricular Function in Chronic Heart Failure Patients With and Without Type 2 Diabetes, n = 243) examined the use of liraglutide in patients with reduced ejection fraction (61,62). In FIGHT, there was no difference in the primary endpoint of a rank score of a composite of death, time to heart failure hospitalization, or time-averaged proportional change in NT-proBNP concentration by randomized treatment group (61). In LIFE, there was no difference in the primary endpoint (left ventricular ejection fraction) by randomized treatment group, but serious cardiac events were more common in the active (12 events) than in the placebo (3 events) arm (p = 0.04) (62). Ongoing cardiovascular outcome trials of other GLP-1RA may shed further light on whether this class of medications is safe and effective in patients with heart failure. Prospective cardiovascular outcomes trials of the GLP-1RAs dulaglutide and albiglutide are currently underway (63,64).

5.2.3. GLP-1RAs: Non-CV Benefits

Although it has yet to be confirmed in an independent randomized trial, analyses of existing trials suggest that the GLP-1RAs may provide renal benefits. In LEADER, liraglutide was associated with an approximately 20% reduction in the risk of a composite outcome of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease regardless of baseline eGFR. This result was primarily due to a 26% reduction in persistent macroalbuminuria. In SUSTAIN-6, semaglutide was associated with a 36% reduction in the risk of persistent macroalbuminuria, persistent doubling of the serum creatinine accompanied by an eGFR ≤45 mL/min/1.73 m^2, or the need for continuous renal replacement therapy (although this benefit was driven mainly by reduction in albuminuria).

Weight loss, ranging from 2% to 4% of total body weight for liraglutide and exenatide and up to 10% for semaglutide, may occur with use of GLP-1RA therapy, although generally at higher doses than those targeted for CV risk reduction (65,66). Whether associated with weight loss or another mechanism, GLP-1RAs may also modestly lower blood pressure, but can also lead to elevations in heart rate. Compared with placebo (plus usual care), use of liraglutide produced a 20% reduction in the occurrence of confirmed hypoglycemia and a 31% reduction in severe hypoglycemia (10).

5.2.4. GLP-1RAs: Safety Concerns

The contraindications and safety concerns of GLP-1RAs are included in **Table 8**. The most frequently reported side effects of GLP-1RAs are nausea and vomiting (60). These gastrointestinal symptoms are usually transient for longer-acting GLP-1RAs and can be mitigated by gradual dose escalation (67) and educating patients to reduce meal size. GLP-1RAs may also increase the risk of gallbladder disease, including acute cholecystitis (10,68).