Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John J V McMurray

Summary
Background Glucagon-like peptide-1 (GLP-1) receptor agonists differ in their structure and duration of action and have been studied in trials of varying sizes and with different patient populations, with inconsistent effects on cardiovascular outcomes reported. We aimed to synthesise the available evidence by doing a systematic review and meta-analysis of cardiovascular outcome trials of these drugs.

Methods We searched MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials for eligible placebo-controlled trials reporting major adverse cardiovascular events (MACE; ie, cardiovascular death, stroke, or myocardial infarction) up to June 15, 2019. We did a meta-analysis using a random-effects model to estimate overall hazard ratios (HRs) for MACE, its components, death from any cause, hospital admission for heart failure, kidney outcomes, and key safety outcomes (severe hypoglycaemia, pancreatitis, and pancreatic cancer). We also examined MACE in several subgroups based on patient characteristics (history of cardiovascular disease, BMI, age, baseline HbA1c, and baseline estimated glomerular filtration rate), trial duration, treatment dosing interval, and structural homology.

Findings Of 27 publications screened, seven trials, with a combined total of 56 004 participants, were included: ELIXA (lixisenatide), LEADER (lixisenatide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), Harmony Outcomes (albiglutide),REWIND (dulaglutide), and PIONEER 6 (oral semaglutide). Overall, GLP-1 receptor agonist treatment reduced MACE by 12% (HR 0·88, 95% CI 0·82–0·94; p<0·001). There was no statistically significant heterogeneity across the subgroups examined. HRs were 0·88 (95% CI 0·81–0·96; p=0·003) for death from cardiovascular causes, 0·84 (0·76–0·93; p<0·001) for fatal or non-fatal stroke, and 0·91 (0·84–1·00; p=0·043) for fatal or non-fatal myocardial infarction. GLP-1 receptor agonist treatment reduced all-cause mortality by 12% (0·88, 0·83–0·95; p=0·001), hospital admission for heart failure by 9% (0·91, 0·83–0·99; p=0·028), and a broad composite kidney outcome (development of new-onset macroalbuminuria, decline in estimated glomerular filtration rate [or increase in creatinine], progression to end-stage kidney disease, or death attributable to kidney causes) by 17% (0·83, 0·78–0·89; p=0·001), mainly due to a reduction in urinary albumin excretion. There was no increase in risk of severe hypoglycaemia, pancreatitis, or pancreatic cancer.

Interpretation Treatment with GLP-1 receptor agonists has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with type 2 diabetes.

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Introduction
Prevention of non-fatal and fatal cardiovascular events is a key goal of the management of patients with type 2 diabetes.1,2 In addition to blood pressure-lowering and cholesterol-lowering therapies, two of the newer classes of antihyperglycaemic drugs—sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists—have been shown to reduce cardiovascular risk.3

The GLP-1 receptor agonists decrease HbA1c by stimulating glucose-dependent insulin secretion and by reducing glucagon secretion, gastric emptying, and appetite.4–7 GLP-1 receptor agonist treatment also leads to modest improvements in lipids and reductions in blood pressure and bodyweight, with a low risk of hypoglycaemia. However, the drugs in this class differ in their structure and duration of action and have been studied in trials of varying sizes and with different patient populations, and in individual trials the effects of these drugs on cardiovascular outcomes have not been consistent.4–8 We did a systematic review and meta-analysis of all the large, placebo-controlled, cardiovascular outcome trials of GLP-1 receptor agonists, to obtain robust estimates of the effects of this class of drugs on different
Research in context

Evidence before this study
Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of glucose-lowering drugs used in the treatment of type 2 diabetes. We searched MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials for eligible placebo-controlled trials reporting major adverse cardiovascular events (MACE; a composite of cardiovascular death, stroke, or myocardial infarction) up to June 15, 2019. Various drugs in this class with differing structures and durations of action have been studied in randomised, placebo-controlled, cardiovascular outcome trials of varying size and with different patient populations, with inconsistent effects on cardiovascular outcomes reported. Previous meta-analyses of cardiovascular outcome trials have not included some of the more recently reported major trials of drugs within the class.

Added value of this study
Our systematic review and meta-analysis includes data from seven large-scale cardiovascular outcome trials, pooling data for lixisenatide, liraglutide, injectable semaglutide, exenatide, albglutide, dulaglutide, and oral semaglutide, making it the largest pooled study of the effect of GLP-1 receptor agonists on cardiovascular and kidney outcomes in patients with type 2 diabetes. Furthermore, compared with previous meta-analyses, it includes data for a greater number of patients without cardiovascular outcomes overall and in various patient subgroups, as well as examining kidney outcomes and key safety outcomes.

Methods
Search strategy and selection criteria
We aimed to identify published randomised, placebo-controlled trials testing GLP-1 receptor agonists in patients with type 2 diabetes. Both injectable and oral agents were included. We further restricted the search to trials with a primary outcome including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. We searched MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials for reports published up to June 15, 2019, using the following search terms: “glucagon-like peptide-1 receptor agonists”, “cardiovascular mortality”, “myocardial infarction”, “stroke”, “heart failure”, “lixisenatide”, “exenatide”, “liraglutide”, “semaglutide”, “albiglutide”, “dulaglutide”, “placebo”, and “randomized clinical trial”. We restricted our search to trials including more than 500 patients. Included trials were assessed for bias with the Cochrane risk-of-bias tool.⁷

Data were extracted by SLK and RR, with conflicts over study inclusion resolved by consensus.

Data analysis
Cardiovascular outcomes of interest were major adverse cardiovascular events (MACE; a composite outcome comprised of cardiovascular death, myocardial infarction, and stroke), each of the components of this outcome, hospital admission for heart failure, and death from any cause. We also examined kidney and safety outcomes. Two kidney outcomes were examined: worsening of kidney function, represent an important treatment opportunity to reduce morbidity and mortality in patients with type 2 diabetes.

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Summary statistics from the individual trials included were used, because individual level data were not available. Relevant hazard ratios (HRs) and 95% CIs were obtained from primary and secondary trial reports and their supplementary appendix files. Estimates from each study were combined by use of inverse variance-weighted averages of logarithmic HRs in random-effects analysis. Inter-study heterogeneity was assessed with the I² index and Cochran’s Q test. We considered I² values lower than 25% to indicate low heterogeneity, values of 26–50% to indicate moderate heterogeneity, and values greater than 50% to indicate high heterogeneity; Cochran’s Q statistic p values below 0·05 were considered indicators for significant heterogeneity. In order to provide a measure of absolute risk, we calculated a number needed to treat (NNT) for each cardiovascular, mortality, and kidney outcome using the method of Altman and Andersen; the median duration of follow-up over which the NNTs applied was estimated by a weighted average of the trials. Fragility index, which is the minimum number of events needed to change from a non-event to an event in order to render a significant result non-significant, was calculated for the primary three-component MACE outcome using the method described by Walsh and colleagues. Interactions between treatment and subgroups were examined with a test for heterogeneity, with a p value below 0·05 regarded as significant. All analyses were done with Stata version 14.

Role of the funding source
There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Of 27 articles screened for eligibility, seven trials with a total of 56004 patients were included in the meta-analysis (figure 1). In order of when their primary results were reported, these were ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), Harmony Outcomes (albiglutide), REWIND (dulaglutide), and PIONEER 6 (oral semaglutide). The key trial and patient characteristics at baseline are presented in the table and in the appendix (pp 1–2). All included trials were assessed for bias with the Cochrane risk-of-bias tool and all were assessed as high quality with a low risk of bias (appendix p 2).

All trials were of substantial size (>3000 patients). ELIXA enrolled patients with a recent acute coronary syndrome event whereas the study populations in all other trials consisted of patients with stable cardiovascular disease or a mixture of those with stable cardiovascular disease and those with cardiovascular risk factors. In all seven trials, local investigators were encouraged to manage participants in accordance with local guidelines (and could use most non-study glucose-lowering treatments as desired). In six of the seven trials, the mean between-treatment group difference in HbA₁c was in the range of 0·3–0·7%. All trials apart from ELIXA had MACE as the primary endpoint; in ELIXA, an expanded composite including the MACE components and hospital admission for unstable angina was used. Lixisenatide (ELIXA), liraglutide (LEADER), and oral semaglutide (PIONEER 6) were given daily, whereas the remaining GLP-1 receptor agonists were given once weekly. PIONEER 6 differed from the remaining trials in that semaglutide and placebo were taken orally whereas the treatments were given subcutaneously in the other studies.

Mean age at baseline ranged from 60 years in ELIXA to 66 years in PIONEER 6 and REWIND. The highest proportion of women was in REWIND (46%) compared with between 31% and 39% in the remaining trials. The proportion of patients with established cardiovascular disease at baseline ranged from 100% in ELIXA and Harmony Outcomes to 31% of those in REWIND (table). Kidney function was similar across trials (with median eGFR ranging from 74 to 80 mL/min per m²). Median HbA₁c was lowest in REWIND and ELIXA (7·1% and 7·7%, respectively).
In the pooled analysis, treatment with a GLP-1 receptor agonist led to a 12% relative risk reduction in MACE (HR 0.88, 95% CI 0.83–0.94; p<0.0001; figure 2). The NNT to prevent one MACE event was 75 (95% CI 50–151) over an estimated median follow-up of 3.2 years. The overall fragility index was 202 (appendix p 7). When assessing the components of the composite MACE outcome separately, GLP-1 receptor agonist use led to a reduction in risk of death from cardiovascular causes (HR 0.88, 95% CI 0.81–0.96; p<0.0001), fatal or non-fatal stroke (0.84, 0.76–0.93; p<0.0001), and fatal or non-fatal myocardial infarction (0.91, 0.84–1.00; p=0.043; figure 2).

In subgroup analyses, there was no statistical heterogeneity between the effect of a GLP-1 receptor agonist in primary prevention patients (those without established cardiovascular disease) and those with cardiovascular disease at baseline: the HR was 0.95 (95% CI 0.83–1.08) for primary prevention and 0.86 (0.79–0.94) for secondary prevention (pinteraction=0.22; figure 3). Similarly, we found no heterogeneity for the effect of GLP-1 receptor agonist therapy when examined by baseline HbA1c (low vs high HbA1c), shorter compared with longer trial follow-up (<3 years vs ≥3 years median follow-up), or drug dosing interval (daily vs weekly dosing), reflecting duration of drug action. The one possible exception was the comparison of exendin 4-based drugs (lirinestat and exenatide) and those drugs more homologous with human GLP-1 (all other drugs studied); this analysis suggested possible heterogeneity, although the interaction p value was not significant: HR 0.95 (95% CI 0.85–1.06) for exendin 4-based drugs, compared with 0.84 (0.79–0.90) for human GLP-1-based drugs (pinteraction=0.06; figure 3). Compared with placebo, treatment with a GLP-1 receptor agonist reduced the risk of death from any cause by 12% (HR 0.88, 95% CI 0.83–0.95; p=0.001), giving an NNT to prevent one death of 108 (77–260; figure 4) over an estimated median follow-up of 3.2 years. The

<table>
<thead>
<tr>
<th>Drug</th>
<th>ELIXA (n=6068)</th>
<th>LEADER (n=9340)</th>
<th>SUSTAIN-6 (n=3297)</th>
<th>EXSCEL (n=14752)</th>
<th>Harmony Outcomes (n=9463)</th>
<th>REWIND (n=9901)</th>
<th>PIONEER 6 (n=3183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lixisenatide</td>
<td>4576 (75%)</td>
<td>7238 (77%)</td>
<td>2736 (83%)</td>
<td>11275 (76%)</td>
<td>6583 (70%)</td>
<td>7498 (76%)</td>
<td>2300 (72%)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>4576 (75%)</td>
<td>7238 (77%)</td>
<td>2736 (83%)</td>
<td>11275 (76%)</td>
<td>6583 (70%)</td>
<td>7498 (76%)</td>
<td>2300 (72%)</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>4576 (75%)</td>
<td>7238 (77%)</td>
<td>2736 (83%)</td>
<td>11275 (76%)</td>
<td>6583 (70%)</td>
<td>7498 (76%)</td>
<td>2300 (72%)</td>
</tr>
<tr>
<td>Exenatide</td>
<td>77 (1.3)</td>
<td>127 (1.9)</td>
<td>10 (1.5)</td>
<td>81 (1.0)</td>
<td>87 (1.5)</td>
<td>73 (1.3)</td>
<td>82 (1.6)</td>
</tr>
</tbody>
</table>

**Table: Baseline characteristics and use of glucose-lowering drugs across included trials**

Numerical data are mean (SD) or n (%), unless otherwise specified. GLP-1 = glucagon-like peptide 1. eGFR = estimated glomerular filtration rate. NR = not reported. DPP-4 = dipeptidyl peptidase-4. SGLT2 = sodium-glucose co-transporter-2. eGFR data are median (IQR) for SUSTAIN-6 and EXSCEL.
risk of hospital admission for heart failure was reduced by 9% in patients treated with a GLP-1 receptor agonist (HR 0·91, 95% CI 0·83–0·99; p=0·028), giving an NNT to prevent one event of 312 (165–2810; figure 4) over the estimated median follow-up of 3·2 years.

Data for kidney events were not available for Harmony Outcomes or PIONEER 6, so these trials were excluded from the analysis of these outcomes. Treatment with a GLP-1 receptor agonist reduced the broader composite kidney outcome (which consisted of development of macroalbuminuria, worsening kidney function [doubling of serum creatinine or 40% or greater decline in eGFR], end-stage kidney disease, and kidney-related death) by 17% (HR 0·83, 95% CI 0·78–0·89), with an NNT to prevent one event of 62 (48–96) over the estimated median follow-up of 3·2 years (figure 4). This finding was mainly due to a reduction in urinary albumin excretion (appendix p 4).20,21 The narrower worsening of kidney function outcome was reduced by 13%, but this finding was not significant (HR 0·87, 0·73–1·03); the corresponding NNT was 245 (118 to –1064 [upper bound is negative to indicate number needed to harm]; figure 4).

### Table: Three-component MACE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GLP-1 receptor agonist n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>NNT (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELOX</td>
<td>400/3034 (13%)</td>
<td>392/3034 (13%)</td>
<td>1·02 (0·89–1·17)</td>
<td>0·78</td>
<td></td>
</tr>
<tr>
<td>LEADER</td>
<td>608/4668 (13%)</td>
<td>604/4667 (15%)</td>
<td>0·87 (0·78–0·97)</td>
<td>0·035</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>108/1648 (7%)</td>
<td>105/1649 (9%)</td>
<td>0·74 (0·58–0·95)</td>
<td>0·056</td>
<td></td>
</tr>
<tr>
<td>EXSCEL</td>
<td>839/7356 (11%)</td>
<td>836/7356 (11%)</td>
<td>0·91 (0·83–1·00)</td>
<td>0·061</td>
<td></td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>338/4731 (7%)</td>
<td>342/4732 (9%)</td>
<td>0·78 (0·68–0·90)</td>
<td>&lt;0·0001</td>
<td></td>
</tr>
<tr>
<td>REWIND</td>
<td>594/4949 (12%)</td>
<td>592/4952 (12%)</td>
<td>0·88 (0·79–0·99)</td>
<td>0·026</td>
<td></td>
</tr>
<tr>
<td>PIONEER 6</td>
<td>65/1593 (4%)</td>
<td>65/1592 (5%)</td>
<td>0·79 (0·57–1·11)</td>
<td>0·17</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2948/27377 (11%)</td>
<td>3304/28027 (12%)</td>
<td>0·88 (0·82–0·94)</td>
<td>75 (50–151)</td>
<td>&lt;0·0001</td>
</tr>
</tbody>
</table>

- **Cardiovascular death**
  - ELOX: 156/3034 (5%) vs 158/3034 (5%)
  - LEADER: 219/4668 (5%) vs 218/4667 (6%)
  - SUSTAIN 6: 44/1648 (3%) vs 45/1649 (3%)
  - EXSCEL: 340/7356 (5%) vs 340/7356 (5%)
  - Harmony Outcomes: 122/4731 (3%) vs 122/4731 (3%)
  - REWIND: 337/4949 (6%) vs 337/4952 (6%)
  - PIONEER 6: 15/1593 (1%) vs 15/1592 (2%)

- **Overall**
  - 12777/27977 (5%) vs 1471/28027 (5%)

- **Fatal or non-fatal myocardial infarction**
  - ELOX: 270/3034 (9%) vs 261/3034 (9%)
  - LEADER: 292/4668 (6%) vs 296/4667 (7%)
  - SUSTAIN 6: 154/1648 (3%) vs 155/1649 (4%)
  - EXSCEL: 483/7356 (7%) vs 483/7356 (7%)
  - Harmony Outcomes: 182/4731 (4%) vs 182/4732 (5%)
  - REWIND: 233/4949 (5%) vs 233/4952 (5%)
  - PIONEER 6: 37/1593 (2%) vs 37/1592 (2%)

- **Overall**
  - 1540/27977 (6%) vs 1662/28027 (6%)

- **Fatal or non-fatal stroke**
  - ELOX: 67/3034 (2%) vs 60/3034 (2%)
  - LEADER: 172/4668 (4%) vs 170/4667 (4%)
  - SUSTAIN 6: 30/1648 (2%) vs 30/1649 (2%)
  - EXSCEL: 187/7356 (3%) vs 187/7356 (3%)
  - Harmony Outcomes: 94/4731 (2%) vs 98/4732 (2%)
  - REWIND: 158/4949 (3%) vs 159/4952 (4%)
  - PIONEER 6: 12/1593 (1%) vs 12/1592 (1%)

- **Overall**
  - 7221/27977 (3%) vs 852/28027 (3%)

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**Figure 2:** Risk of MACE and each of its components

Three-component MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs are calculated over an estimated median follow-up of 3·2 years. MACE—major adverse cardiovascular events. GLP-1—glucagon-like peptide-1. NNT—number needed to treat. *For PIONEER 6, data for fatal and non-fatal myocardial infarction and stroke were not available, so numbers and estimates refer to non-fatal myocardial infarction and non-fatal stroke exclusively.
The incidence of severe hypoglycaemia, pancreatitis, and pancreatic cancer did not differ between GLP-1 receptor agonist treatment and placebo (appendix p 9). The incidence of retinopathy also did not differ between GLP-1 receptor agonist treatment and placebo (appendix p 9).

**Discussion**

Our meta-analysis includes data for 13 084 (30%) more patients, 13 94 (29%) more MACE endpoint events, 1818 (95%) more kidney events, and about 56 patients, 1394 (29%) more MACE endpoint events, and >32 kg/m². ‡In REWIND, the age group categories used were <66 and ≥66 years; in LEADER, the age group categories used were ≤32 kg/m² · 0% in Harmony Outcomes, >7 2% in REWIND, and >8 · 5% in SUSTAIN-6, >8·0% in EXSCEL, >8 · 5% in PIONEER 6. Inn REWIND, the BMI categories used were <32 kg/m² and >32 kg/m². *High baseline HbA1c was defined as >7%

The reduction in myocardial infarction (9% relative risk reduction for fatal or non-fatal myocardial infarction) was less robust, although was directionally concordant. The NNT for MACE in our meta-analysis was 75 (95% CI 50–151) over an estimated median duration of follow-up of 3-2 years. Notably, the relative risk reduction in MACE in a recent meta-analysis of cardiovascular outcomes reported in the various GLP-1 receptor agonist trials. These include differences in the specific molecule tested, in the patients enrolled, and in the duration of follow-up. Albiluglutide, dulaglutide, lixisenatide, and semaglutide are more similar, structurally, to native GLP-1, whereas exenatide and lixisenatide are based, structurally, on exendin-4.26,27 Duration of treatment effect also differs substantially between the drugs studied, although effect duration does not reflect structural
homology, with some GLP-1 receptor agonists of each type having a short pharmacologic half-life (eg, lixisenatide 2–3 h and liraglutide 12 h), and with others having a long half-life (eg, dulaglutide 120 h and subcutaneous semaglutide 170 h) or being available as a sustained-release formulation (exenatide), reflected in daily versus weekly dosing. The oral formulation of semaglutide used in PIONEER 6 required daily dosing. With the seven trials now available, it was possible to examine whether these pharmacological characteristics, and their permutations, affect treatment efficacy. Although duration of drug action did not seem to modify the treatment effect, there was a suggestion of a possible interaction related to chemical structure, with a potentially smaller effect on MACe of drugs based on exendin-4 (although this finding did not reach the threshold for significance). However, this apparent interaction could be unduly influenced by ELIXA, which was unique in recruiting patients with a recent acute coronary syndrome (and also used a very short-acting agent, administered once daily), and poor adherence in EXSCEL (40% permanent treatment discontinuation), or might be a chance finding. The ongoing AMPLITUDE-O cardiovascular outcome trial (NCT03496298) of efpeglenatide, a long-acting, exendin-4 receptor agonist, will provide more insights into MACe and cardiovascular safety.

### Table 1: GLP-1 receptor agonist treatment effect on cardiovascular outcomes

<table>
<thead>
<tr>
<th>GLP-1 receptor agonist</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>NNT (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELIXA</td>
<td>212/3034 (7%)</td>
<td>0.94 (0.78–1.13)</td>
<td>108 (77 to 260)</td>
<td>0.001</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>62/1648 (4%)</td>
<td>1.05 (0.74–1.50)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>EXSCEL</td>
<td>507/7356 (7%)</td>
<td>0.86 (0.77–0.97)</td>
<td>0.016*</td>
<td></td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>196/4733 (4%)</td>
<td>0.95 (0.79–1.16)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>REWIND</td>
<td>536/4949 (11%)</td>
<td>0.90 (0.80–1.01)</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>PIONEER 6</td>
<td>23/3591 (1%)</td>
<td>0.51 (0.31–0.84)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1916/27977 (7%)</td>
<td>2146/28027 (8%)</td>
<td>0.88 (0.83–0.95)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Composite kidney outcome including macroalbuminuria

<table>
<thead>
<tr>
<th>GLP-1 receptor agonist</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>NNT (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>172/2539 (6%)</td>
<td>0.84 (0.68–1.02)</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>62/1648 (4%)</td>
<td>1.11 (0.77–1.61)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>EXSCEL</td>
<td>239/7355 (3%)</td>
<td>0.91 (0.77–1.12)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>REWIND</td>
<td>213/4949 (4%)</td>
<td>0.88 (0.80–1.01)</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>PIONEER 6</td>
<td>21/3591 (1%)</td>
<td>0.80 (0.69–1.44)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1716/26160 (9%)</td>
<td>2017/20142 (10%)</td>
<td>0.83 (0.78–0.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Worsening of kidney function

<table>
<thead>
<tr>
<th>GLP-1 receptor agonist</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>NNT (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>35/3932 (1%)</td>
<td>1.16 (0.74–1.83)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>87/6688 (2%)</td>
<td>0.89 (0.67–1.29)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>EXSCEL</td>
<td>18/1648 (1%)</td>
<td>1.28 (0.64–2.58)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>REWIND</td>
<td>246/4656 (5%)</td>
<td>0.88 (0.74–1.05)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>555/20753 (3%)</td>
<td>662/20762 (3%)</td>
<td>0.87 (0.73–1.03)</td>
<td>0.098</td>
</tr>
</tbody>
</table>

Figure 4: All-cause mortality, hospital admission for heart failure, and kidney outcomes

Data for kidney outcomes were not available for Harmony Outcomes or PIONEER 6. The broader composite kidney outcome including macroalbuminuria consisted of development of macroalbuminuria, doubling of serum creatinine or 40% or greater decline in estimated glomerular filtration rate (eGFR), development of end-stage kidney disease, or death due to kidney disease (details in appendix [pp 3–4]; for EXSCEL, data are for new-onset macroalbuminuria alone. The narrower worsening of kidney function outcome was defined as either doubling of serum creatinine or 40% or greater decline in eGFR (details in appendix [pp 3–4]; for EXSCEL, the narrower worsening of kidney function outcome included development of end-stage kidney disease or death due to kidney disease. NNTs are calculated over an estimated median follow-up of 3.2 years. GLP-1=glucagon-like peptide-1. NNT=number needed to treat. *Not regarded as significant because of hierarchical statistical testing plan. †Negative value indicates a number needed to harm.
based GLP-1 receptor agonist, should provide more evidence to address this question.

The difference in patient population enrolled in the various GLP-1 receptor agonist trials has also been considered a potential explanation for the difference in outcomes among the studies.\(^1\) Notably, the absence of a clear reduction in the primary MACE endpoint in EXSCEL has been attributed to the higher proportion of patients without established cardiovascular disease included in that trial, compared with the preceding GLP-1 receptor agonist trials. The inclusion of PIONEER 6 and, especially, REWIND allowed us to examine this question, with an almost doubling in the number of primary prevention patients, overall, exposed to a GLP-1 receptor agonist. However, the number of MACE outcome events in the primary prevention patients was small, limiting the statistical power of this analysis. Although there was no heterogeneity identified for the effect of GLP-1 receptor agonist treatment on MACE in primary versus secondary prevention patients (suggesting a beneficial effect irrespective of the presence or absence of established cardiovascular disease), the statistical test for interaction is weak. Therefore, we cannot be certain that any relative risk reduction in primary prevention patients would be the same as in secondary prevention patients, and, even if it was, the absolute risk reduction in the primary prevention population will be smaller, and the treatment likely to be less cost-effective, because individuals without established cardiovascular disease are at lower baseline risk than those with established cardiovascular disease. As such, these additional data might not be sufficiently robust to challenge the guideline recommendations only to use GLP-1 receptor agonists to reduce the risk of cardiovascular events in patients with established cardiovascular disease.\(^2\)

Duration of follow-up was a further potential explanation for discrepancy in trial outcomes, with, for example, the much shorter follow-up in ELIXA (median 2-1 years) than in LEADER (median 3-8 years), highlighted as an important difference between the first two large cardiovascular outcome trials with a GLP-1 receptor agonist. However, duration of follow-up did not seem to modify the benefit of treatment on the composite MACE outcome in our analysis.

Two of the other subgroups merit discussion. The effect of GLP-1 receptor agonist treatment on MACE was consistent across subgroups based on age and kidney function. Because older age and lower eGFR were associated with higher rates of MACE, the absolute benefit is likely to be greater in these subgroups.

This updated meta-analysis also shows for the first time that treatment with a GLP-1 receptor agonist reduces the risk of hospital admission for heart failure, although the reduction in risk was small in relative (HR 0.91, 95% CI 0.83–0.99) and absolute (NNT 312, 95% CI 165–2810) terms and was not statistically robust. This effect was also much smaller than seen with SGLT2 inhibitors, which have shown a relative risk reduction of 31% (21–39) and an NNT of 100 (79–147) over a similar median duration of follow-up (3.2 vs 3.3 years). Nevertheless, a GLP-1 receptor agonist might be an alternative in a patient with heart failure (or kidney impairment) who cannot take a SGLT2 inhibitor because of intolerance or a contraindication.\(^3\) The explanation for why GLP-1 receptor agonists should have a beneficial effect on heart failure outcomes is not clear, especially since these drugs have not shown any benefit in trials done in patients with established heart failure with reduced ejection fraction.\(^4\)

One possibility is that this favourable effect in the meta-analysis is secondary to reduction in myocardial infarction, a common precursor of heart failure. In this context, it is notable that the largest reductions in heart failure were in the two trials (Harmony Outcomes and LEADER) with the greatest reduction in myocardial infarction. This hypothesis, however, needs further investigation, for example with examination of the time sequence of cardiovascular events in individual patients.

Overall, GLP-1 receptor agonists are clearly cardioprotective drugs. The time course of their effects, apparent in the individual trials, and the types of cardiovascular events prevented, suggest that GLP-1 receptor agonists have mainly an anti-atherothrombotic effect. This profile is distinct from that of the SGLT2 inhibitors, which show an effect on cardiovascular outcomes much more rapidly, with a more pronounced effect on heart failure, raising the possibility of therapeutic synergy from the combination of these two classes of antidiabetes drugs.\(^1\)

With respect to kidney outcomes, although we found that GLP-1 receptor agonists clearly reduced the risk of worsening of kidney function when assessed with a broad composite outcome, this effect was driven by a reduction in urinary albumin excretion, and the benefit based on decline in eGFR (or increase in creatinine) was non-significant and less pronounced than the effect seen with SGLT2 inhibitors.\(^5\)\(^6\) The relative risk reduction in the harder kidney endpoint in a pooled analysis of the three large, broadly inclusive, cardiovascular outcome trials of SGLT2 inhibitors was 45% (95% CI 36–52), with an NNT of 79 (69–99),\(^1\) compared with a non-significant 13% (HR 0.87, 0.73–1.03; NNT 245 [118 to 1064 (number needed to harm)]) with GLP-1 receptor agonists in the present meta-analysis.\(^1\)

Notably, the results of our meta-analysis suggest that previous concerns about pancreatitis and pancreatic cancer with GLP-1 receptor agonists seem unfounded, and there was also no increase in risk of severe hypoglycaemia or thyroid cancer. We also identified no overall increase in adverse eye outcomes, although these were inconsistently defined in the included trials, a deficit that should be remedied in future studies. The outcomes reported did not require systematic eye examination and this too is required for a full understanding of the effect
of any glucose-lowering therapy on eye health. A dedicated trial of this type is currently underway with semaglutide (FOCUS trial [NCT03811561]). Other limitations of our meta-analysis include the absence of patient-level data, restriction of subgroup analyses to the primary three-component MACE outcome, and our ability to examine only the secondary endpoints and adverse events of special interest reported by the investigators of the included trials.

In conclusion, the results of our up-to-date meta-analysis show that, in patients with type 2 diabetes, GLP-1 receptor agonists reduced three-component MACE and its individual components, as well as all-cause mortality and risk of hospital admission for heart failure. Treatment with a GLP-1 receptor agonist also reduced the risk of worsening kidney function, due mainly to a decrease in development of macroalbuminuria. These benefits were obtained without an increase in risk of severe hypoglycaemia, pancreatic adverse effects, or thyroid cancer.

Contributors
Data extraction was done by RR and SLK and the analyses were done by SLK and replicated by KFD, supervised by PSJ. All authors were involved in data interpretation and the writing or editing of the report.

Declaration of interests
NS has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Napp Pharmaceuticals, and Sanofi, and has received grant support from Boehringer Ingelheim. DP is an investigator on the EMPA-KIDNEY trial (investigating empagliflozin in patients with chronic kidney disease), funded by a grant from Boehringer Ingelheim to the University of Oxford (Oxford, UK), but he obtains no salary support from the grant; DP’s employer, the Clinical Trial Service Unit at the University of Oxford, has a staff policy of not accepting honoraria or consultancy fees from industry. PSJ has received advisory board or speaker fees from Novartis, Boehringer Ingelheim, and Cytokinetika, and research grants from Boehringer Ingelheim. His employer, the University of Glasgow (Glasgow, UK), has received payment for his work on trials funded by AstraZeneca. MCP has received consultancy fees from Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Napp Pharmaceuticals, and Eli Lilly. JVV’s employer, the University of Glasgow, has been paid by AbbVie, Aegerion, AstraZeneca, Bayer, Bristol-Myers Squibb, DiAscor, GSK, Merck Sharp & Dohme, Novartis, Resverlogix, and Theracos for his participation in clinical trials and by Alnylam, AstraZeneca, Cardurion, Novartis, and Pfizer for consultancy, advisory board membership, or lectures. SLK, RR, KFD, and LJ declare no competing interests.

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