# Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

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## Summary

**Background** Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk with high glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) concentrations. We assessed the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control.

**Methods** This multicentre, randomised, double-blind, placebo-controlled trial was done at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo. Randomisation was done by a computer-generated random code with stratification by site. All investigators and participants were masked to treatment assignment. Participants were followed up at least every 6 months for incident cardiovascular and other serious clinical outcomes. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes), which was assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01394952.

**Findings** Between Aug 18, 2011, and Aug 14, 2013, 9901 participants (mean age 66·2 years [SD 6·5], median $HbA_{1c}$ 7·2% [IQR 6·6–8·1], 4589 [46·3%] women) were enrolled and randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952). During a median follow-up of 5·4 years (IQR 5·1–5·9), the primary composite outcome occurred in 594 (12·0%) participants at an incidence rate of 2·4 per 100 person-years in the dulaglutide group and in 663 (13·4%) participants at an incidence rate of 2·7 per 100 person-years in the placebo group (hazard ratio [HR] 0·88, 95% CI 0·79–0·99; p=0·026). All-cause mortality did not differ between groups (536 [10·8%] in the dulaglutide group *vs* 592 [12·0%] in the placebo group; HR 0·90, 95% CI 0·80–1·01; p=0·067). 2347 (47·4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34·1%) participants assigned to placebo (p<0·0001).

**Interpretation** Dulaglutide could be considered for the management of glycaemic control in middle-aged and older people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

**Funding** Eli Lilly and Company.

## Introduction

Despite the widespread use of many proven cardio-protective therapies and a concomitant fall in risk of cardiovascular events[1] during the past 20 years, diabetes continues to increase the risk of death and cardiovascular events by 1·5–2 times.[2,3] Although reasons for this higher incidence are debated, the importance of knowing whether glucose-lowering drugs alter these outcomes has justified many large cardiovascular trials in this population.[4] Evidence that three glucagon-like peptide-1 (GLP-1) receptor agonists[5–8] and three sodium-glucose co-transporter-2 (SGLT2) inhibitors[9,10] reduce cardio-vascular events in middle-aged and older (≥50 years) people with type 2 diabetes and mean glycated haemo-globin $A_{1c}$ ($HbA_{1c}$) concentrations of 8·0% or more has changed clinical practice guidelines[11,12] and fuelled debate regarding mechanisms linking diabetes to cardiovascular disease.

Dulaglutide is a GLP-1 receptor agonist approved for the management of hyperglycaemia in people with type 2 diabetes in many countries. It comprises two modified human GLP-1 molecules covalently linked

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See Online for appendix

## Research in context

### Evidence before this study

We searched PubMed for reports published in English between Jan 1, 2010, and March 31, 2019, of double-blind, randomised, placebo-controlled trials that were designed to test the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on incident cardiovascular events in people with type 2 diabetes. Search terms were "type 2 diabetes", "GLP1-RA", "glucagon-like peptide receptor 1 agonist", "glucagon-like peptide receptor 1 analogue", "lixisenatide", "liraglutide", "semaglutide", "taspoglutide", "albiglutide", "dulaglutide", "cardiovascular disease", and "randomized controlled trial". This search identified five trials that assessed the effects of lixisenatide (ELIXA; n=6068), albiglutide (Harmony Outcomes; n=9463), liraglutide (LEADER; n=9340), semaglutide (SUSTAIN-6; n=3297), or long-acting exenatide (EXSCEL; n=14752) versus placebo on incident cardiovascular outcomes in people with type 2 diabetes whose mean age ranged from 54 years to 64 years and mean glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) ranged from 7·7% to 8·8%. The trials were done in people with previous cardiovascular disease (ELIXA and Harmony Outcomes), or with a prevalence of cardiovascular disease ranging from 73% to 83% (LEADER, SUSTAIN-6, and EXSCEL). Median follow-up durations ranged from 1·6 years to 3·8 years. Trials that reported a reduced hazard ratio (HR) for the primary composite cardiovascular outcome of the first occurrence of non-fatal myocardial infarction or stroke, or death from cardiovascular causes were LEADER (HR 0·87, 95% CI 0·78–0·97), SUSTAIN-6 (HR 0·74, 0·58–0·95), and Harmony Outcomes (HR 0·78, 0·68–0·90). These five trials suggested that GLP-1 receptor agonists might only reduce cardiovascular outcomes in people with previous cardiovascular disease. They also were unable to determine the cardiovascular effects of GLP-1 receptor agonists across a wide range of glycaemic control.

### Added value of this study

The REWIND trial of 9901 people had a long median follow-up period of 5·4 years, recruited a low proportion of people (31·5%) with previous cardiovascular disease, a high proportion of women (46·3%), and followed people with a mean $HbA_{1c}$ of 7·3%. Findings showed that weekly injections of the GLP-1 receptor agonist dulaglutide reduced cardiovascular outcomes in both men and women with or without previous cardiovascular disease, and had an effect size similar to that observed in the other GLP-1 receptor agonist cardiovascular outcomes trials.

### Implications of all the available evidence

GLP-1 receptor agonists that have been shown to reduce cardiovascular outcomes should be considered for the management of glycaemic control in people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

to an IgG4 heavy chain molecule, has a half-life of 5 days, and is administered subcutaneously at weekly doses of 0·75 mg or 1·5 mg.[13] Evidence that it safely reduces glucose concentration, blood pressure, weight,[14] and albuminuria,[15] and has other actions suggesting possible cardiovascular benefits[16] supported its testing in a large cardiovascular superiority trial. Moreover, the fact that the cardiovascular effects of other GLP-1 receptor agonists were being tested in middle-aged people with high $HbA_{1c}$ concentrations and a 4% or higher annual risk of cardiovascular events highlighted the need to test the effect of dulaglutide on cardiovascular events in people with a broader cardiovascular risk and a wider range of glycaemic control. Thus, the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial was designed to assess whether the addition of dulaglutide to the diabetes medication regimen of middle-aged and older people with type 2 diabetes safely reduces the incidence of cardiovascular outcomes compared with placebo.

## Methods

### Study design and participants

REWIND was a multicentre, randomised, double-blind, placebo-controlled trial done at 371 sites in 24 countries. Details of the study design and baseline characteristics of participants have been published previously.[17] Men and women (aged ≥50 years) with established or newly detected type 2 diabetes whose $HbA_{1c}$ was 9·5% or less (with no lower limit) on stable doses of up to two oral glucose-lowering drugs with or without basal insulin therapy were eligible if their body-mass index (BMI) was at least 23 kg/m². Additionally, patients aged 50 years or older had to have vascular disease (ie, a previous myocardial infarction, ischaemic stroke, revascularisation, hospital admission for unstable angina, or imaging evidence of myocardial ischaemia); those aged 55 years or older had to have myocardial ischaemia, coronary, carotid, or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1·73 m², or albuminuria; and those aged 60 years or older had to have at least two of tobacco use, dyslipidaemia, hypertension, or abdominal obesity. Key exclusion criteria were an eGFR[18] less than 15 mL/min per 1·73 m², cancer in the previous 5 years, severe hypoglycaemia in the previous year, life expectancy less than 1 year, a coronary or cerebrovascular event within the previous 2 months, and plans for revascularisation. A complete list of trial inclusion and exclusion criteria is given in the appendix (pp 151–55). The REWIND protocol was approved by research ethics boards for all sites and all participants provided written informed consent. The trial was carefully monitored by members of an independent data monitoring committee who reviewed accruing and unblinded data every 6 months.

The study consisted of two phases: a run-in period and a treatment period. During the 3-week single-blind placebo run-in period, all patients received placebo and were instructed on how to inject study drug. Patients were instructed to remain on their antihyperglycaemic therapy with the exception of patients taking a dipeptidyl peptidase-4 (DPP-4) inhibitor or GLP-1 receptor agonist at screening, who discontinued these therapies at the start of the run-in period.

### Randomisation and masking

Participants who were 100% adherent to weekly placebo injections during the single-blind run-in period and who still met eligibility criteria were randomly assigned to weekly subcutaneous injections of either masked dulaglutide 1·5 mg or the same volume of masked placebo (containing the same excipients but without dulaglutide) using a preloaded syringe. Syringes containing dulaglutide and placebo were identical in appearance. Randomisation was done by a computer-generated random code with an interactive web response system with stratification by site. All investigators and participants were masked to treatment allocation. The independent data monitoring committee and the statisticians supporting the committee's activities were the only people with access to unblinded data.

### Procedures

During the treatment period, participants in both groups were instructed to inject study drug on the same day at approximately the same time, each week. Participants were seen at 2 weeks, 3 months, and 6 months and then every 3 months for drug dispensing and every 6 months for detailed assessments until 1200 confirmed primary outcomes had accrued. Assessments included cardiovascular events, adverse events, vital signs, and periodic questionnaires, laboratory tests, and electrocardiograms (ECGs). Investigators were advised to promote a healthy lifestyle and to manage glucose concentrations according to local guidelines and were free to add any glucose-lowering drug apart from another GLP-1 receptor agonist or pramlintide. Management of blood pressure, lipids, other cardiovascular risk factors, and medical conditions was at the discretion of either the study investigator or the patient's usual physician(s) as informed by current country guidelines. Unless consent was explicitly withdrawn, all randomly assigned participants were followed up until the end of the trial, irrespective of adherence to study medication. Those who stopped study medication were encouraged to restart it unless there was a clear contraindication.

### Outcomes

The primary endpoint was the first occurrence of any component of the composite outcome, which comprised non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown causes. The

seven secondary outcomes were a composite clinical microvascular outcome comprising diabetic retinopathy (defined as photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy) or renal disease (defined as development of a urinary albumin-to-creatinine ratio >33·9 mg/mmol in those with a lower baseline concentration, a sustained 30% or greater decline in eGFR [ie, based on two consecutive eGFR concentrations], or chronic renal replacement therapy); hospital admission for unstable angina; each component of the primary composite cardiovascular outcome; death; and heart failure requiring either hospital admission or an urgent visit requiring therapy. Potential cardiovascular outcomes, all deaths, and pancreatic and thyroid safety outcomes were adjudicated by an independent clinical endpoint committee that was masked to treatment assignment. Criteria for adjudication of clinical events are listed in the appendix (pp 12–27).
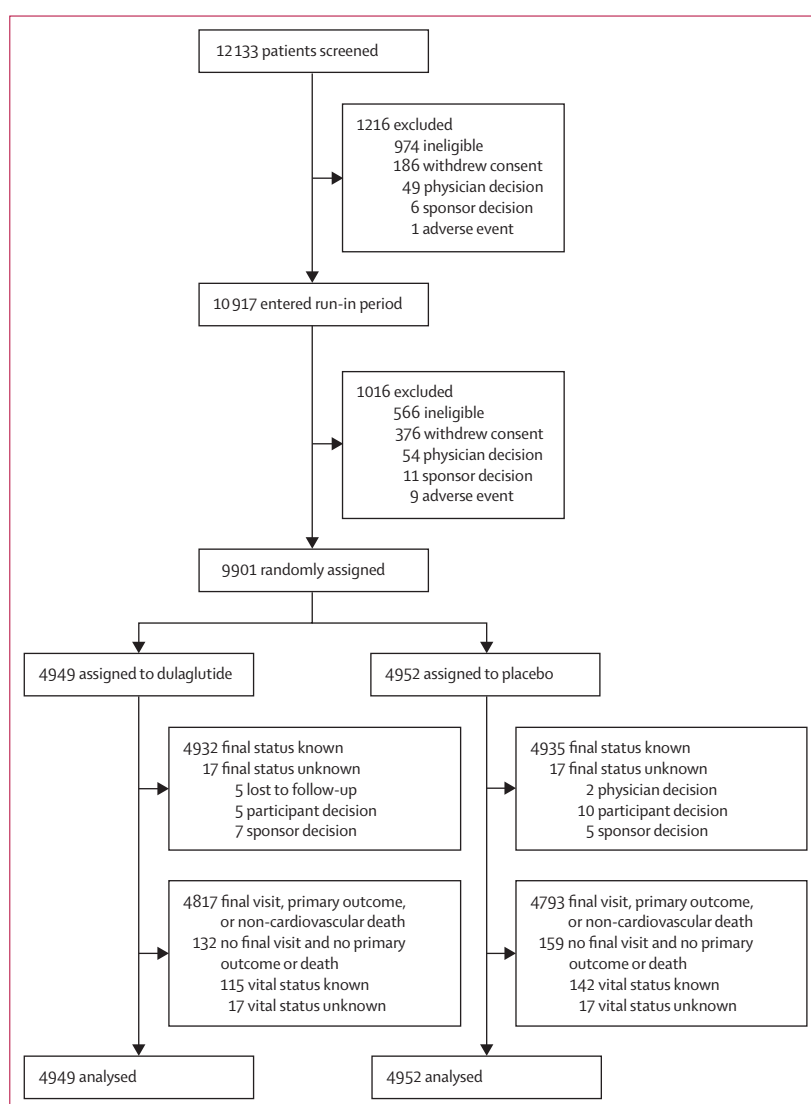


*Figure 1:* Trial profile

Prespecified and all other adverse events were reported by investigators on case report forms. They included study drug discontinuation; acute pancreatitis; cancer;

| | Dulaglutide (n=4949) | Placebo (n=4952) |
|---|---|---|
| Age (years) | 66·2 (6·5) | 66·2 (6·5) |
| **Sex** | | |
| Female | 2306 (46·6%) | 2283 (46·1%) |
| Male | 2643 (53·4%) | 2669 (53·9%) |
| **Race** | | |
| White | 3754 (75·9%) | 3744 (75·6%) |
| Current tobacco use | 694 (14·0%) | 713 (14·4%) |
| Cardiovascular disease* | 1560 (31·5%) | 1554 (31·4%) |
| Cardiovascular event† | 1028 (20·8%) | 1007 (20·3%) |
| Hypertension | 4605 (93·0%) | 4619 (93·3%) |
| Previous heart failure | 421 (8·5%) | 432 (8·7%) |
| **Diabetes** | | |
| Duration of diabetes (years)‡ | 10·5 (7·3); 9·5 (5·5–14·5) | 10·6 (7·2); 9·5 (5·5–14·5) |
| Diabetic retinopathy | 448 (9·1%) | 443 (8·9%) |
| HbA$_{1c}$ (%)‡ | 7·3 (1·1); 7·2 (6·6–8·1) | 7·4 (1·1); 7·2 (6·6–8·1) |
| eGFR <60 mL/min per 1·73 m² | 1081 (21·8%) | 1118 (22·6%) |
| Albuminuria§ | 1707 (34·5%) | 1760 (35·5%) |
| **Antidiabetic medications** | | |
| Metformin | 4022 (81·3%) | 4015 (81·1%) |
| Sulfonylurea | 2270 (45·9%) | 2282 (46·1%) |
| Insulin | 1189 (24·0%) | 1174 (23·7%) |
| DPP-4 inhibitor | 266 (5·4%) | 298 (6·0%) |
| Thiazolidinedione | 100 (2·0%) | 68 (1·4%) |
| Other glucose-lowering drugs | 14 (0·3%) | 18 (0·4%) |
| **Cardiovascular** | | |
| Body-mass index (kg/m²) | 32·3 (5·7) | 32·3 (5·8) |
| Systolic blood pressure (mm Hg) | 137·1 (16·6) | 137·3 (17·0) |
| Diastolic blood pressure (mm Hg) | 78·4 (9·8) | 78·5 (9·9) |
| Heart rate (beats per min) | 71·4 (10·7) | 71·6 (11·0) |
| Serum creatinine (µmol/L) | 83·7 (27·4) | 84·5 (27·3) |
| eGFR (mL/min per 1·73 m²) | 75·3 (61·6–91·8) | 74·7 (61·2–90·6) |
| UACR (mg/mmol) | 1·80 (0·70–6·60) | 1·88 (0·70–7·38) |
| Cholesterol (mmol/L) | 4·52 (1·16) | 4·52 (1·16) |
| LDL cholesterol (mmol/L) | 2·56 (0·98) | 2·56 (0·98) |
| HDL cholesterol (mmol/L) | 1·18 (0·33) | 1·18 (0·36) |
| Triglycerides (mmol/L) | 1·60 (1·15–2·20) | 1·60 (1·20–2·25) |
| **Cardiovascular medications** | | |
| ACE inhibitor or ARB | 4009 (81·0%) | 4059 (82·0%) |
| β blocker | 2237 (45·2%) | 2274 (45·9%) |
| Other blood pressure drug | 2767 (55·9%) | 2833 (57·2%) |
| Statin | 3279 (66·3%) | 3268 (66·0%) |
| Fibrate | 452 (9·1%) | 446 (9·0%) |
| Antiplatelet | 2662 (53·8%) | 2680 (54·1%) |

Data are mean (SD), n (%), or median (IQR), unless otherwise stated. HbA$_{1c}$=glycated haemoglobin A$_{1c}$. eGFR=estimated glomerular filtration rate. DPP-4=dipeptidyl peptidase-4. UACR=urinary albumin-to-creatinine ratio. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *Myocardial infarction, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial ischaemia on imaging or stress test, or coronary, carotid, or peripheral revascularisation. †Myocardial infarction or ischaemic stroke. ‡Data are mean (SD); median (IQR). §UACR 3·39 mg/mmol or more.

*Table 1:* Baseline characteristics

C-cell hyperplasia; serious hepatic, gastrointestinal, renal, or urinary events; immune reactions; supraventricular tachycardia; conduction disorders; or severe hypoglycaemia.

## Statistical analysis

Assuming a primary outcome rate of 2% per year in the placebo group, a two-sided significance level of 5%, a 3-year recruitment period, and an annual dropout rate of 0·15%, follow-up of at least 9600 people for a maximum of 8 years, and accrual of 1200 unique primary outcomes was estimated to provide at least 90% power to detect a hazard ratio (HR) of 0·82 or lower for the primary outcome and 80% power to detect an HR of 0·85 or lower. The independent data monitoring committee did a formal interim analysis for superiority after 756 unique primary outcomes had occurred, after which continuation of the trial was recommended.

All efficacy and safety analyses were done according to an intention-to-treat approach that included all randomly assigned participants irrespective of adherence, as described in the protocol and prespecified statistical analysis plan (appendix pp 42–319). Participants were censored at the time of the last known follow-up date. Continuous data were summarised as either means and SDs or medians and IQRs, and count data were summarised as numbers and percentages.

All outcomes occurring on or after randomisation were included in the analysis. Incidence rates were estimated as the number of first events per 100 person-years of outcome-specific follow-up (ie, time from randomisation until either the first occurrence of the outcome or the last follow-up with no outcome). Kaplan-Meier estimates were used to generate cumulative risks and Cox proportional hazards models were used to determine the effect of the intervention on the outcome and to estimate HRs and 95% CIs. The assumptions of the Cox models were verified by plotting the log of negative log of the survival function against the log of time, and consistency of the effect across the three components of the composite outcome was assessed by a composite treatment heterogeneity test.[19] All reported p values are two-sided. To account for the significance level of 0·009 used for the interim analysis and maintain an overall type I error of 0·05, the final adjusted p value for declaring superiority for the primary outcome was 0·0467.[20] To address multiplicity related to testing the effect of allocation on the secondary outcomes, a predetermined, graphical approach for multiple comparisons was used to strongly control the overall type I error.[21–23]

The effect of the intervention on the primary outcome was tested in seven predefined subgroups (ie, age, sex, BMI, duration of diabetes, baseline HbA$_{1c}$, history of cardiovascular disease, and geographical region) by including the subgroup and interaction term in the Cox model. Tests for nominally significant interactions between treatment and the seven prespecified subgroups

were not adjusted for multiple testing. The change from baseline in continuous variables was analysed using linear mixed models with baseline value as a covariate, participant as a random effect, and fixed effects for treatment, visit, and treatment–visit interaction, and reported as the least-squares mean (LSM) value.[24] A set of plausible ranges for laboratory tests were defined before unblinding (appendix p 34) and tests with values outside these ranges were excluded from the analyses. The proportion of participants in each group who had prespecified adverse events of special interest were compared using log-rank tests, and the proportion who had serious adverse events and adverse events were compared using $\chi^2$ tests. Data were analysed with SAS software (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT01394952.

### Role of the funding source

### Results

Between Aug 18, 2011, and Aug 14, 2013, 12 133 patients were screened at 371 sites in 24 countries. 10 917 eligible patients began the 3-week run-in period, of whom 9901 were randomly assigned to treatment group (dulaglutide, n=4949; placebo, n=4952; figure 1). Follow-up ended on Aug 21, 2018.

Mean age of participants was 66·2 years [SD 6·5], and 4589 [46·3%] were female (table 1, appendix p 35).[17] At baseline, 3114 (31·5%) participants reported previous cardiovascular disease and 2199 (22·2%) had a baseline eGFR less than 60 mL/min per 1·73 m². The median duration of diabetes was 9·5 years (IQR 5·5–14·5), median HbA_{1c} was 7·2% (IQR 6·6–8·1), and median eGFR was 74·9 mL/min per 1·73 m² (IQR 61·4–91·1).

During a median follow-up of 5·4 years (IQR 5·1–5·9) comprising 51 820 person-years, the primary composite outcome status was known in 9610 (97·1%) participants (figure 1). 2092 (42·3%) of 4949 participants assigned to dulaglutide and 2171 (43·8%) of 4952 participants assigned to placebo had at least one discontinuation of study drug during follow-up, whereas 3621 (73·2%) assigned to dulaglutide and 3520 (71·1%) assigned to placebo were taking study drug at the last visit. Participants assigned to dulaglutide took study drug for

82·2% of the follow-up time from randomisation until either a primary outcome event or final follow-up, compared with 83·1% of the follow-up time for patients assigned to placebo. Study drug was well tolerated; 451 (9·1%) participants assigned to dulaglutide and 310 (6·3%) assigned to placebo permanently stopped study drug during follow-up because of an adverse event. There were no between-group differences in use of other medications at baseline (table 1), but fewer participants in the dulaglutide group than in the placebo group were taking a GLP-1 receptor agonist, SGLT2 inhibitor, metformin, sulfonylurea, insulin, or angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker at the last visit (appendix p 36).

The primary composite outcome occurred in 594 (12·0%) participants (2·4 per 100 person-years) assigned to dulaglutide and 663 (13·4%) participants (2·7 per 100 person-years) assigned to placebo (HR 0·88, 95% CI 0·79–0·99; p=0·026; figure 2, table 2). Consistent effects were observed for all three components of the composite primary outcome (p_{heterogeneity}=0·89),[19] with HRs of 0·91 (95% CI 0·78–1·06; p=0·21) for cardiovascular death, 0·96 (0·79–1·16; p=0·65) for non-fatal myocardial infarction, and 0·76 (0·61–0·95; p=0·017) for non-fatal stroke (figure 2, table 2).

When assessed within subgroups, the HR of the intervention on the primary outcome was similar in participants with and without previous cardiovascular
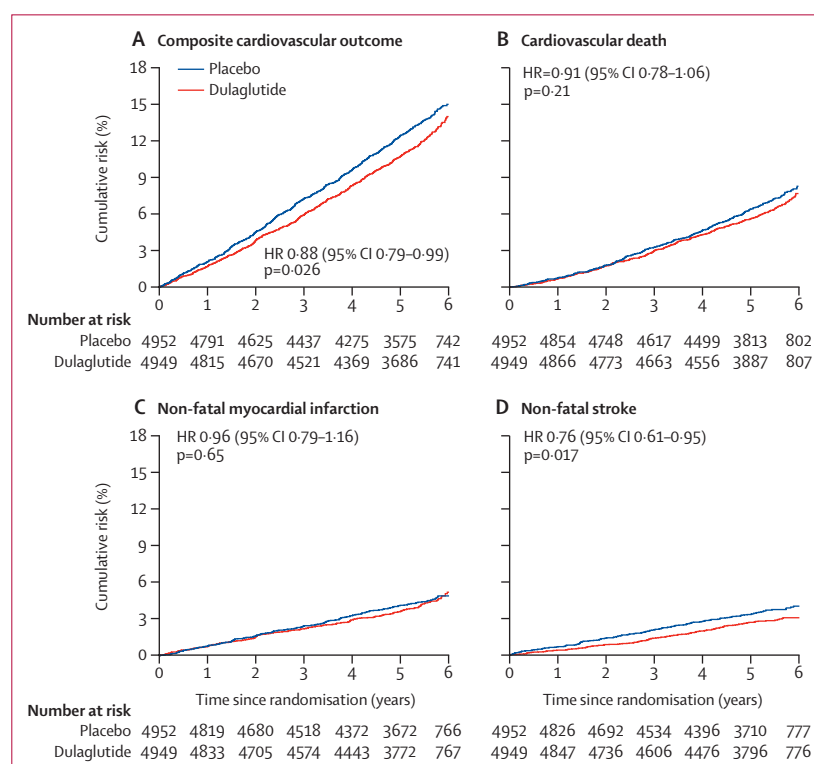


*Figure 2:* Cumulative incidence of cardiovascular outcomes
HR=hazard ratio. HbA_{1c}=glycated haemoglobin A_{1c}.

| | Dulaglutide (n=4949) | | Placebo (n=4952) | | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|---|---|
| | Number of patients (%) | Incidence rate (number of events per 100 person-years) | Number of patients (%) | Incidence rate (number of events per 100 person-years) | | |
| Primary composite outcome | 594 (12·0%) | 2·35 | 663 (13·4%) | 2·66 | 0·88 (0·79–0·99)* | 0·026 |
| Myocardial infarction | 223 (4·5%) | 0·87 | 231 (4·7%) | 0·91 | 0·96 (0·79–1·15) | 0·63 |
| Non-fatal myocardial infarction | 205 (4·1%) | 0·80 | 212 (4·3%) | 0·84 | 0·96 (0·79–1·16) | 0·65 |
| Fatal myocardial infarction | 26 (0·5%) | 0·10 | 20 (0·4%) | 0·08 | 1·29 (0·72–2·30) | 0·40 |
| Stroke | 158 (3·2%) | 0·61 | 205 (4·1%) | 0·81 | 0·76 (0·62–0·94) | 0·010 |
| Non-fatal stroke | 135 (2·7%) | 0·52 | 175 (3·5%) | 0·69 | 0·76 (0·61–0·95) | 0·017 |
| Fatal stroke | 26 (0·5%) | 0·10 | 33 (0·7%) | 0·13 | 0·78 (0·47–1·30) | 0·34 |
| Cardiovascular death† | 317 (6·4%) | 1·22 | 346 (7·0%) | 1·34 | 0·91 (0·78–1·06) | 0·21 |
| Non-cardiovascular death | 219 (4·4%) | 0·84 | 246 (5·0%) | 0·95 | 0·88 (0·73–1·06) | 0·18 |
| All-cause death | 536 (10·8%) | 2·06 | 592 (12·0%) | 2·29 | 0·90 (0·80–1·01) | 0·067 |
| Hospital admission for heart failure or urgent visit | 213 (4·3%) | 0·83 | 226 (4·6%) | 0·89 | 0·93 (0·77–1·12) | 0·46 |
| Hospital admission for unstable angina | 88 (1·8%) | 0·34 | 77 (1·6%) | 0·30 | 1·14 (0·84–1·54) | 0·41 |
| Composite microvascular outcome (eye or renal outcome) | 910 (18·4%) | 3·76 | 1019 (20·6%) | 4·31 | 0·87 (0·79–0·95) | 0·0020 |
| Eye outcome‡ | 95 (1·9%) | 0·37 | 76 (1·5%) | 0·30 | 1·24 (0·92–1·68) | 0·16 |
| Renal outcome§ | 848 (17·1%) | 3·47 | 970 (19·6%) | 4·07 | 0·85 (0·77–0·93) | 0·0004 |

All hazard ratios (HRs) were estimated with Cox proportional hazards models and p values are two-sided. *After accounting for α=0·009 spent on the primary outcome for the interim analysis, the α for the final analysis is 0·0467, and the HR is 0·88 (95·33% CI 0·79–0·99). †Includes deaths of unknown cause. ‡Photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy. §New macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy.

*Table 2:* **Primary and secondary outcomes**

disease ($p_{interaction}$=0·97), in participants whose $HbA_{1c}$ was less than 7·2% or greater-than or equal to 7·2% ($p_{interaction}$=0·75), and in participants analysed according to age, sex, duration of diabetes, and BMI (figure 3). There was nominally significant heterogeneity with respect to geographical region ($p_{interaction}$=0·0080). Similar HRs were also noted when the effect of dulaglutide was explored in post-hoc subgroups based on a previous cardio-vascular event (ie, myocardial infarction or ischaemic stroke), different $HbA_{1c}$ or BMI categories, or ethnicity (appendix p 37).

The incidence of the composite microvascular outcome was lower in participants assigned to dulaglutide than in those assigned to placebo (3·8 per 100 person-years vs 4·3 per 100 person-years, respectively; HR 0·87, 95% CI 0·79–0·95; table 2, appendix p 30). This difference was characterised by fewer composite renal outcomes in the dulaglutide group than in the placebo group (3·5 per 100 person-years vs 4·1 per 100 person-years, respectively; HR 0·85, 95% CI 0·77–0·93). Dulaglutide did not significantly affect the incidence of all-cause mortality, heart failure, revascularisation, hospital admissions, fractures, or cholelithiasis (table 2; appendix p 31, 38).
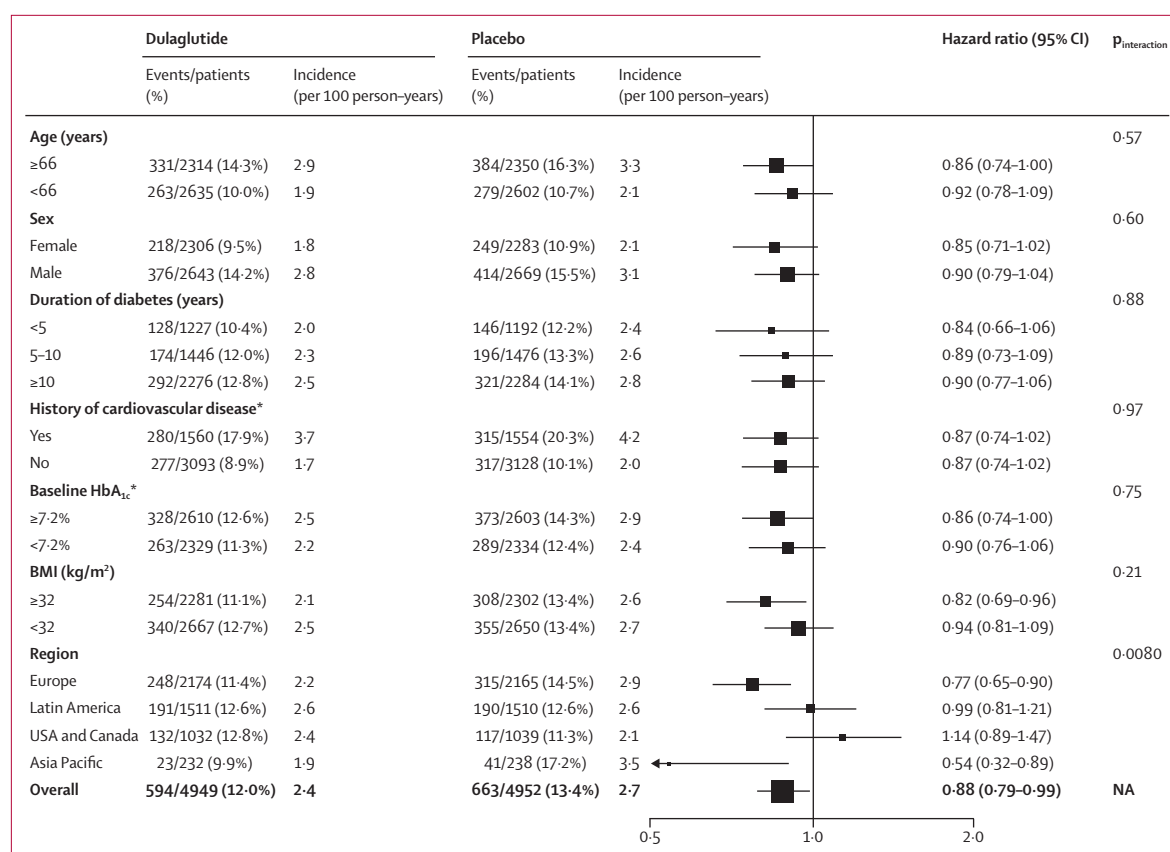
During follow-up, differences from baseline were greater in the dulaglutide group than in the placebo group for several measurements. Compared with participants in the placebo group, participants assigned to dulaglutide had a 0·61% (95% CI 0·58–0·65) lower LSM $HbA_{1c}$ (p<0·0001), 1·46 kg (1·25–1·67) lower LSM bodyweight (p<0·0001), 0·53 kg/m² (0·46–0·61) lower LSM BMI (p<0·0001), 1·70 mm Hg (1·33–2·07) lower LSM systolic blood pressure (p<0·0001), 0·49 mm Hg (0·25–0·73) lower LSM mean arterial blood pressure, 1·82 mm Hg (1·53–2·12) lower LSM pulse pressure, 1·87 beats per min (1·62–2·11) higher LSM heart rate (p<0·0001), 0·07 mmol/L (0·03–0·10) lower LSM total cholesterol, 0·05 mmol/L (0·02–0·08) lower LSM LDL cholesterol, and a lower ratio of waist-to-hip circumference in men and women (figure 4, appendix pp 32, 39).

Frequencies of prespecified adverse events of special interest, including first study drug discontinuation, serious gastrointestinal events, severe hypoglycaemia, cancers, or pancreatitis, did not differ significantly between the dulaglutide and placebo groups (table 3). The numbers of serious adverse events did not differ significantly between groups (appendix p 40). However, 2347 (47·4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34·1%) participants assigned to placebo (p<0·0001; appendix p 41).

## Discussion

This long-duration randomised controlled trial of people with type 2 diabetes and only a 31·5% prevalence of previous cardiovascular disease showed that a weekly

| | Dulaglutide | | Placebo | | | Hazard ratio (95% CI) | $p_{interaction}$ |
|---|---|---|---|---|---|---|---|
| | Events/patients (%) | Incidence (per 100 person–years) | Events/patients (%) | Incidence (per 100 person–years) | | | |
| **Age (years)** | | | | | | | 0·57 |
| ≥66 | 331/2314 (14·3%) | 2·9 | 384/2350 (16·3%) | 3·3 | | 0·86 (0·74–1·00) | |
| <66 | 263/2635 (10·0%) | 1·9 | 279/2602 (10·7%) | 2·1 | | 0·92 (0·78–1·09) | |
| **Sex** | | | | | | | 0·60 |
| Female | 218/2306 (9·5%) | 1·8 | 249/2283 (10·9%) | 2·1 | | 0·85 (0·71–1·02) | |
| Male | 376/2643 (14·2%) | 2·8 | 414/2669 (15·5%) | 3·1 | | 0·90 (0·79–1·04) | |
| **Duration of diabetes (years)** | | | | | | | 0·88 |
| <5 | 128/1227 (10·4%) | 2·0 | 146/1192 (12·2%) | 2·4 | | 0·84 (0·66–1·06) | |
| 5–10 | 174/1446 (12·0%) | 2·3 | 196/1476 (13·3%) | 2·6 | | 0·89 (0·73–1·09) | |
| ≥10 | 292/2276 (12·8%) | 2·5 | 321/2284 (14·1%) | 2·8 | | 0·90 (0·77–1·06) | |
| **History of cardiovascular disease*** | | | | | | | 0·97 |
| Yes | 280/1560 (17·9%) | 3·7 | 315/1554 (20·3%) | 4·2 | | 0·87 (0·74–1·02) | |
| No | 277/3093 (8·9%) | 1·7 | 317/3128 (10·1%) | 2·0 | | 0·87 (0·74–1·02) | |
| **Baseline HbA$_{1c}$*** | | | | | | | 0·75 |
| ≥7·2% | 328/2610 (12·6%) | 2·5 | 373/2603 (14·3%) | 2·9 | | 0·86 (0·74–1·00) | |
| <7·2% | 263/2329 (11·3%) | 2·2 | 289/2334 (12·4%) | 2·4 | | 0·90 (0·76–1·06) | |
| **BMI (kg/m²)** | | | | | | | 0·21 |
| ≥32 | 254/2281 (11·1%) | 2·1 | 308/2302 (13·4%) | 2·6 | | 0·82 (0·69–0·96) | |
| <32 | 340/2667 (12·7%) | 2·5 | 355/2650 (13·4%) | 2·7 | | 0·94 (0·81–1·09) | |
| **Region** | | | | | | | 0·0080 |
| Europe | 248/2174 (11·4%) | 2·2 | 315/2165 (14·5%) | 2·9 | | 0·77 (0·65–0·90) | |
| Latin America | 191/1511 (12·6%) | 2·6 | 190/1510 (12·6%) | 2·6 | | 0·99 (0·81–1·21) | |
| USA and Canada | 132/1032 (12·8%) | 2·4 | 117/1039 (11·3%) | 2·1 | | 1·14 (0·89–1·47) | |
| Asia Pacific | 23/232 (9·9%) | 1·9 | 41/238 (17·2%) | 3·5 | | 0·54 (0·32–0·89) | |
| **Overall** | **594/4949 (12·0%)** | **2·4** | **663/4952 (13·4%)** | **2·7** | | **0·88 (0·79–0·99)** | **NA** |

*Figure 3:* **Subgroup analyses for the primary cardiovascular outcome**
The size of each box is proportional to the number of events. BMI=body-mass index. NA=not applicable. *Participants were not included in a category if the criteria or test result needed to assign them to a category were unknown or missing.

injection of 1·5 mg dulaglutide reduced the risk of cardiovascular outcomes compared with placebo, with the Kaplan-Meier curves starting to diverge within the first year. Across the three components of the composite primary outcome, the greatest between-group difference was seen in the number of non-fatal strokes. In this population of people with a mean duration of type 2 diabetes of 10 years, in whom 25% had a baseline HbA$_{1c}$ less than 6·6% and 25% had a level more than 8·1%, dulaglutide durably reduced HbA$_{1c}$ by a mean absolute amount of 0·6% more than placebo while not increasing hypoglycaemia. It also modestly reduced weight, LDL cholesterol, and systolic blood pressure, modestly increased heart rate, and was well tolerated with high adherence. For every 60 people with type 2 diabetes and additional cardiovascular risk factors who were treated with dulaglutide for a median of 5·4 years versus placebo, one cardiovascular event was prevented. The number needed to treat is 18 for people with a previous cardio-vascular event.

The REWIND trial differs from previous cardiovascular outcomes trials with GLP-1 receptor agonists[7,8] in several ways. First, the other trials were designed to show non-inferiority to placebo with respect to cardiovascular events, whereas REWIND prospectively tested the hypothesis that dulaglutide was superior. Second, most of the participants in REWIND did not have previous cardiovascular disease or a previous cardiovascular event. Thus, the average cardiovascular incidence of participants assigned to placebo was 2·7%, which was lower than the annual placebo incidence rates for the same composite outcome of 3·9% or higher in the other trials.[5] Moreover, the broad inclusion criteria, high proportion of women, and the representativeness of the recruited participants[25] in REWIND suggest that dulaglutide might be effective for both primary and secondary cardiovascular prevention in a high proportion of people with type 2 diabetes. Third, the 5·4-year median follow-up was much longer than that in the other cardiovascular outcomes trials, in which median follow-up ranged from 1·5 years to 3·8 years,[5,7] showing that the cardiovascular benefits of GLP-1 receptor agonists extend much longer than previously reported. Fourth, our trial shows the durability and safety of the effect of dulaglutide on glucose, blood pressure, and weight, and represents the longest trial of the effect of a GLP-1 receptor agonist on these measures. Finally, our findings show that dulaglutide reduces cardiovascular events in people with HbA$_{1c}$
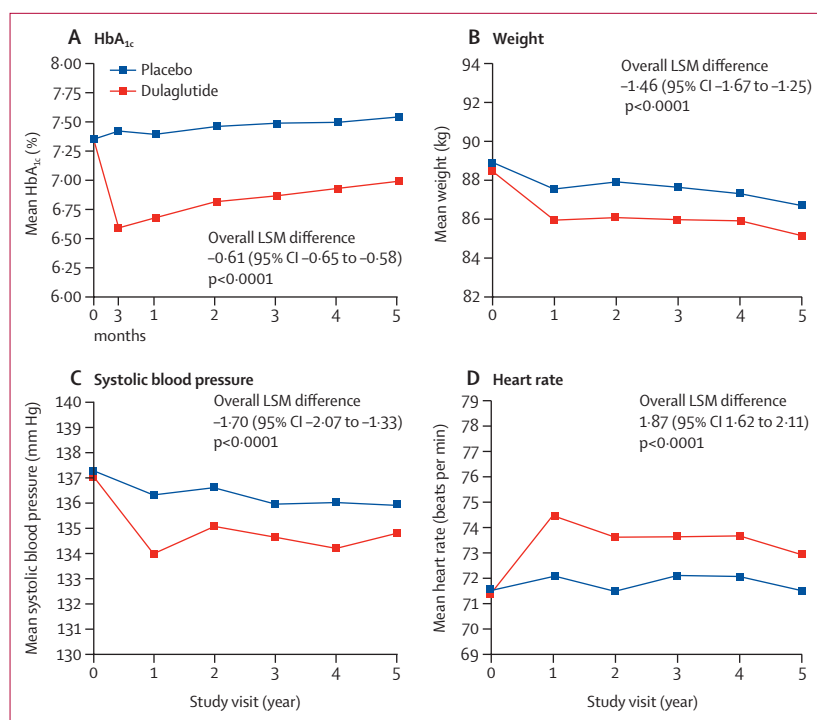
**Figure 4:** Continuous measures during follow-up
LSM=least-square means. HbA$_{1c}$=glycated haemoglobin A$_{1c}$.

| | Dulaglutide (n=4949) | Placebo (n=4952) | Log-rank test p value |
|---|---|---|---|
| First study drug discontinuation | 2092 (42·3%) | 2171 (43·8%) | 0·38 |
| Acute pancreatitis* | 23 (0·5%) | 13 (0·3%) | 0·11 |
| Imaging and enzymes† | 4 (0·1%) | 3 (0·1%) | 0·71 |
| Imaging, enzymes, and symptoms‡ | 4 (0·1%) | 3 (0·1%) | 0·71 |
| Any cancer§ | 351 (7·1%) | 348 (7·0%) | 0·98 |
| Medullary thyroid carcinoma or C-cell hyperplasia¶ | 1 (<0·1%) | 0 | 0·32 |
| Thyroid cancer | 7 (0·1%) | 3 (0·1%) | 0·21 |
| Pancreatic cancer | 19 (0·4%) | 12 (0·2%) | 0·22 |
| Serious hepatic event | 25 (0·5%) | 40 (0·8%) | 0·057 |
| Serious renal or urinary event‖ | 84 (1·7%) | 93 (1·9%) | 0·46 |
| Immune reactions | 8 (0·2%) | 20 (0·4%) | 0·022 |
| Serious gastrointestinal event | 120 (2·4%) | 117 (2·4%) | 0·87 |
| Supraventricular tachycardia or cardiovascular conduction disorders | 216 (4·4%) | 192 (3·9%) | 0·26 |
| Severe hypoglycaemia | 64 (1·3%) | 74 (1·5%) | 0·38 |

*Based on the first occurrence of acute pancreatitis, diagnosed on the basis of at least two of the three diagnostic criteria (symptoms, elevated pancreatic enzymes, or an abnormal pancreatic image). †The subset of participants with first acute pancreatitis who had both elevated pancreatic enzymes and an abnormal pancreatic image. ‡The subset of participants with first acute pancreatitis who had all three of elevated pancreatic enzymes, an abnormal pancreatic image, and symptoms. §Excluding non-melanoma skin cancers. ¶There were no cases of medullary thyroid carcinoma. ‖Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

**Table 3:** Prespecified adverse events of special interest reported during the trial

concentrations both within and higher than guideline-recommended targets, without increasing weight or the risk of hypoglycaemia, and has effect sizes that are

similar to those in the other trials with higher baseline HbA$_{1c}$ concentrations.[5–7,26,27]

Several possibilities could account for the salutary effects of dulaglutide and other GLP-1 receptor agonists on cardiovascular outcomes. These include the reduction in HbA$_{1c}$, LDL cholesterol, blood pressure, and weight. Emerging evidence also suggests that these drugs might independently improve endothelial function, endothelial cell responses to ischaemia, and platelet function, and might have direct neuroprotective effects.[28] These drugs might also attenuate progression of atherosclerosis, vascular inflammation, and vasoconstriction.[29]

Irrespective of the mechanism, the unique features of this trial add to a growing body of literature describing the cardiovascular effects of GLP-1 receptor agonists,[8] and suggest that most middle-aged and older people with type 2 diabetes can achieve cardiovascular benefits with GLP-1 receptor agonists such as dulaglutide. Consistent with the findings from three cardiovascular outcomes trials of other GLP-1 receptor agonists,[5,6,27,30] the REWIND trial raises the possibility of a greater effect on stroke than on myocardial infarction. Although it also raises the possibility of some geographical variation of effect, this variation loses statistical significance after accounting for the seven subgroups that were assessed (for which the Bonferroni-corrected p value for significance is <0·05/7 or 0·007), and might therefore be a spurious finding. Finally, the suggestion of a protective effect of dulaglutide on renal outcomes is consistent with the other trials in which renal outcomes were reported,[5,6,27] and supports further analyses of these effects. The long-term effect of dulaglutide on renal outcomes has been assessed in an exploratory analysis, published elsewhere.[31]

Strengths of these findings include the trial's broad and representative inclusion criteria and recruited parti-cipants,[25] long follow-up, high retention, measurement of clinically relevant outcomes, and investigator freedom to use any non-GLP-1 receptor agonist drug. Although less than a third of participants had previous cardiovascular disease, the observed cardiovascular effect size is similar to the HR of 0·87 from a meta-analysis of outcome trials of other GLP-1 receptor agonists in mainly secondary prevention populations.[32] This observation, and the fact that there was a numerically greater use of proven cardioprotective drugs in the placebo group (which might have diminished the effect size of dulaglutide) further support these findings. The major limitation is the observation that more than 25% of participants were not taking study drug at the time of their last visit. Although this might have also diminished the benefit of allocation to dulaglutide, the observation that participants took study drug for more than 80% of the follow-up time is reassuring.

Our findings show that the addition of dulaglutide to the medical regimen of people with type 2 diabetes and a broad range of glycaemic control reduced a composite of cardiovascular outcomes over a 5 year period. Moreover,

our results suggest that dulaglutide could be added to the management of people with diabetes and additional cardiovascular risk factors to reduce glucose concentrations, minimise hypoglycaemia, reduce weight and blood pressure, and reduce cardiovascular events.

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