Key information

Balance of benefits and harms. Data for cardiovascular and kidney outcomes, and cardiometabolic benefits, are summarized below.

Cardiovascular outcomes. There are currently 8 published large RCTs examining cardiovascular outcomes for injectable GLP-1 RA[347,372–382] and 1 trial of an oral GLP-1 RA (Figure 28).[383] Of these, 5 studies (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER],[379] Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes [SUSTAIN-6],[374] Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus [HARMONY],[373] and Researching Cardiovascular Events With a Weekly Incretin in Diabetes [REWIND],[372] and Effect of Efpeglenatide on Cardiovascular Outcomes [AMPLITUDE-O][347]) have confirmed cardiovascular benefit of 5 injectable GLP-1 RA with significant reductions in MACE for liraglutide, semaglutide, albiglutide, dulaglutide, and efpeglenatide respectively. The other agents (lixisenatide, exenatide, and oral semaglutide) have been shown to have cardiovascular safety, but without significant effects on cardiovascular risk reduction.

The LEADER trial (evaluating liraglutide) included 9340 individuals with T2D and HbA1c ≥7% with high cardiovascular risk defined as established CVD, CKD G3 or higher, age ≥60 years, or a major CVD risk factor.[379] Of note, the LEADER trial also included 220 individuals with an eGFR of 15–30 ml/min per 1.73 m^2. The LEADER trial compared once-daily liraglutide to placebo and followed participants for a median of 3.8 years for primary MACE outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. There was a 13% reduction in MACE (HR: 0.87; 95% CI: 0.78–0.97) conferred by liraglutide.

In the LEADER trial, the risk reduction for the primary composite MACE outcome was even greater among individuals with CKD G3a or greater severity (eGFR <60 ml/min per 1.73 m^2) compared to those with an eGFR ≥60 ml/min per 1.73 m^2 (HR: 0.69; 95% CI: 0.57–0.85 vs. HR: 0.94; 95% CI: 0.83–1.07, respectively, *P*-interaction = 0.01).[384] This benefit was seen across each separate cardiovascular outcome. Notably, liraglutide (compared to placebo) conferred an impressive 49% reduction for nonfatal stroke, with HR: 0.51 (95% CI: 0.33–0.80) for eGFR <60 ml/min per 1.73 m^2 versus HR: 1.07 (95% CI: 0.84–1.37) for eGFR ≥60 ml/min per 1.73 m^2. Although subgroup analyses should be considered cautiously, these findings suggest that efficacy among individuals with CKD is at least as great as that for those without CKD.

The SUSTAIN-6 trial (evaluating injectable semaglutide) enrolled 3297 patients with T2D and HbA1c ≥7% with CVD, CKD G3 or higher, or age ≥60 years with at least 1 major CVD risk factor.[374] A total of 83% of participants had CVD, CKD, or both, with 10.7% having CKD only and 13.4% having both CKD and CVD. SUSTAIN-6 found that once-weekly semaglutide compared to placebo reduced the primary composite MACE outcome by 26% (HR: 0.74; 95% CI: 0.58–0.95). In subgroup analysis, there was no evidence of effect heterogeneity by CKD subgroup, with similar MACE reduction for those with an eGFR <30 ml/min per 1.73 m^2 versus ≥30 ml/min per 1.73 m^2 (*P*-interaction = 0.98) and similar reduction for those with an eGFR <60 ml/min per 1.73 m^2 versus ≥60 ml/min per 1.73 m^2 (*P*-interaction = 0.37).

The HARMONY trial (evaluating albiglutide) evaluated 9463 participants with T2D and high cardiovascular risk with HbA1c ≥7%.[373] Of note, an eGFR <30 ml/min per 1.73 m^2 was an exclusion criterion. HARMONY found that albiglutide (dosed once weekly) compared to placebo reduced the primary MACE outcome (cardiovascular death, myocardial infarction, or stroke) over a median duration of follow-up of 1.6 years in the overall cohort by 22% (HR: 0.78; 95% CI: 0.68–0.90). There was no significant heterogeneity of treatment benefit for the primary cardiovascular outcome among the eGFR subgroups of <60 ml/min per 1.73 m^2, ≥60–90 ml/min per 1.73 m^2, and ≥90 ml/min per 1.73 m^2 (*P*-interaction = 0.19). At this time, albiglutide is currently not available on the market, so this is not an option for patients.

The REWIND trial (evaluating dulaglutide) included 9901 adults with T2D with HbA1c of ≤9.5% (with no lower limit and mean HbA1c of 7.2%).[372,377] An eGFR <15 ml/min per 1.73 m^2 was an exclusion criterion. The REWIND trial enrolled a low proportion of patients with established CVD (31.5%); thus, it is largely considered a primary prevention trial. The REWIND trial also included a significant number of individuals with CKD. Over a median follow-up of 5.4 years, the primary MACE outcome (composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or CVD death) was 12% lower with once-weekly dulaglutide compared to placebo (HR: 0.88; 95% CI: 0.79–0.99). The reduction in primary cardiovascular outcome was similar among those with versus without previous CVD (*P*-interaction = 0.97).

The AMPLITUDE-O trial studied the cardiovascular safety of efpeglenatide in 4076 patients with T2D and high cardiovascular risk or CKD, including 89.6% with established CVD. Efpeglenatide was superior to placebo for the primary MACE outcome, with HR for the primary outcome of 0.73 (95% CI: 0.58–0.92), and comparable MACE risk reduction in participants with eGFR <71 ml/min per 1.73 m^2 with HR for primary outcome of 0.67 (95% CI: 0.50–0.91).[347]

In contrast, the Evaluation of LIXisenatide in Acute Coronary Syndrome (ELIXA; lixisenatide)[381] and the EXenatide Study of Cardiovascular Event Lowering (EXSCEL; exenatide)[376,378] trials did not show a cardiovascular benefit with GLP-1 RA, nor did they find increased harm, confirming cardiovascular safety. Differences in the results of the ELIXA and EXSCEL trials, compared with the more favorable results seen in the LEADER, SUSTAIN, HARMONY, and REWIND trials, may stem from differences in GLP-1 RA molecular structures, half-lives, and formulations, study design, or the