



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.

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Introduction

Despite the widespread use of many proven cardio-protective therapies and a concomitant fall in risk of cardiovascular events¹ 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 cardiovascular events in middle-aged and older (≥50 years) people with type 2 diabetes and mean glycated haemoglobin 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 benefits¹⁶ 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 eGFR¹⁸ 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 micro-vascular 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).

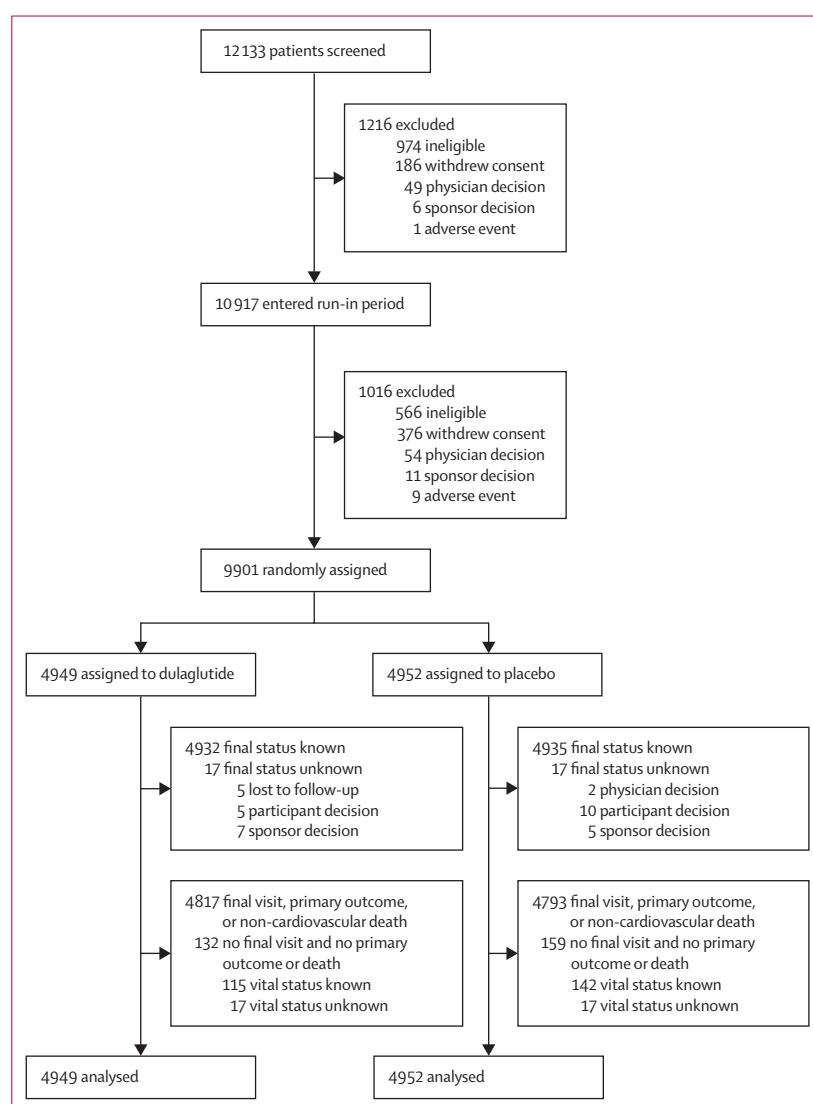


Figure 1: Trial profile

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

C-cell hyperplasia; serious hepatic, gastrointestinal, renal, or urinary events; immune reactions; supra-ventricular 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

	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 m ²	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/m ²)	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 m ²)	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

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 χ^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

The trial was sponsored and funded by Eli Lilly and Company led by an international steering committee coordinated by the Population Health Research Institute in Hamilton, Canada, which also did all data analyses. Site management and data collection were provided by ICON Clinical Research. Scientists employed by the funder were on the steering committee and contributed to trial design, trial implementation, and data interpretation. All authors and the sponsor jointly made the decision to submit for publication. 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

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 ($p_{\text{heterogeneity}}=0.89$),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

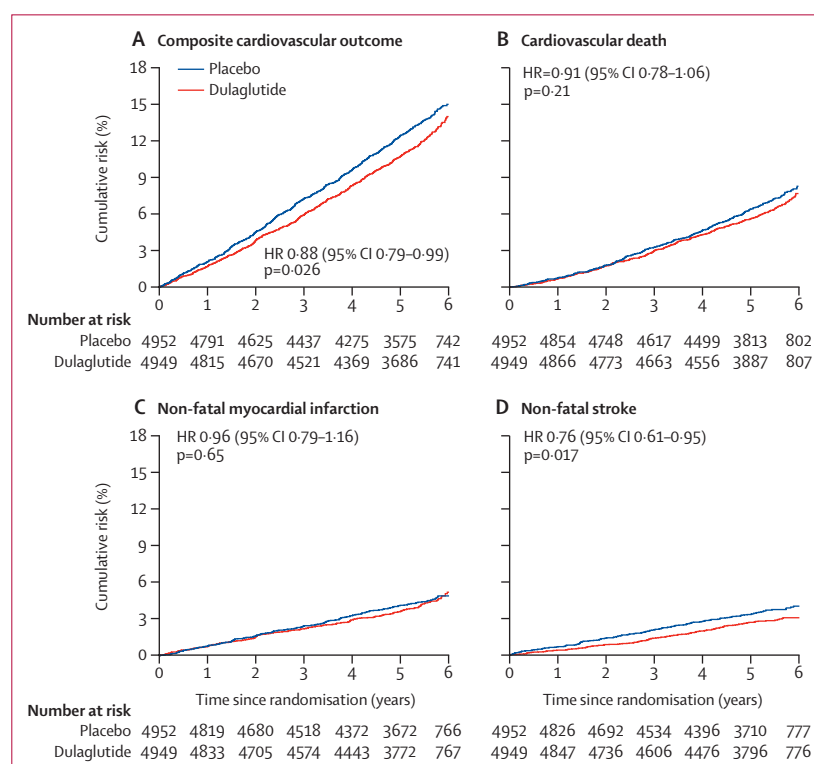


Figure 2: Cumulative incidence of cardiovascular outcomes

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 $\alpha=0.009$ 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% 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 ($p_{\text{interaction}}=0.97$), in participants whose HbA_{1c} was less than 7.2% or greater-than or equal to 7.2% ($p_{\text{interaction}}=0.75$), 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 ($p_{\text{interaction}}=0.0080$). Similar HRs were also noted when the effect of dulaglutide was explored in post-hoc subgroups based on a previous cardiovascular 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

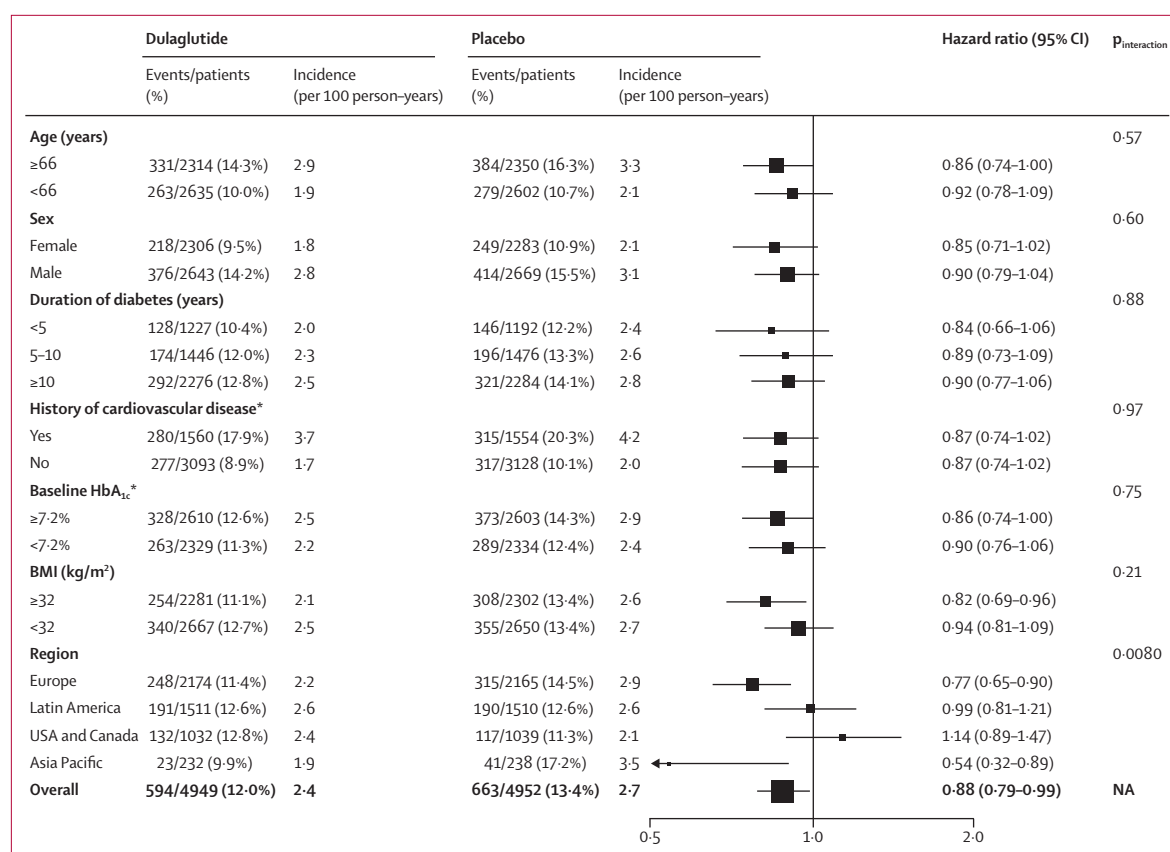


Figure 3: Subgroup analyses for the primary cardiovascular outcome

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 cardiovascular 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 participants²⁵ 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}

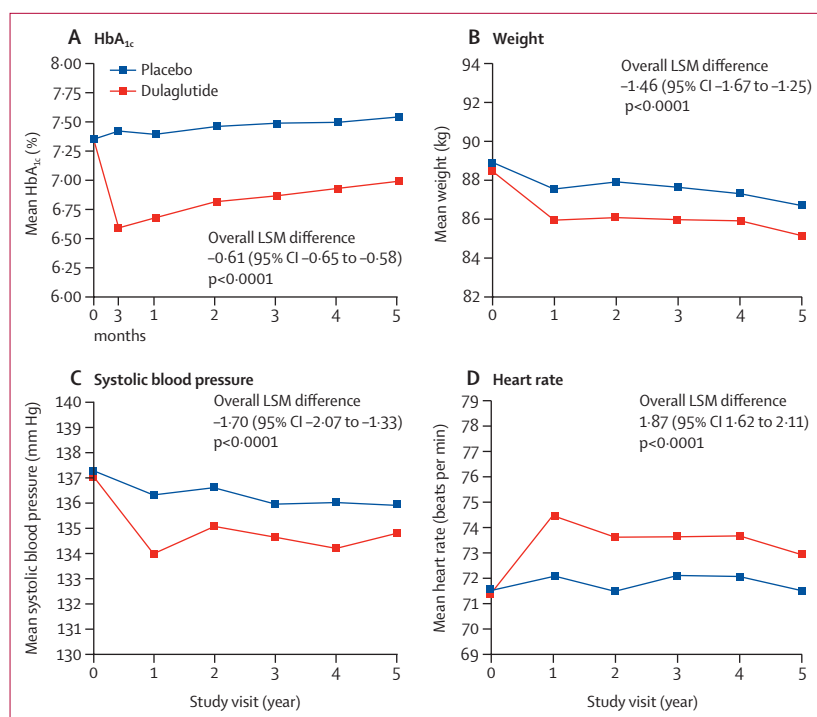


Figure 4: Continuous measures during follow-up
 LSM=least-square means. HbA_{1c}=glycated haemoglobin A_{1c}.

	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 participants,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.

Contributors

HCG (REWIND Chair) prepared the first draft of the report, and together with HMC, GRD, RD, ML, PP, JP, JSR, MCR, LR, and DX reviewed the literature, provided overall trial leadership, and interpreted the data. LD, PR-M, GW, and CMA did or confirmed the statistical analyses, and LD and PR-M prepared the figures. All other authors led the trial overall or in their respective countries and all authors critically reviewed and revised the report before submission.

Declaration of interests

HCG holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly, AstraZeneca, Merck, Novo Nordisk, and Sanofi; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Janssen, Sanofi, Kowa, and Cirus. HMC reports research grants from Eli Lilly, AstraZeneca, Regeneron, Pfizer, Roche, Sanofi, and Novo Nordisk; honoraria for speaking from Eli Lilly and Regeneron; consulting fees from Eli Lilly, Novartis, Regeneron, Sanofi, and Novo Nordisk; and shares in Bayer and Roche. RD reports research grants from the Population Health Research Institute, Duke Clinical Research Institute, Montreal Health Innovations Coordinating Center, CPC Clinical Research, DalCor, Amgen, Lepetit, and Cirus; honoraria for speaking from Sanofi; and consulting fees from Sanofi and Cirus. MCR reports grants to his institution from Eli Lilly, AstraZeneca, and Novo Nordisk; honoraria for consulting from Adocia, DalCor, GlaxoSmithKline, and Theracos; and honoraria for speaking from Sanofi. LR reports grants from the Swedish Heart Lung Foundation, Stockholms Läns Landsting, and Boehringer Ingelheim, and fees for consulting and speaking from Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Merck, and Bayer. ML is employed by Eli Lilly, owns stock, and has a patent pending. JSR is employed by Eli Lilly and has a patent pending. CMA is employed by Eli Lilly and owns stock. DX reports grants from Cadila, Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, Pfizer, Bristol-Myers Squibb, the UK Medical Research Council, and the Wellcome Trust. JB reports consulting fees from Eli Lilly, ReCor, and Medtronic. WCC reports grants from Eli Lilly. EF reports consulting and speaking fees from AstraZeneca, Boehringer Ingelheim, Bioton, Mundipharma, MSD, Novartis, Novo Nordisk, and Servier. MH reports honoraria for speaking from Sanofi, Novo Nordisk, Amgen, MSD, and AstraZeneca. FL reports grants from the Population Health Research Institute. LAL reports grants from Eli Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, and GSK; honoraria for speaking from Eli Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Novo Nordisk, and Sanofi; and consulting fees from Eli Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Novo Nordisk, Sanofi, and Servier. JES reports grants from Eli Lilly, and consulting fees or speaking honoraria from AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, Mylan, Boehringer Ingelheim, Merck Sharp and Dohme, and Abbott. TT-K reports consulting fees from Bayer, AstraZeneca, and Hamilton Health Sciences. All other authors declare no competing interests.

Data sharing

The data sharing policy is described in the appendix (pp 28–29).

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Is it time to REWIND the cardiorenal clock in diabetes?



Following the regulatory requirements of 2008, randomised trials of glucose-lowering therapies have demonstrated safety, and in some cases superiority, with respect to cardiorenal outcomes. Sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to reduce cardiorenal outcomes across a broad spectrum of type 2 diabetes in the presence or absence of established vascular disease, and across a broad range of kidney function.¹ These benefits appear independent of glycaemic control and are mediated through a range of mechanisms including effects on systemic and renal haemodynamics.² The greatest cardiovascular benefit is seen for heart failure, with a relative risk reduction of more than 30% observed across the trials.^{1,2} These therapies have also shown kidney protection, decreasing the risks of kidney failure and reduction in kidney function by a third on top of standard of care.^{1,3,4}

The dipeptidyl peptidase-4 inhibitors have shown, in patients with established atherosclerotic vascular disease or multiple risk factors, neutrality for major adverse cardiovascular events and composite renal outcomes.⁵ Heterogeneity in cardiovascular outcomes has been noted with the glucagon-like peptide-1 (GLP-1) receptor agonists, with some showing superiority for major adverse cardiovascular events, and others neutrality.⁶ From a renal perspective, GLP-1 receptor agonists reduced albuminuria but did not prevent a decline in estimated glomerular filtration rate (eGFR) or end-stage kidney disease.^{6,7} Incretin-based therapies have not consistently affected rates of hospital admission for heart failure, and in some instances, might have worsened this outcome.

In *The Lancet*, Hertzel Gerstein and colleagues^{8,9} report cardiovascular and renal outcomes from the REWIND trial. 9901 individuals (46% women, mean age 66 years) with type 2 diabetes, inadequate glycaemic control, and an eGFR of at least 15 mL/min per 1.73 m² were randomly assigned to the GLP-1 receptor agonist dulaglutide (1.5 mg once weekly) or placebo, in addition to baseline medical therapies. More than two-thirds of the participants were considered to be in the primary cardiovascular prevention with risk factors category; the secondary prevention cohort included patients with atherosclerotic vascular disease with or without history of a cardiovascular event (myocardial infarction

or ischaemic stroke). The primary outcome (the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes or unknown causes) occurred in 594 (12.0%) of 4949 participants in the dulaglutide group and in 663 (13.4%) of 4952 participants in the placebo group (hazard ratio [HR] 0.88, 95% CI 0.79–0.99, $p=0.026$), with consistent benefits observed in the primary and secondary prevention cohorts.⁸ The renal composite outcome, which was studied in an exploratory analysis, occurred in 848 (17.1%) participants in the dulaglutide group and in 970 (19.6%) participants in the placebo group (HR 0.85, 95% CI 0.77–0.93, $p=0.0004$).⁹ Dulaglutide was associated with a modest reduction in glycated haemoglobin A_{1c} (HbA_{1c}), bodyweight, and blood pressure, and a small increase in heart rate. There was no imbalance in serious adverse events between groups.

Several features of the REWIND trial deserve mention. Compared with previous studies of GLP-1 receptor agonists, individuals included in the REWIND trial were at a lower risk of cardiovascular events, with an average incidence of major adverse cardiovascular events in the placebo group of 2.7%. The study enrolled the largest primary prevention cohort as far as we are aware thus far, and showed no heterogeneity in efficacy relative to those with established atherosclerotic vascular disease. As has been reported in previous GLP-1 receptor agonist trials,^{10,11} the absolute risk reduction was higher in patients with atherosclerotic vascular disease compared with those without the condition (number needed to treat for dulaglutide to prevent one cardiovascular event over 5.4 years was 18 in patients with a previous cardiovascular event and 60 in those with type 2 diabetes and additional cardiovascular risk factors). The REWIND trial, to our knowledge, had the longest follow-up (5.4 years), highest proportion of women (46%), and lowest baseline median HbA_{1c} (7.2%), as well as showing efficacy over and above excellent background therapy, which, similar to other GLP-1 receptor agonist studies, was independent of baseline glycaemia, duration of diabetes, and weight.¹² The magnitude of benefit on the composite cardiovascular outcome (12%) was modest, and numerically lower than that seen in the positive GLP-1



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receptor agonist studies—namely, LEADER, SUSTAIN-6, and Harmony Outcomes—but consistent with the overall effect size from a meta-analysis of all previous GLP-1 receptor agonist trials.⁶ The primary outcome seemed to be driven largely by a reduction in stroke; a trend that was also observed with semaglutide in SUSTAIN-6.¹³ No difference was seen between groups in hospital admission for heart failure.

From a renal perspective, the composite outcome of the first occurrence of new macroalbuminuria, a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy was reported on the basis of an exploratory analysis. The renal benefits are noteworthy, particularly the observation that dulaglutide reduced the risk of eGFR decline when assessed by either a 30%, 40%, or 50% decline in eGFR, with an intriguing suggestion of clearer benefits for the latter two outcomes alone or in combination with end-stage kidney disease. The magnitude of eGFR preservation (between-group difference of 0.42 mL/min per 1.73 m²) was observed as a result of most patients being on an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and in the context of a baseline median eGFR of 75 mL/min per 1.73 m², although it appears to be of smaller magnitude than that seen with the SGLT2 inhibitors.¹⁴ Although mechanisms of action were not studied, the vascular and renal benefits of GLP-1 receptor agonists, mediated independently of HbA_{1c}, blood pressure, and weight changes, are well described.^{3,14,15} REWIND also adds to the emerging thesis that human GLP-1 receptor agonists show superiority (versus exendin-4 based agents) in terms of major adverse cardiovascular events. Limitations of the REWIND trial include that about a quarter of the patients were not on study drug at the completion of the study (similar to other studies of GLP-1 receptor agonists in which duration of follow-up was shorter), and the renal outcomes were exploratory and should be studied in further trials.

How do we integrate this growing body of evidence into a treatment approach? Although SGLT2 inhibitors and GLP-1 receptor agonists are recommended in patients with established atherosclerotic vascular disease, we now have evidence from the DECLARE-TIMI 58⁶ and REWIND trials that SGLT2 inhibitors and GLP-1 receptor agonists afford cardiovascular superiority even in primary prevention; with SGLT2 inhibitors preventing heart failure and GLP-1 receptor agonists preventing

atherosclerotic events, and both potentially affording renal protection. If we are to reduce the burgeoning pump, pipes, and filter complications of diabetes,¹⁶ we will need to overcome clinical inertia, and embrace these disease-modifying therapies early, and preferably in combination. The REWIND trial makes a strong case in this regard.

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