Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis

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Summary

Background Glucagon-like peptide-1 (GLP-1) receptor agonists are effective glucose-lowering drugs. Findings from cardiovascular outcome trials showed cardiovascular safety of GLP-1 receptor agonists, but results for cardiovascular efficacy were varied. We aimed to examine overall cardiovascular efficacy for lixisenatide, liraglutide, semaglutide, and extended-release exenatide.

Methods In this systematic review and meta-analysis, we analysed data from eligible trials that assessed the safety and efficacy of GLP-1 receptor agonists compared with placebo in adult patients (aged 18 years or older) with type 2 diabetes and had a primary outcome including, but not limited to, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. We searched PubMed and MEDLINE without language restrictions up to Sept 18, 2017, for eligible trials. We did a meta-analysis of available trial data using a random-effects model to calculate overall hazard ratios (HRs) for cardiovascular efficacy outcomes and odds ratios for key safety outcomes.

Findings Of 12 articles identified in our search and screened for eligibility, four trials of cardiovascular outcomes of GLP-1 receptor agonists were identified: ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide), and EXSCEL (extended-release exenatide). Compared with placebo, GLP-1 receptor agonist treatment showed a significant 10% relative risk reduction in the three-point major adverse cardiovascular event primary outcome (cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke; HR 0·90, 95% CI 0·82–0·99; p=0·033), a 13% RRR in cardiovascular mortality (0·87, 0·79–0·96; p=0·007), and a 12% relative risk reduction in all-cause mortality (0·88, 0·81–0·95; p=0·002), with low-to-moderate between-trial statistical heterogeneity. No significant effect of GLP-1 receptor agonists was identified on fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure. Overall, no significant differences were seen in severe hypoglycaemia, pancreatitis, pancreatic cancer, or medullary thyroid cancer reported between GLP-1 receptor agonist treatment and placebo.

Interpretation Our findings show cardiovascular safety across all GLP-1 receptor agonist cardiovascular outcome trials and suggest that drugs in this class can reduce three-point major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality risk, albeit to varying degrees for individual drugs, without significant safety concerns. GLP-1 receptor agonists have a favourable risk–benefit balance overall, which should allow the choice of drug to be individualised to each patient's needs.

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Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists are effective treatments for type 2 diabetes, which lower glucose concentrations without weight gain (often with weight loss) and with low risk for hypoglycaemia.[1] Their association with modest reductions in systolic blood pressure and lipid concentrations make them suitable candidates for use in patients with type 2 diabetes at increased risk of cardiovascular disease.[2] In these patients, cardiovascular disease remains the leading cause of death. Although there is evidence that improved glucose control can confer a modest cardiovascular benefit, some glucose-lowering medications might increase, rather than reduce cardiovascular risk. This paradox has prompted international regulatory agencies to revise diabetes drug approval processes, requiring cardiovascular safety to be shown for all new drug applications. To further facilitate a common assessment of cardiovascular risk, trials must evaluate important cardiovascular outcomes including cardiovascular mortality, myocardial infarction, and stroke.

Four cardiovascular outcomes trials evaluating the efficacy and safety of GLP-1 receptor agonists have been completed to date: ELIXA (lixisenatide),[3] LEADER (liraglutide),[4] SUSTAIN 6 (semaglutide),[5] and EXSCEL (extended-release exenatide).[6] Results from all four trials showed cardiovascular safety (non-inferiority compared with placebo), with findings from two trials (LEADER

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Research in context

Evidence before this study

Glucagon-like peptide-1 (GLP-1) receptor agonists are effective glucose-lowering drugs for the treatment of type 2 diabetes. Four randomised controlled trials of cardiovascular outcomes with GLP-1 receptor agonists (lixisenatide, liraglutide, semaglutide, and extended-release exenatide) have all shown cardiovascular safety for this class of drugs, but had mixed results for cardiovascular efficacy. To examine the overall risk–benefit profile for GLP-1 receptor agonists, we aimed to synthesise the data available by searching PubMed and MEDLINE for reports of randomised controlled trials and meta-analyses that compared GLP-1 receptor agonists with placebo, and that had a primary outcome including, but not limited to, cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke. The search terms used were "glucagon-like peptide-1 receptor agonist", "exenatide", "liraglutide", "lixisenatide", "semaglutide", "dulaglutide", "albiglutide", "placebo", "cardiovascular mortality", "myocardial infarction", and "stroke". Searches done up until Sept 18, 2017, confirmed that only the ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide), and EXSCEL (extended-release exenatide) trials met the specified criterion of including cardiovascular outcomes of interest in the primary outcome.

Added value of this study

Our meta-analysis of study-level data from the four trials showed an overall 10% relative risk reduction with GLP-1 receptor agonist therapy in the three-point composite outcome of cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke. There was also an overall relative risk reduction in cardiovascular mortality and all-cause mortality. No significant differences were seen between GLP-1 receptor agonist-treated and placebo-treated patients for the incidence of severe hypoglycaemia, pancreatitis, pancreatic cancer, or medullary thyroid cancer. Overall, these data show a favourable risk–benefit profile for GLP-1 receptor agonists, although there were differences between individual drugs with respect to their effect on cardiovascular outcomes in the separate trials.

Implications of all the available evidence

The ability of GLP-1 receptor agonists to reduce cardiovascular morbidity and mortality in patients with type 2 diabetes who are at moderate-to-high cardiovascular risk, in addition to their proven glucose-lowering ability, represents a major therapeutic advance. Treatment decisions about GLP-1 receptor agonists for individuals with type 2 diabetes should be based on factors important to patients, including convenience, potency, ease of delivery, tolerability, and price, as well as their effect on cardiovascular risk.

and SUSTAIN 6) showing significant reductions in their primary three-point major adverse cardiovascular events (MACE) outcome (cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke).[4,5] Only liraglutide was associated with significant reductions in all-cause mortality and cardiovascular mortality, and only semaglutide was associated with a significant reduction in non-fatal stroke outcomes. These varying findings raise important questions about the generalisability of GLP-1 receptor agonist trials to the drug class as a whole.

We synthesised data available from ELIXA, LEADER, SUSTAIN 6, and EXSCEL in a meta-analysis to examine the overall effect of GLP-1 receptor agonists on cardiovascular efficacy and key safety outcomes.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched PubMed and MEDLINE without language restrictions to identify all eligible trials with a primary outcome including, but not limited to, cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke (outcomes required by regulatory agencies for cardiovascular safety studies in diabetes), comparing the safety and efficacy of GLP-1 receptor agonists with that of placebo, in adult patients with type 2 diabetes. The search terms used were "glucagon-like peptide-1 receptor agonist", "exenatide", "liraglutide", "lixisenatide", "semaglutide", "dulaglutide", "albiglutide", "placebo", "cardiovascular mortality", "myocardial infarction", and "stroke". The search was filtered to include only randomised controlled trials or meta-analyses of human data. Searches were done up until Sept 18, 2017. Data were extracted by RAP and MAB, with conflicts over study inclusion resolved by consensus. Inclusion criteria specified that cardiovascular outcomes of interest were included as part of the primary outcome. This meta-analysis was not prospectively registered in PROSPERO.

Neither ethics approval nor patient consent was required for this analysis.

For an **example of information from a pharmaceutical company's website** see http://www.novonordisk-trials.com/Website/pdf/registry/15076-3748-ctr-redacted.pdf

Data analysis

Results in trial reports (primary trial results and subsequent secondary publications), and their accompanying supplementary materials, were used as the primary source of information. Publicly available additional sources, including, but not limited to, the US Food and Drug Administration, European Medicines Agency, and pharmaceutical company websites, were searched to identify any additional data. When data items were not available, requests for the information were sent to the corresponding authors of trial articles. We assessed the methodological quality of included randomised controlled trials by calculating a Jadad score[7] for each trial. We calculated hazard ratios (HR) and 95% CIs for cardiovascular efficacy outcomes, and numbers of events for safety outcomes were analysed by treatment group.

The primary efficacy outcome for this meta-analysis was the effect of GLP-1 receptor agonists on the incidence of three-point MACE, compared with placebo. We did additional analyses for cardiovascular mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, all-cause mortality, hospital admission for heart failure, and hospital admission for unstable angina. As time to hospital admission for unstable angina was not a prespecified endpoint for EXSCEL, a post-hoc analysis was done in the intention-to-treat population, using a Cox proportional hazards model, stratified by previous cardiovascular event status with treatment as an explanatory variable, and Kaplan-Meier event rates were calculated. We included only adjudicated, confirmed outcomes in the analysis.

HRs and 95% CIs for cardiovascular efficacy outcomes were synthesised using a random-effects model meta-analysis. We assessed heterogeneity of treatment effects between trials using the I^2 index and Cochran's Q test, with p values of less than 0·05 for Cochran's Q test representing significant heterogeneity. I^2 index thresholds describing the degree of heterogeneity[8] are 25% or lower (low), 26–50% (moderate), and greater than 50% (high).

The safety outcomes of interest were severe hypoglycaemia, acute pancreatitis, pancreatic cancer, and medullary thyroid cancer. Event definitions used in each trial are listed in the appendix and include adjudicated, confirmed outcomes, with the exception of severe hypoglycaemia (unadjudicated in all identified trials) and non-pancreatic neoplasms (unadjudicated in ELIXA). We did a random-effects model meta-analysis on the safety outcome event numbers to produce an overall odds ratio (OR) and 95% CI. We applied inverse-variance weights to log-OR estimates from individual trials to obtain the weighted mean log-OR estimate, which was then exponentiated to obtain the overall OR estimate. Heterogeneity of treatment effects across the trials was assessed using the I^2 index and Cochran's Q test. An analysis accounting for the different follow-up times between trials was not possible because safety outcome HRs could not be obtained in all cases.

All analyses were done using Biostat Comprehensive Meta-Analysis software (version 2.0).

Role of the funding source

The study was designed by the EXSCEL trial clinical leads and executive committee (MAB, RAP, RJM, NJP, SMG, JBB, JCC, NI, APM, PÖ, NRP, AR, BZ, AH, and RRH), two members of which were employed by the study funder. The funder of the study had no role in data collection or data analysis. Apart from those listed as authors on this manuscript, the funder had no role in study design, data interpretation, or writing of the report. All analyses were done independently by the Duke Clinical Research Institute (Durham, NC, USA). RAP and RRH had full access to all data required to complete the analysis. 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 12 articles screened for eligibility, four trials (including 33 457 participants) were eligible and included in the meta-analysis (figure 1). ELIXA compared lixisenatide (up to a maximum dose of 20 µg once per day) with placebo in 6068 patients with type 2 diabetes who had had an acute coronary event and had a mean HbA_{1c} of 7·7% (60·7 mmol/mol), followed up for a median of 2·1 years. LEADER compared liraglutide 1·8 mg once per day with placebo in 9340 patients with type 2 diabetes and established cardiovascular disease (81%) or cardiovascular risk factors and a mean HbA_{1c} of 8·7% (70·6 mmol/mol), followed up for a median of 3·8 years. SUSTAIN 6 compared semaglutide (0·5 mg or 1·0 mg once per week) with placebo in 3297 patients with type 2 diabetes and established cardiovascular disease (83%) or cardiovascular risk factors and a mean HbA_{1c} of 8·7% (70·6 mmol/mol), followed up for a median of 2·1 years. EXSCEL compared extended-release exenatide (2 mg once per week) with placebo in 14 752 patients with type 2 diabetes and established cardiovascular disease (73%) or without previous cardiovascular events and a median HbA_{1c} of 8·0% (IQR 7·3–8·9; 63·9 mmol/mol [56·3–73·8]), followed up for a median of 3·2 years (IQR 2·2–4·4; table).[3–6] Each of the four included trials had a calculated Jadad score of 5, suggestive of high methodological quality. The primary outcome for LEADER, SUSTAIN 6, and EXSCEL was a three-point MACE, whereas ELIXA used a four-point MACE that added hospital admission for unstable angina to the three-point MACE components. Key trial design features and patient characteristics are listed in the table. Patients were of similar ages (60–65 years), 61–70% were men,

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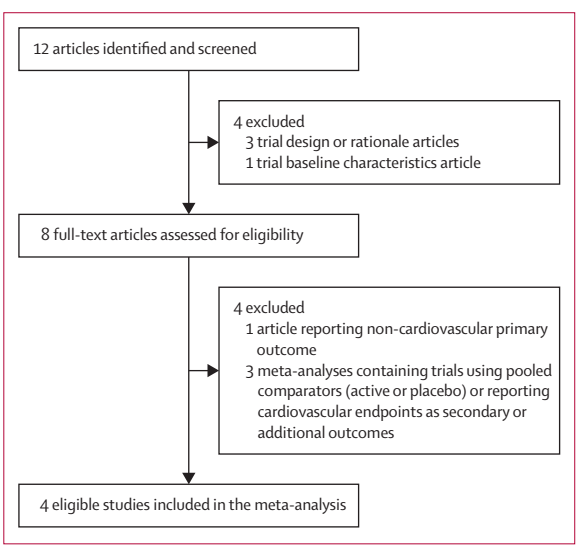

Figure 1: **Study selection**

	ELIXA (n=6068)	LEADER (n=9340)	SUSTAIN 6 (n=3297)	EXSCEL (n=14 752)
Study treatment	Lixisenatide (up to 20 µg once per day)	Liraglutide (1·8 mg once per day)	Semaglutide (0·5 mg or 1·0 mg once per week)	Exenatide (2 mg once per week)
Key inclusion criteria	HbA_{1c} 5·5–11·0% (36·6–96·7 mmol/mol); acute coronary syndrome within 180 days; age ≥30 years	HbA_{1c} ≥7·0% (≥53·0 mmol/mol); age ≥50 years with cardiovascular disease, chronic heart failure (NYHA class II or III), chronic kidney disease (stage 3 or higher), or age ≥60 years with at least one cardiovascular risk factor	HbA_{1c} ≥7·0% (≥53·0 mmol/mol); age ≥50 years with cardiovascular disease, chronic heart failure (NYHA class II or III), chronic kidney disease (stage 3 or higher), or age ≥60 years with at least one cardiovascular risk factor	HbA_{1c} 6·5–10·0% (47·5–85·8 mmol/mol); established cardiovascular disease and primary prevention; age ≥18 years
Key safety exclusion criteria	History of unexplained pancreatitis, chronic pancreatitis, pancreatectomy; personal or family history of medullary thyroid cancer or genetic conditions that predispose to medullary thyroid cancer (eg, multiple endocrine neoplasia syndromes)	Family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid cancer; personal history of non-familial medullary thyroid cancer; screening calcitonin value ≥50 ng/L	History of chronic pancreatitis or idiopathic acute pancreatitis; personal or family history of multiple endocrine neoplasia type 2 or familial medullary thyroid cancer; personal history of non-familial medullary thyroid cancer; screening calcitonin value ≥50 ng/L	History of pancreatitis; personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2; screening calcitonin >40ng/L*
Glycaemic management	If screening HbA_{1c} <8·5%, pre-emptive downtitration of insulin, meglitinides or sulfonylureas at baseline randomisation visit (visit 2, week 0); investigator managed as per clinical guidelines after randomisation; uptitration of study treatment dose as tolerated; adjustment of background AHA therapy (concomitant DPP-4i and GLP-1 receptor agonist prohibited)	If screening HbA_{1c} ≤8·0%, pre-emptive downtitration of premixed insulin by minimum 20% (if screening HbA_{1c} >8·0%, pre-emptive downtitration of premixed insulin should also be considered); dose escalation 0·6 mg to 1·8 mg over 2 weeks after randomisation as tolerated; 2 weeks after randomisation, adjustment of concomitant AHAs at investigator's discretion (if glycaemic targets not achieved using maximum tolerable dose of study treatment), including insulin and oral agents (concomitant DPP-4i, GLP-1 receptor agonist and pramlintide prohibited); if hypoglycaemia required medication reduction, non-trial AHAs were reduced first (insulins, meglitinides, sulfonylureas)	If screening HbA_{1c} ≤8·0%, pre-emptive downtitration of premixed insulin by minimum 20% (if screening HbA_{1c} >8·0%, pre-emptive downtitration of premixed insulin allowed if increase in hypoglycaemic events; adjustment of concomitant AHAs at investigator's discretion; concomitant DPP-4i, GLP-1 receptor agonist, and pramlintide prohibited)	All antihyperglycaemic regimens adjusted by usual care providers in line with local or national guidelines; adjustments to antihyperglycaemic regimen permitted any time after randomisation, but investigators asked to avoid this until HbA_{1c} levels reflected initial effects of randomised study medication; adjustment of concomitant AHAs at usual care provider discretion (GLP-1 receptor agonist prohibited, but DPP-4i permitted); if hypoglycaemia required medication reduction, non-trial AHAs were reduced first
Statistical analysis	Primary analysis: simultaneous assessment for non-inferiority (upper bound of the 95% CI <1·3) and superiority (upper bound of the 95% CI <1·0) for MACE-4 endpoint, no hierarchical testing; secondary cardiovascular endpoints: MACE-4 and congestive heart failure; MACE-4, congestive heart failure, and coronary revascularisation, no hierarchical testing or adjustment for multiple testing	Primary analysis: assessment for non-inferiority (upper bound of the 95% CI <1·3) for the MACE-3 endpoint, hierarchical testing strategy used, requiring demonstration of non-inferiority before testing for superiority (upper bound of the 95% CI <1·0) for MACE-3 endpoint; secondary cardiovascular endpoints: MACE-3 and revascularisation, congestive heart failure, or unstable angina; MACE-3 components; non-cardiovascular death; all-cause mortality, no hierarchical testing or adjustment for multiple testing	Primary analysis: assessment for non-inferiority (upper bound of the 95% CI <1·8) for MACE-3 endpoint, testing for superiority was not prespecified and not adjusted for multiple testing; secondary cardiovascular endpoints: MACE-3 and revascularisation, congestive heart failure, or unstable angina; MACE-3, revascularisation, congestive heart failure, and unstable angina components; non-cardiovascular death; all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, no hierarchical testing or adjustment for multiple testing	Primary analysis: hierarchical assessment of non-inferiority (upper bound of the 95% CI <1·3) followed by superiority (upper bound of the 95% CI <1·0) for MACE-3 endpoint; secondary cardiovascular endpoints; conditional on demonstrating superiority of MACE-3: hierarchical testing for superiority in the following order: all-cause mortality, each component of the cardiovascular composite, hospital admission for acute coronary syndrome, hospital admission for heart failure
Age (years)	59·9 (9·7)†	64·2 (7·2)†	64·6 (7·4)	61·9 (9·4)
Sex				
Men	4207 (69%)	6003 (64%)	2002 (61%)	9149 (62%)
Women	1861 (31%)	3337 (36%)	1295 (39%)	5603 (38%)
BMI (kg/m^2)	30·1 (5·6)†	32·5 (6·3)†	32·8 (6·2)	32·7 (6·4)
White	4576 (75%)	7238 (78%)	2736 (83%)	11 175 (76%)
Diabetes duration (years)	9·2 (8·2)†	12·8 (8·0)†	13·9 (8·1)	13·1 (8·3)
HbA_{1c} (%)	7·7 (1·3)†	8·7 (1·6)†	8·7 (1·5)	8·1 (1·0)
Proportion with established cardiovascular disease‡	6068 (100%)	7598 (81%)	2735 (83%)	10 782 (73%)
Proportion with heart failure	1358 (22%)†	1667 (18%)†	777 (24%)	2389 (16%)
Systolic blood pressure (mm Hg)	129·0 (17·0)†	135·9 (17·8)†	135·6 (17·2)	135·4 (16·9)†

(Table continues on next page)

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and 75–83% were white. Mean diabetes duration was between 9·3 and 13·9 years, and mean baseline HbA_{1c} ranged from 7·7% to 8·7% (60·7–70·6 mmol/mol). The median duration of follow-up ranged from 2·1 to 3·8 years, and the number of participants who had a confirmed primary outcome varied from 254 participants (SUSTAIN 6) to 1744 participants (EXSCEL).

In the meta-analysis for three-point MACE, use of GLP-1 receptor agonists in ELIXA, LEADER, SUSTAIN 6, and EXSCEL was associated with a significant 10% relative risk reduction (HR 0·90, 95% CI 0·82–0·99; p=0·033), compared with placebo, with a non-significant, moderate degree of heterogeneity between trials (figure 2).

There was a significant relative risk reduction in cardiovascular mortality of 13% compared with placebo (HR 0·87, 0·79–0·96; p=0·007), and a significant relative risk reduction in all-cause mortality of 12% (0·88, 95% CI 0·81–0·95; p=0·002), with no heterogeneity for either outcome (I^2=0%; figure 2). Compared with placebo, no significant effects of GLP-1 receptor agonists were seen for fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure, with no significant heterogeneity for any of these endpoints (figure 2, appendix).

In our analysis of safety outcomes, compared with placebo, no significant effect of GLP-1 receptor agonists was seen on the proportions of patients who had severe hypoglycaemia (OR 0·93, 95% CI 0·74–1·18; p=0·56), although there was a significant high degree of heterogeneity between trials (p=0·01; figure 3). No significant effects were seen on the proportions of patients reported to have acute pancreatitis (0·90, 0·63–1·28; p=0·54) or pancreatic cancer (0·83, 0·33–2·11; p=0·70). There were four medullary thyroid carcinomas reported in LEADER and EXSCEL (two with GLP-1 receptor agonist and two with placebo), but no medullary thyroid cancer events were reported in either group of SUSTAIN 6 or ELIXA,[9] precluding a meta-analysis (appendix).

Papillary thyroid cancers were reported in ELIXA (n=2, one in each treatment group),[10] LEADER (n=8, five in the liraglutide group and three in the placebo group),[11] SUSTAIN 6 (n=3, one in the semaglutide 1 mg treatment group and two in the placebo group; Lindegaard MLS, Novo Nordisk, personal communication), and in EXSCEL (n=14, ten in the exenatide group and four in the placebo group)—an overall numerical imbalance of 17 in the GLP-1 receptor agonist groups versus ten in the placebo groups (appendix).

Discussion

The results of four cardiovascular outcomes trials using GLP-1 receptor agonists, which included a total of 33 457 participants, provide a large quantity of evidence in which to evaluate the overall effect of GLP-1 receptor agonists on cardiovascular efficacy and key safety outcomes of interest. Because individual trials are frequently

	ELIXA (n=6068)	LEADER (n=9340)	SUSTAIN 6 (n=3297)	EXSCEL (n=14 752)
(Continued from previous page)				
Diastolic blood pressure (mm Hg)	NA	77·2 (10·3)†	77·0 (10·0)	78·2 (10·3)†
LDL cholesterol (mmol/L)	2·0 (0·9)†	2·3 (0·9)†	2·1 (1·2)	2·4 (1·0)†
HDL cholesterol (mmol/L)	1·1 (0·3)†	1·2 (0·3)†	1·1 (0·7)	1·1 (0·9)†
Insulin use	2374 (39%)	4159 (45%)	1913 (58%)	6838 (46%)
Metformin use	4021 (66%)	7136 (76%)	2414 (73%)	11 295 (77%)
Sulfonylurea use	2004 (33%)	4721 (51%)	1410 (43%)	5401 (37%)
Thiazolidinedione use	95 (2%)	573 (6%)	76 (2%)	579 (4%)
DPP-4 inhibitor use	NA	6 (<1%)	5 (<1%)	2203 (15%)
SGLT2 inhibitor use	NA	NA	5 (<1%)	77 (1%)
Median duration of follow-up (years)	2·1	3·8	2·1	3·2 (2·2–4·4)
Primary outcome	MACE-4 (non-inferiority)	MACE-3 (non-inferiority)	MACE-3 (non-inferiority)	MACE-3 (superiority for efficacy, non-inferiority for safety)
Participants with a primary outcome	805	1302	254	1744
Primary outcome (HR and 95% CI)	1·02 (0·89–1·17) p<0·001 for non-inferiority p=0·81 for superiority	0·87 (0·78–0·97) p<0·001 for non-inferiority p=0·01 for superiority	0·74 (0·58–0·95) p<0·001 for non-inferiority p=0·02 for superiority	0·91 (0·83–1·00) p<0·001 for non-inferiority p=0·06 for superiority

Data are n, %, or mean (SD), unless otherwise specified. HbA_{1c}=glycated haemoglobin. NYHA=New York Heart Association. AHA=antihyperglycaemic agent. DPP-4=dipeptidyl peptidase 4. GLP-1=glucagon-like peptide-1. MACE-4=four-point MACE (cardiovascular-related death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina requiring hospital admission). MACE-3=three-point major adverse cardiovascular events (cardiovascular-related death, non-fatal myocardial infarction, or non-fatal stroke). NA=not available. SGLT2=sodium-glucose co-transporter-2. HR=hazard ratio. *Initial exclusion threshold value for calcitonin screening was >100 ng/L; value was amended to >40 ng/L in protocol amendment 2 (May, 2011). Randomisation was permitted before return of the calcitonin values; if calcitonin thresholds for exclusion were exceeded, patients remained in the trial, but study drug was discontinued. †Data are for active treatment group, overall data (active and placebo groups) not available. ‡History of cardiovascular, cerebrovascular, or peripheral vascular disease.

Table: **Key trial design features and baseline participant characteristics**

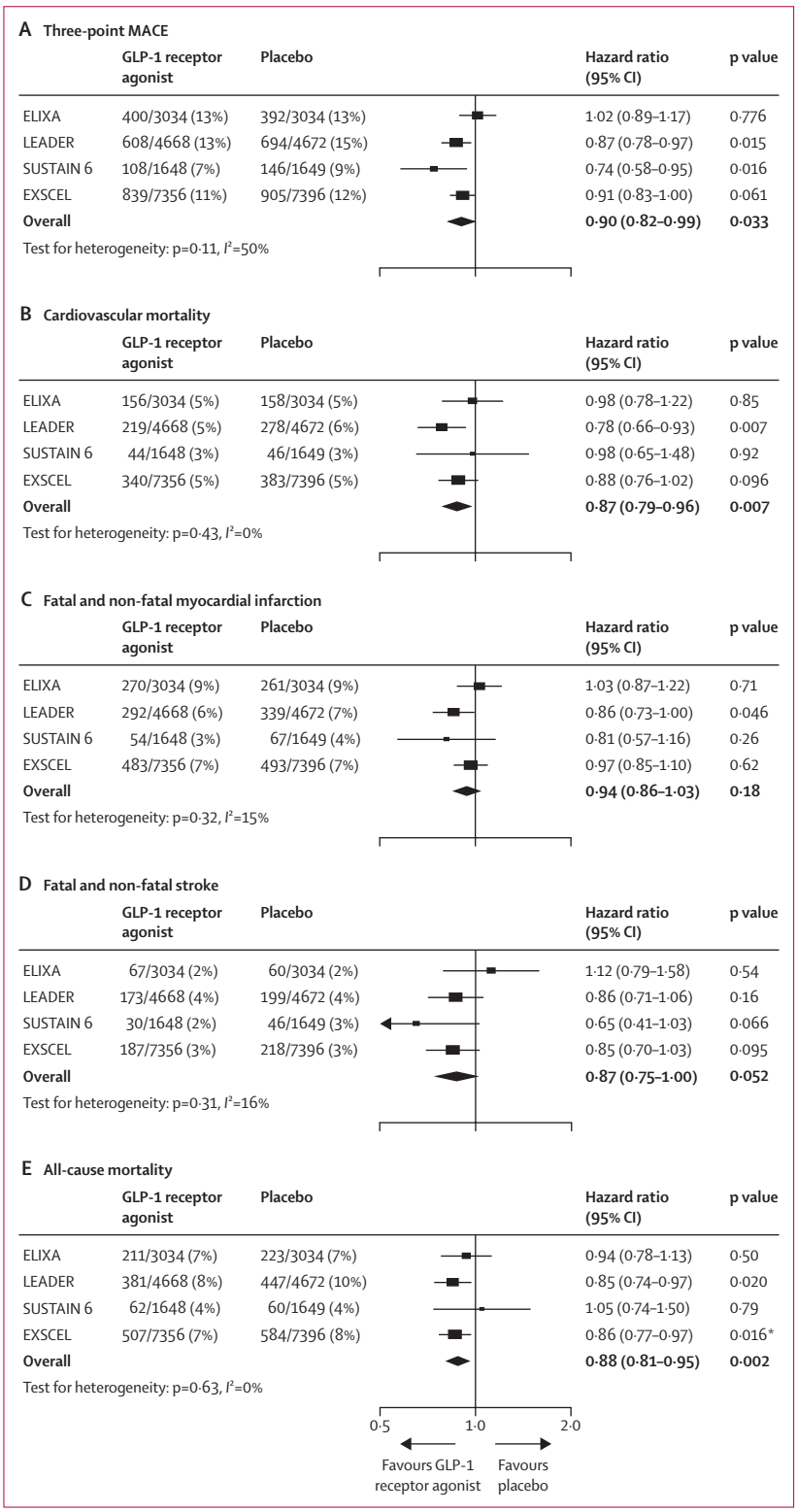

Figure 2: **Cardiovascular and mortality outcomes**
Three-point MACE is a composite of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. MACE=major adverse cardiovascular events. GLP-1=glucagon-like peptide-1. *Within-trial difference in all-cause mortality in EXSCEL was not regarded as significant on the basis of the hierarchical statistical testing plan.

underpowered to evaluate single components of a composite primary outcome or to clarify the effect on less common safety events, we did meta-analyses on all the available data to better understand the risk–benefit profile of the GLP-1 receptor agonist drug class.

Overall, GLP-1 receptor agonist treatment was associated with significant relative risk reductions in three-point MACE (a composite of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke), cardiovascular mortality, and all-cause mortality, all with low-to-moderate evidence of between-trial statistical heterogeneity. Overall, there was no significant effect of GLP-1 receptor agonists on important secondary outcomes of fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure.

The consistency of cardiovascular safety across the class, reduced numbers of three-point MACE in three of the four reported trials (although significant in the primary analysis only for one trial [LEADER]), and reduced numbers of cardiovascular deaths in the GLP-1 receptor agonist group of all four trials, although individually significant only within LEADER, lend support to the hypothesis that the cardiovascular effects of GLP-1 receptor agonists might be mediated via antiatherogenic mechanisms that decrease cardiovascular risk over time. These mechanisms might include direct and indirect effects of GLP-1 receptor agonist on common cardiovascular risk factors (eg, decreased blood pressure), anti-inflammatory pathways, cardiac output, ischaemic conditioning, and endothelial function.[2]

The larger number of three-point MACE in the active treatment group of ELIXA (400 *vs* 393) gave rise to a non-significant, moderate degree of statistical heterogeneity in the meta-analysis. Contributing factors could include use of a shorter-acting GLP-1 receptor agonist (lixisenatide) in ELIXA or varying degrees of study medication adherence among the trials, which was lowest in EXSCEL with a once-weekly preparation. The potency of each drug might also differ, as suggested by differing degrees of HbA_{1c} lowering in head-to-head trials, lowest for lixisenatide and highest for semaglutide and liraglutide.[12–15] Further reassurance of overall cardiovascular safety of GLP-1 receptor agonists is provided by neutral effects on fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admissions for heart failure, and hospital admissions for unstable angina. The neutral effect seen in ELIXA for all its cardiovascular efficacy endpoints could be related to important differences in the enrolled population compared to the other trials—inclusion only of patients following a recent acute coronary syndrome event, those of younger age, shorter duration of diabetes, and with only median 2·1 years of follow-up.

From a safety standpoint, our findings showed no overall increase in pancreatitis, pancreatic cancer, or severe hypoglycaemia associated with GLP-1 receptor agonist therapy, although there was significant heterogeneity

between trials for pancreatic cancer and severe hypoglycaemia events. For hypoglycaemia, the heterogeneity might relate to differences in the protocol-specified management of concomitant antihyperglycaemic therapies (eg, pre-emptive downtitration of insulin or sulfonylureas) at baseline or during follow-up, the definitions of hypoglycaemic events used (appendix), the overall glucose control of the enrolled populations, or the frequency of within-trial use of concomitant glucose-lowering drugs that predispose to hypoglycaemia. Potentially discordant findings for pancreatic cancer are less likely to be attributable to features of trial design or conduct than are findings for hypoglycaemia. Differences between enrolled study populations are not clearly correlated with cancer outcomes, and all four studies prospectively collected and adjudicated pancreatic cancer events using similar criteria. In this analysis, LEADER was an outlier, with an OR nearly three times that of the other studies, which all had ORs of less than 1. This within-trial imbalance in pancreatic cancer events remains unexplained, and a chance finding cannot be excluded. Additional analyses of LEADER, including both adjudicated pancreatic cancer events and pancreatic cancers identified from death adjudication information (using less stringent definitions for pancreatic cancer), identified four additional events in the placebo group, bringing the total to 13 events in the liraglutide group and nine in the placebo group,[4] suggesting a lower effect on pancreatic cancer than was seen in the primary analysis. It is reassuring that our meta-analysis identified no excess of pancreatic cancers in the GLP-1 receptor agonist group overall, but the small number of accrued events (32 with GLP-1 receptor agonist and 34 with placebo) and a significant degree of heterogeneity between trials means that these pooled findings for pancreatic cancer should be interpreted with caution.

An early concern for the GLP-1 receptor agonist class was the potential for an increased risk of thyroid C-cell adenomas and medullary thyroid carcinomas, a finding seen in animal data, but not replicated in human beings.[16] Medullary thyroid cancers are rare, and meta-analyses can be a useful tool to combine available data across trials. However, small event numbers and trials with no reported events in either treatment group makes interpretation of the combined results in this analysis difficult. None of the trials included in our analysis showed meaningful changes in calcitonin concentrations associated with active treatment. An unexpected finding in LEADER and EXSCEL was an imbalance favouring placebo in papillary thyroid cancer incidence, but similar trends were not seen in ELIXA and SUSTAIN 6 (appendix). Although GLP-1 receptors have been identified by immunocytochemistry in some papillary thyroid carcinomas, suggesting potential of GLP-1 receptor agonist to affect cell growth rates, these findings have not been consistent across all studies.[17,18] The pathophysiology of both papillary and medullary thyroid cancers suggests that transformation of normal to potentially malignant cells is a chronic process unlikely to be detected during the comparatively brief follow-up provided in these trials.

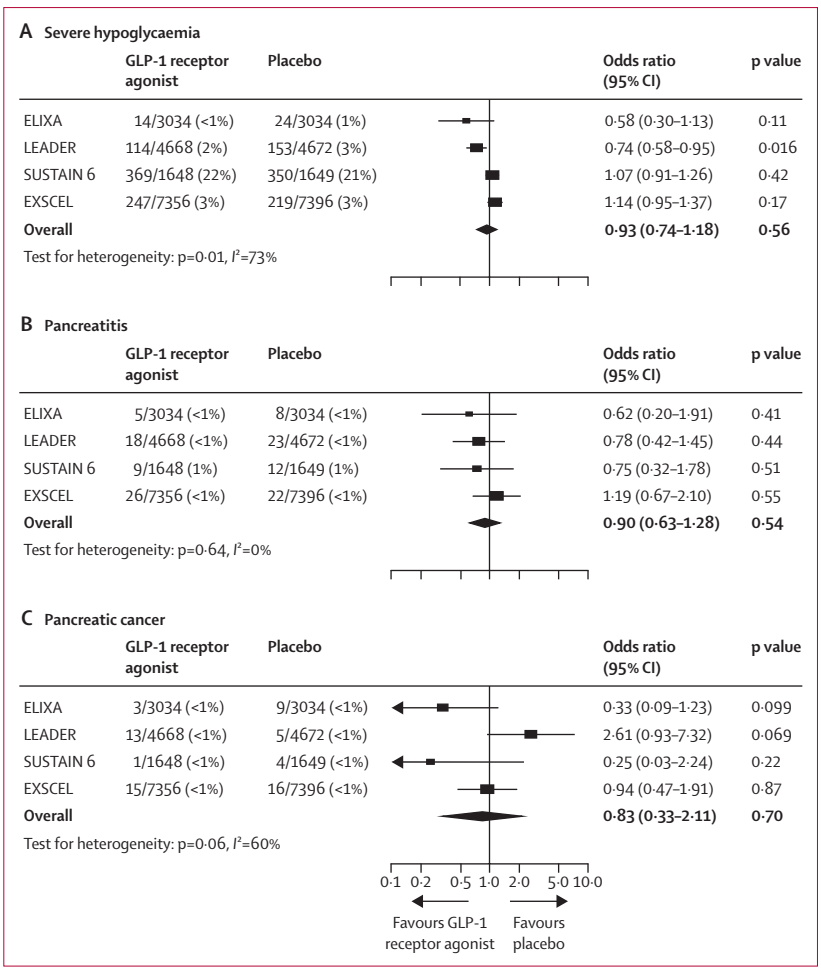

Figure 3: **Safety outcomes**
GLP-1=glucagon-like peptide-1.

The strengths of this meta-analysis were that all trials included were large, multinational, randomised, and placebo-controlled, and prospectively collected events of interest using similar definitions and adjudication processes. The exception is for severe hypoglycaemic events, for which there were minor differences in event definitions, but more importantly, in the protocol-specified management of concomitant glucose-lowering medications, which might have affected rates of hypoglycaemia. These factors make head-to-head comparisons of rates of hypoglycaemia difficult to interpret among the trials and have substantial effects on the meta-analysis, meaning that these findings should be interpreted with caution.

This analysis has several limitations. Patient-level data is considered the gold standard for meta-analysis. In our analysis, we used only aggregate data, which restricts our ability to investigate further any subgroups of interest, to quantify cumulative follow-up time for safety events,

or to fully understand the implications of any missing data. However, the use of common event definitions across trials, particularly for cardiovascular efficacy outcomes, ensures that our analysis has not been compromised by meaningful differences in event ascertainment or adjudication processes. Our findings are also limited by the duration of follow-up for the included studies. Although the studies are considered long-term outcomes studies, they still only span 2–4 years, a fraction of the time patients are likely to use a GLP-1 receptor agonist in clinical practice. Although it is reassuring that there are no suggestions of harm for pancreatitis and cancer outcomes, neither the individual trials, nor this meta-analysis, can exclude additional benefits or harms that might accrue over longer exposure times. Furthermore, no head-to-head cardiovascular outcomes trials have been done for this drug class, limiting detection of outcome differences between GLP-1 receptor agonists of different structure or potency. Finally, the generalisability of these aggregate treatment effect sizes is informed by the populations studied and, as such, is less applicable to patients with diabetes who are at low cardiovascular risk.

Overall, this meta-analysis shows a consistent finding of cardiovascular safety across all GLP-1 receptor agonist drugs evaluated and suggests that this class of glucose-lowering drugs seems to reduce three-point MACE, cardiovascular mortality, and all-cause mortality, albeit with possible differences between individual drugs reflected in the individual trial results. We have not identified any evidence of harm from severe hypoglycaemia, pancreatitis, or pancreatic cancer. Early concerns about GLP-1 receptor agonist-induced medullary thyroid cancers have not been substantiated in this analysis, although the available data do not permit robust conclusions.

The capacity of drugs in the GLP-1 receptor agonist class to reduce major adverse cardiovascular events in patients with type 2 diabetes at moderate-to-high cardiovascular risk and to do so without detrimental effects on other safety parameters represents a major therapeutic advance. Existing data show that the risk–benefit profile for the GLP-1 receptor agonist class seems favourably balanced, but categorisation of drugs by class is less useful when making individual patient treatment decisions. Differences between the GLP-1 receptor agonist drugs do exist in their structure, potency, and effect on cardiovascular risk. The choice of GLP-1 receptor agonist for an individual patient should be based on available evidence for effects on cardiovascular risk, and incorporate drug characteristics important to patients, such as convenience, potency, ease of delivery, tolerability, and price.

Contributors

MAB contributed to the literature search, study design, data collection, data analysis, data interpretation, and figure design, and drafted and edited the report. RAP contributed to the literature search, data collection, figure design, and data interpretation, and edited the report. PM and YL did the statistical analysis, contributed to figure design, and edited the report. JBB, RJM, NJP, JCC, SMG, NI, APM, PÖ, NRP, AR, BZ, and AFH contributed to the study design, data interpretation, and editing of the report. RRH contributed to the study design and data interpretation, and edited the report.

Declaration of interests

MAB has received research support from AstraZeneca, GlaxoSmithKline, and Merck; participated in advisory boards, steering committees, or data safety monitoring boards for Boehringer Ingelheim, AstraZeneca, NovoNordisk, and Theracos; and received honoraria for participation in academic conferences from Sanofi. YL has received grants from Amylin Pharmaceuticals (a wholly owned subsidiary of AstraZeneca), Merck, Janssen Research and Development, GlaxoSmithKline, and Bayer Healthcare. JBB has received grants, non-financial support, and consulting fees and travel reimbursement from AstraZeneca and grants from the US National Institutes of Health (award UL1TR001111); grants, non-financial support, and consulting fees and travel reimbursement from Eli Lilly, GI Dynamics, Merck, AstraZeneca, Lexicon, Orexigen, Takeda, Sanofi, and Novo Nordisk; non-financial support and consulting fees and travel reimbursement from Elcylex Therapeutics, Metavention, vTv Therapeutics, and Adocia; grants from Medtronic Minimed, Johnson & Johnson, Boehringer Ingelheim, GlaxoSmithKline, Scion NeuroStim, Theracos, and Bayer; grants and consulting fees from Intarcia Therapeutics; and consulting fees and travel reimbursement from PhaseBio Pharmaceuticals, Dance Biopharm, Insulin Algorithms, Dexcom, Fractyl, Shenzen HighTide, and NovaTarg; and is a member of the board for the non-profit organisation AstraZeneca HealthCare Foundation. RJM has received grants from AstraZeneca, and grants from GlaxoSmithKline and personal fees from Boehringer Ingelheim. NJP holds stocks or shares in Freedom Health, Physician Partners, RXAdvance, and Florida Medical Associates. JCC has received research grants or honoraria for consultancy or lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and Sanofi (all proceeds have been donated to the Chinese University of Hong Kong to support research and education; the Chinese University of Hong Kong has received research grants and sponsorships from these companies). SMG, NI, and PÖ are employees of AstraZeneca. PÖ holds stocks and shares in AstraZeneca. APM has received honoraria from Bayer, Novartis, Cardiorentis, and Fresenius for participation in study committees. NRP has received speaker's fees, taken part in advisory boards, and received honorarium for steering committee attendance from Novo Nordisk; personal fees from Servier, Takeda, Novo Nordisk, and AstraZeneca; and grants from Diabetes UK, the UK National Institute for Health Research Efficacy and Mechanism Evaluation programme, Julius Clinical, and the British Heart Foundation. AR has received remuneration for advisory board meetings from Merck Sharp & Dohme and AstraZeneca; honoraria for lectures from Bayer, Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Sanofi-Aventis, and Novartis; and research grant support from AstraZeneca, Merck Sharp & Dohme, Novartis, and Sanofi-Aventis. BZ has received personal fees from Abbott, Janssen, Sanofi, Eli Lilly, and Merck; and grants and personal fees from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. AFH has received research funding from AstraZeneca, GlaxoSmithKline, Merck, and Novartis; and consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Merck, Novartis, and Pfizer. RRH has received grants from AstraZeneca; and grants and personal fees from Bayer, Boehringer Ingelheim, and Merck; personal fees from Novartis, Amgen, and Servier; and has taken part in the advisory board or independent data monitoring committee from Elcelyx, GlaxoSmithKline, Janssen, and Takeda. RAP and PM declare no competing interests.

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