Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial

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Summary

Background Two glucagon-like peptide-1 (GLP-1) receptor agonists reduced renal outcomes in people with type 2 diabetes at risk for cardiovascular disease. We assessed the long-term effect of the GLP-1 receptor agonist dulaglutide on renal outcomes in an exploratory analysis of the REWIND trial of the effect of dulaglutide on cardiovascular disease.

Methods REWIND was a multicentre, randomised, double-blind, placebo-controlled trial 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 and followed up at least every 6 months for outcomes. Urinary albumin-to-creatinine ratios (UACRs) and estimated glomerular filtration rates (eGFRs) were estimated from urine and serum values measured in local laboratories every 12 months. The primary outcome (first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), secondary outcomes (including a composite microvascular outcome), and safety outcomes of this trial have been reported elsewhere. In this exploratory analysis, we investigate the renal component of the composite microvascular outcome, defined as the first occurrence of new macroalbuminuria (UACR >33·9 mg/mmol), a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01394952.

Findings Between Aug 18, 2011, and Aug 14, 2013, 9901 participants were enrolled and randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952). At baseline, 791 (7·9%) had macroalbuminuria and mean eGFR was 76·9 mL/min per 1·73 m² (SD 22·7). During a median follow-up of 5·4 years (IQR 5·1–5·9) comprising 51 820 person-years, the renal outcome developed in 848 (17·1%) participants at an incidence rate of 3·5 per 100 person-years in the dulaglutide group and in 970 (19·6%) participants at an incidence rate of 4·1 per 100 person-years in the placebo group (hazard ratio [HR] 0·85, 95% CI 0·77–0·93; p=0·0004). The clearest effect was for new macroalbuminuria (HR 0·77, 95% CI 0·68–0·87; p<0·0001), with HRs of 0·89 (0·78–1·01; p=0·066) for sustained decline in eGFR of 30% or more and 0·75 (0·39–1·44; p=0·39) for chronic renal replacement therapy.

Interpretation Long-term use of dulaglutide was associated with reduced composite renal outcomes in people with type 2 diabetes.

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Introduction

Diabetic kidney disease is diagnosed by an estimated glomerular filtration rate (eGFR) of less than 90 mL/min per 1·73 m² or a urinary albumin-to-creatinine ratio (UACR) of 30 mg/g (3·39 mg/mmol) or more. It affects up to 40% of people with diabetes,[1] in whom it is an independent risk factor for cardiovascular disease, hypertension, retinal disease, and premature death. Moreover, diabetes accounts for up to 45% of people with incident end-stage kidney disease.[2] Findings from large randomised controlled trials have shown that chronic renal outcomes can be reduced by intensive glucose control[3] and blood pressure lowering,[4] blockade of the renin–angiotensin system with either angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and sodium-glucose co-transporter-2 (SGLT2) inhibitors.[1,2,5,6] The effect of glucagon-like peptide-1 (GLP-1) receptor agonists on renal outcomes has also been assessed in large cardiovascular outcomes trials of people with type 2 diabetes. In addition to improved glucose control, and lowered blood pressure and bodyweight, trials of liraglutide, semaglutide, and

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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 and powered to test the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on incident cardiovascular outcomes in people with type 2 diabetes and additional cardiac risk factors and that reported the effect of the intervention on renal outcomes. 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", "renal disease", "renal function", "renal", "cardiovascular disease", and "randomized controlled trial". This search identified three cardiovascular outcomes trials that reported the effects of lixisenatide (ELIXA; n=6068), liraglutide (LEADER; n=9340), and semaglutide (SUSTAIN-6; n=3297) versus placebo on incident renal outcomes in middle-aged people (age ≥50 years) with type 2 diabetes. Mean glycated haemoglobin A_{1c} (HbA_{1c}) ranged from 7·7% to 8·7%, the proportion with an eGFR of 60 mL/min per 1·73 m² or more ranged from 70% to 77%, and median follow-up durations ranged from 2·1 years to 3·8 years. The composite renal outcome for both the LEADER and SUSTAIN-6 trials (new macroalbuminuria, doubling of serum creatinine concentration and estimated glomerular filtration rate [eGFR] less than 45 mL/min per 1·73 m², renal replacement therapy, or renal death) was reduced by the GLP-1 receptor agonist compared with placebo, with hazard ratios (HRs) of 0·78 (95% CI 0·67–0·92) and 0·64 (0·46–0·88), respectively. No composite renal outcome was prespecified for ELIXA. Reported renal outcomes in ELIXA were time to new macroalbuminuria (HR 0·81, 95% CI 0·66–0·99) and doubling of serum creatinine (HR 1·16, 0·74–1·83). All three trials suggested that the main renal effects of the GLP-1 receptor agonists were on progression of albuminuria, with modest effects on eGFR. These findings supported exploratory analyses of the effect on dulaglutide on renal outcomes in the REWIND trial.

Added value of this study

Participants in the REWIND trial had a mean baseline HbA_{1c} of 7·3%, a mean baseline eGFR of 76·9 mL/min per 1·73 m², and a 35·0% baseline prevalence of albuminuria, and were followed up for a median of 5·4 years. Dulaglutide reduced the prespecified composite renal outcome of new-onset macroalbuminuria, eGFR decline of 30% or more, or chronic renal replacement therapy, with the clearest effect on the macroalbuminuria component. Additional analyses suggested that the renal effects of dulaglutide could not be completely explained by its effect on glucose concentration or blood pressure.

Implications of all the available evidence

GLP-1 receptor agonists that have been shown to reduce cardiovascular outcomes also seem to have a salutary effect on renal outcomes and particularly albuminuria. Future large prospective trials of the effect of these drugs on prespecified renal outcomes should be done to more clearly characterise their effects on renal function in people with preserved and reduced baseline renal function.

albiglutide reported a significantly reduced hazard of the primary cardiovascular outcome.[6–10] Two of the trials also reported that daily liraglutide injections[9,11] and weekly semaglutide injections[10] reduced the predefined composite renal outcome overall and in people with a reduced eGFR.[11] Moreover, lixisenatide reduced new-onset macroalbuminuria in one trial.[12]

Dulaglutide is a GLP-1 receptor agonist derived from human GLP-1 that is administered weekly by subcutaneous injection. In the REWIND randomised placebo-controlled trial, dulaglutide reduced the risk of cardiovascular events when added to the existing antihyperglycaemic regimens of people with type 2 diabetes.[13] A previous trial reported that dulaglutide reduced the 1-year decline in eGFR in patients with stage 3 or 4 chronic kidney disease;[14] however, the long-term effect of dulaglutide on renal outcomes in people with type 2 diabetes and a much broader range of eGFR and cardiovascular disease risk is unclear. Renal outcomes were prospectively defined and collected in the REWIND trial as part of a secondary composite microvascular outcome; however, the protocol did not prespecify separate analyses of the components of this outcome. We did exploratory analyses of the prospectively defined renal effects of dulaglutide and their relation to glucose and blood pressure lowering within the REWIND trial.

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 have been reported elsewhere.[13,15] Eligible patients were men and women aged 50 years or older with established or newly detected type 2 diabetes and either a previous cardiovascular event or cardiovascular risk factors, whose glycated haemoglobin A_{1c} (HbA_{1c}) was 9·5% or less (with no lower limit), who were taking up to two oral glucose-lowering drugs with or without basal insulin therapy, and whose body-mass index (BMI) was at least 23 kg/m² and eGFR (calculated by the Modification of Diet in Renal Disease equation[16]) was at least 15 mL/min per 1·73 m². Key exclusion criteria were cardiovascular events or stroke within the previous 2 months, renal dialysis, severe hypoglycaemia within the past year, previous pancreatitis, bariatric surgery, or known abnormal gastric emptying. The REWIND trial protocol was approved by research ethics boards at all sites and all participants provided written informed consent.

Randomisation and masking

As described in detail elsewhere,[13,15] participants were randomly assigned (1:1) to weekly subcutaneous injections of either masked dulaglutide 1·5 mg or the same volume of masked placebo using a preloaded syringe. Randomisation was done by a computer-generated random code using an interactive web response system with stratification by site. All investigators and participants were masked to treatment allocation.

Procedures

Participants were seen at 2 weeks, 3 months, and 6 months and then every 6 months for detailed assessments. HbA_{1c} measurements were taken at least every 12 months and were used by investigators to manage glucose concentrations according to local country guidelines (including more frequent HbA_{1c} testing or adding any medication apart from a GLP-1 receptor agonist or pramlintide). Serum creatinine and the urinary albumin-to-creatinine ratio (UACR) were measured in local laboratories every 12 months, and management of renal protective medications, blood pressure, and cardiovascular risk was at the discretion of the investigator throughout the trial, as informed by local guidelines.

Outcomes

Results of the primary outcome (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), secondary outcomes (including the composite clinical microvascular outcome), and safety outcomes of REWIND have been reported elsewhere.[13] Criteria for adjudication of clinical events are listed in the appendix (pp 12–27). The prespecified composite microvascular outcome was the first occurrence of either a clinical retinal outcome (photocoagulation, vitrectomy, or use of anti-vascular endothelial growth factor injections) or a clinical renal outcome. The composite renal outcome was defined as the development of macroalbuminuria (development of UACR >33·9 mg/mmol in people with a lower baseline concentration), a sustained 30% or greater decline in eGFR (ie, based on two consecutive eGFR concentrations), or new chronic renal replacement therapy comprising dialysis or renal transplantation.

Statistical analysis

Sample size calculations for the REWIND trial have been reported elsewhere.[13,15] The REWIND statistical hierarchical testing strategy prespecifed that the effect of dulaglutide on the secondary composite microvascular outcome would be formally assessed if dulaglutide significantly reduced the hazard of the primary cardiovascular outcome and at least one of the components of that outcome at a prespecified level of significance.[15] Whereas the primary outcome was significantly reduced, the effect on the secondary outcomes did not achieve this prespecified level. Therefore, analyses of the composite renal outcome and its components should be viewed as exploratory.

Analyses were done according to an intention-to-treat approach that included all randomly assigned

	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%)
Duration of diabetes (years)	10·5 (7·3)	10·6 (7·2)
Previous diabetic retinopathy	448 (9·1%)	443 (8·9%)
Medications		
Metformin	4022 (81·3%)	4015 (81·1%)
Sulfonylurea	2270 (45·9%)	2282 (46·1%)
Thiazolidinedione	100 (2·0%)	68 (1·4%)
SGLT2 inhibitor	2 (<0·1%)	1 (<0·1%)
Insulin	1189 (24·0%)	1174 (23·7%)
ACE inhibitor	2452 (49·5%)	2463 (49·7%)
ARB	1679 (33·9%)	1693 (34·2%)
ACE inhibitor or ARB	4009 (81·0%)	4059 (82·0%)
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)
Mean arterial pressure (mm Hg)	97·9 (10·7)	98·1 (10·9)
Pulse pressure (mm Hg)	58·7 (13·7)	58·7 (13·9)
HbA_{1c} (%)	7·3% (1·1)	7·4% (1·1)
Serum creatinine (µmol/L)	83·7 (27·4)	84·5 (27·3)
eGFR (mL/min per 1·73 m²)	77·2 (22·7)	76·6 (22·8)
eGFR range (mL/min per 1·73 m²)		
≥90	1299 (26·2%)	1238 (25·0%)
60–89	2435 (49·2%)	2469 (49·9%)
30–59	1031 (20·8%)	1063 (21·5%)
<30	50 (1·0%)	55 (1·1%)
Missing	134 (2·7%)	127 (2·6%)
UACR (mg/mmol)	1·80 (0·70–6·60)	1·88 (0·70–7·38)
Albuminuria*	1707 (34·5%)	1760 (35·5%)
Microalbuminuria†	1325 (26·8%)	1351 (27·3%)
Macroalbuminuria‡	382 (7·7%)	409 (8·3%)
eGFR and albuminuria		
eGFR <60 and albuminuria	497 (10·0%)	544 (11·0%)
eGFR <60 and no albuminuria	521 (10·5%)	522 (10·5%)
eGFR ≥60 and albuminuria	1185 (23·9%)	1191 (24·1%)
eGFR ≥60 and no albuminuria	2353 (47·5%)	2302 (46·5%)
Missing	394 (8·0%)	393 (7·9%)

Data are mean (SD), n (%), or median (IQR). SGLT2=sodium-glucose co-transporter-2. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. HbA_{1c}=glycated haemoglobin A_{1c}. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. *UACR ≥3·39 mg/mmol. †UACR 3·39–33·9 mg/mmol. ‡UACR >33·9 mg/mmol.

Table 1: **Baseline characteristics**

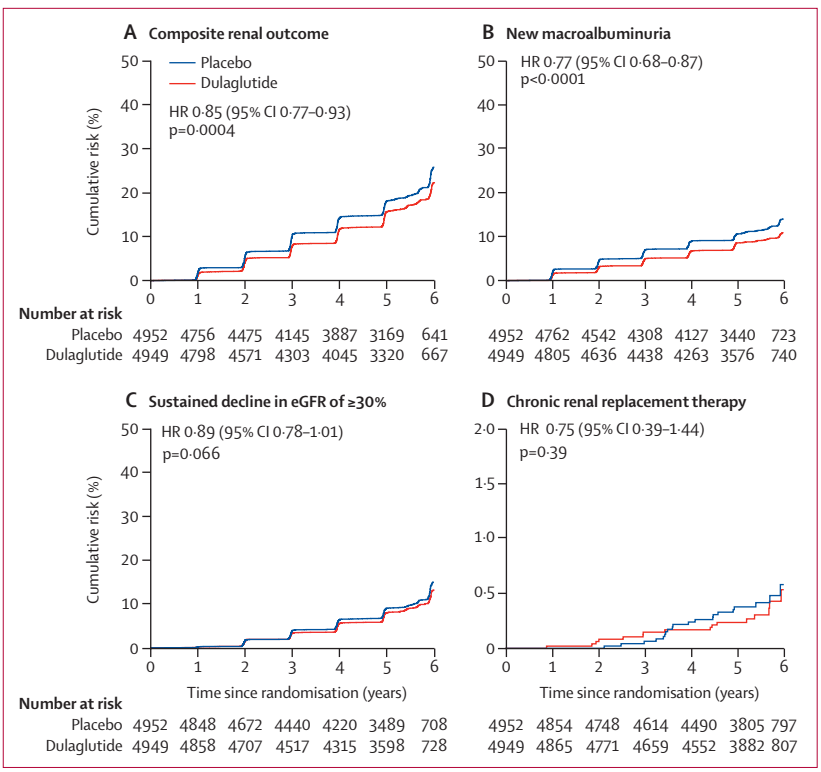

Figure 1: **Cumulative incidence of renal outcomes**
HR=hazard ratio. eGFR=estimated glomerular filtration rate.

participants. Continuous data were summarised as either means and SDs or medians and IQRs, and categorical data were summarised as numbers and percentages. Participants for whom there were no reported renal outcomes were assumed to have been free of the renal outcome at the end of the study or at the time of the participant's last known follow-up. Incidence rates (number per 100 person-years) were calculated for each treatment group, and Kaplan-Meier estimates were used to indicate cumulative incidence risk. The effect of dulaglutide on the composite renal outcome and on each component of that outcome and on any serious renal adverse event linked to acute renal failure was estimated using Cox proportional hazards models, and the effect of dulaglutide within subgroups relevant to renal disease was explored by assessing the subgroup–dulaglutide interaction term in the model. The proportions of participants in each group who had serious adverse renal and urinary events were compared using χ^2 tests. Participants were censored at either the date of the final follow-up visit, the date of death, or the date of discontinuation. Individuals with macroalbuminuria at baseline were included in all analyses but were only counted as having developed the renal outcome if they experienced the eGFR or chronic renal replacement therapy component of the outcome during follow-up. Proportional hazards assumptions for these 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 renal outcome was assessed by a composite treatment heterogeneity test.[17] Robustness of the findings to the competing risk of death was also assessed.[18] All reported p values are two-sided and a nominal level of significance of 0·05 was used. The effect of the intervention on the change from baseline of eGFR and the ratio of natural logarithm-transformed UACR to the baseline value was estimated using linear mixed models with baseline value as a covariate, participant as a random effect, and fixed effects for the baseline value, treatment, visit, and treatment–visit interaction.[19] Least-squares mean (LSM) values were reported for eGFR and least-squares proportional differences in the geometric mean values were reported for the back-transformed UACR.

Whether the effect of dulaglutide on HbA_{1c} and systolic blood pressure could statistically explain its effect on the composite renal outcome was also explored using a mediation analysis approach.[20] First, the updated mean value and the change of these measures from baseline to the last value measured before the renal outcome or end of follow-up was estimated as previously described.[20] Second, the relation between these values and the renal outcome was assessed using a univariable Cox model (ie, with only the measurement as a predictor). Third, if the measurement significantly predicted the renal outcome, the effect size (ie, the adjusted hazard ratio [HR]) of dulaglutide on the composite renal outcome and its components was re-estimated using a separate Cox model that included dulaglutide allocation as a fixed effect, the baseline value of the measurement, and either the updated mean or the change from baseline of each of these two variables as time-dependent covariates. The percentage difference between the adjusted and unadjusted hazard for the effect of dulaglutide (ie, the percentage by which the measure statistically accounted for the effect) was estimated by $100 \times (\ln HR_{unadjusted} - \ln HR_{adjusted}) / \ln HR_{unadjusted}$. All 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.

	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)		
Main analyses of renal effect						
Composite renal outcome	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004
Components of composite renal outcome						
New macroalbuminuria	441 (8·9%)	1·76	561 (11·3%)	2·29	0·77 (0·68–0·87)	<0·0001
Sustained decline in eGFR of ≥30%	453 (9·2%)	1·79	500 (10·1%)	2·00	0·89 (0·78–1·01)	0·066
Chronic renal replacement therapy	16 (0·3%)	0·06	21 (0·4%)	0·08	0·75 (0·39–1·44)	0·39
Serious renal adverse event*	84 (1·7%)	0·32	93 (1·9%)	0·36	0·90 (0·67–1·20)	0·46
Sensitivity analyses of renal effect						
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	587 (11·9%)	2·36	751 (15·2%)	3·10	0·76 (0·68–0·84)	<0·0001
Sustained decline in eGFR of ≥50%	61 (1·2%)	0·24	108 (2·2%)	0·42	0·56 (0·41–0·76)	0·0002
Composite renal outcome with this decline	496 (10·0%)	1·99	649 (13·1%)	2·66	0·74 (0·66–0·84)	<0·0001

eGFR=estimated glomerular filtration rate. *Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

Table 2: **Effect of treatment allocation on renal outcomes**

Results

Between Aug 18, 2011, and Aug 14, 2013, 9901 participants were randomly assigned, 4949 to dulaglutide and 4952 to placebo. Median follow-up was 5·4 years (IQR 5·1–5·9), comprising 51820 person-years. Baseline characteristics and renal protective drugs used at baseline are shown in table 1. Mean HbA_{1c} was 7·3% (SD 1·1), mean eGFR was 76·9 mL/min per 1·73 m² (SD 22·7), 3467 (35·0%) participants had albuminuria (ie, UACR ≥3·39 mg/mmol), and 2199 (22·2%) had an eGFR less than 60 mL/min per 1·73 m². Participants assigned to dulaglutide took study drug for 82·4% of the follow-up time from randomisation until either they had the composite renal outcome or their last follow-up visit, compared with 83·4% of the follow-up time for participants assigned to placebo. At the final visit, fewer participants in the dulaglutide group than in the placebo group were taking drugs linked to long-term improvements in renal outcomes, including an SGLT2 inhibitor (259 [5·3%] of 4932 in the dulaglutide group *vs* 361 [7·3%] of 4935 in the placebo group) or either an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (3739 [75·8%] *vs* 3829 [77·6%]; appendix p 30).

The renal component of the composite microvascular outcome occurred in 848 (17·1%) of 4949 participants assigned to dulaglutide and in 970 (19·6%) of 4952 participants assigned to placebo (HR 0·85, 95% CI 0·77–0·93; p=0·0004; figure 1). This effect was unchanged after accounting for the competing risk of death (HR 0·86, 95% CI 0·78–0·94; p=0·0010).[18] Consistent effects ($p_{interaction}$=0·59 for heterogeneity)[17] were observed for the three components of the composite renal outcome, with HRs of 0·77 (95% CI 0·68–0·87; p<0·0001) for progression to macroalbuminuria, 0·89 (0·78–1·01; p=0·066) for sustained decline in eGFR of 30% or more, and 0·75 (0·39–1·44; p=0·39) for chronic renal replacement therapy (figure 1, table 2). Similar effects of dulaglutide on the composite renal outcome were noted in subgroups defined by eGFR, baseline albuminuria, and the use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (table 3), as well as in subgroups defined by age, sex, duration of diabetes, and HbA_{1c} (appendix p 32). There were no significant differences between the dulaglutide and placebo groups in serious renal and urinary adverse events (appendix p 33).

The robustness of these estimates of the effect of dulaglutide on renal outcome was further explored in a set of sensitivity analyses. These analyses showed that dulaglutide was associated with a reduced incidence of a sustained eGFR decline of 40% or more (HR 0·70, 95% CI 0·57–0·85) and 50% or more (HR 0·56, 0·41–0·76), with corresponding HRs of 0·76 (0·68–0·84) and 0·74 (0·66–0·84) for the respective composite renal outcomes (table 2).

In participants assigned to dulaglutide, the proportional change from baseline in geometric mean UACR was 0·96 (SE 1·02) in the dulaglutide group and 1·17 (SE 1·02) in the placebo group (figure 2, appendix p 31). During follow-up, UACR values were lower in the dulaglutide group than in the placebo group (LSM proportional difference 0·82, 95% CI 0·78–0·86; p<0·0001). The eGFR concomitantly decreased by 1·62 mL/min per 1·73 m² (SE 0·24) in the dulaglutide group and by 1·47 mL/min per 1·73 m² (SE 0·24) in the placebo group during the first year of therapy (p=1·00), and by 4·32 mL/min per 1·73 m² (SE 0·19) in the dulaglutide group and by 4·75 mL/min per 1·73 m² (SE 0·19) in the placebo group during the entire follow-up period, with an overall

	Composite renal outcome				Sustained decline in eGFR of ≥30%				New macroalbuminuria*			
	Dulaglutide	Placebo	HR (95% CI)	$p_{interaction}$ †	Dulaglutide	Placebo	HR (95% CI)	$p_{interaction}$ †	Dulaglutide	Placebo	HR (95% CI)	$p_{interaction}$ †
Overall effect	848/4949 (17·1%)	970/4952 (19·6%)	0·85 (0·78–0·93)	..	453/4949 (9·2%)	500/4952 (10·1%)	0·89 (0·78–1·01)	..	441/4949 (8·9%)	561/4952 (11·3%)	0·77 (0·68–0·87)	..
eGFR (mL/min per 1·73 m²)	..	..	..	0·65	..	..		0·47	..	..	..	0·046
<60	219/1081 (20·3%)	251/1118 (22·5%)	0·88 (0·73–1·05)	..	81/1081 (7·5%)	102/1118 (9·1%)	0·81 (0·60–1·08)	..	154/1081 (14·2%)	171/1118 (15·3%)	0·91 (0·73–1·13)	..
≥60	610/3734 (16·3%)	701/3707 (18·9%)	0·83 (0·75–0·93)	..	372/3734 (10·0%)	398/3707 (10·7%)	0·91 (0·79–1·04)	..	268/3734 (7·2%)	372/3707 (10·0%)	0·70 (0·59–0·81)	..
Baseline albuminuria status	..	..	..	0·66	..	..	..	0·64	..	..	..	0·84
Normoalbuminuria	330/2917 (11·3%)	365/2863 (12·7%)	0·87 (0·75–1·01)	..	214/2917 (7·3%)	237/2863 (8·3%)	0·87 (0·73–1·05)	..	123/2917 (4·2%)	154/2863 (5·4%)	0·78 (0·61–0·99)	..
Microalbuminuria or macroalbuminuria	468/1707 (27·4%)	543/1760 (30·9%)	0·84 (0·74–0·95)	..	224/1707 (13·1%)	240/1760 (13·6%)	0·93 (0·78–1·12)	..	279/1707 (16·3%)	360/1760 (20·5%)	0·76 (0·65–0·89)	..
ACE inhibitor or ARB use	..	..	..	0·23	..	..	..	0·45	..	..	..	0·55
No	146/940 (15·5%)	141/893 (15·8%)	0·97 (0·77–1·22)	..	79/940 (8·4%)	74/893 (8·3%)	1·00 (0·73–1·37)	..	70/940 (7·4%)	77/893 (8·6%)	0·84 (0·61–1·16)	..
Yes	702/4009 (17·5%)	829/4059 (20·4%)	0·83 (0·75–0·92)	..	374/4009 (9·3%)	426/4059 (10·5%)	0·87 (0·76–1·00)	..	371/4009 (9·3%)	484/4059 (11·9%)	0·76 (0·66–0·87)	..

Data are n/N (%) unless otherwise stated. eGFR=estimated glomerular filtration rate. HR=hazard ratio. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *The 791 people with macroalbuminuria at baseline were not eligible to develop the new macroalbuminuria component of the outcome after randomisation. †p value for the interaction of subgroup with allocation.

Table 3: **Effect of dulaglutide on renal outcomes in exploratory subgroups**

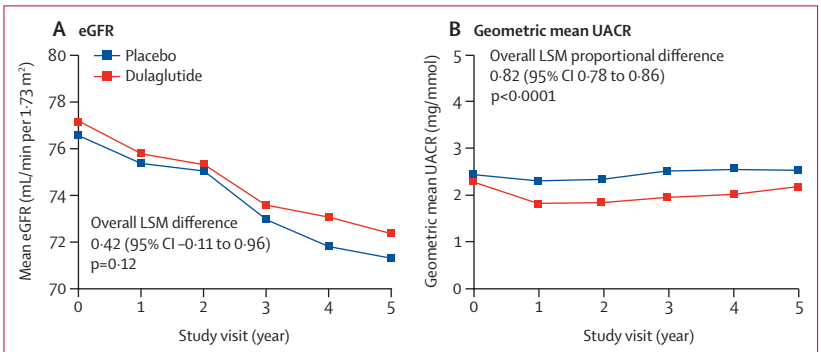

Figure 2: **Change in continuous measures during follow-up**

LSM=least-squares mean. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. The LSM value for eGFR is the difference in change from baseline with dulaglutide versus placebo. The LSM value for UACR is the proportional difference in the change in UACR from baseline with dulaglutide versus placebo.

between-group difference of 0·42 mL/min per 1·73 m² (95% CI –0·11 to 0·96; p=0·12). The effect of dulaglutide on the change in both the UACR and eGFR did not significantly change over time (p value for the interaction of the timing of the measurement visit and treatment p=0·36 for UACR and p=0·056 for eGFR). Reductions from baseline in HbA_{1c} and systolic blood pressure were greater in the dulaglutide group than in the placebo group (between-group differences 0·61% [95% CI 0·58–0·65] and 1·70 mm Hg [1·33–2·07], respectively; appendix p 31).

In view of clinical trial evidence that reductions in HbA_{1c}[3] and lowering of systolic blood pressure[4] reduce renal outcomes, the contribution of the observed dulaglutide-mediated reduction in HbA_{1c} and systolic blood pressure to its overall renal effect was then assessed. This was done by confirming that changes in both HbA_{1c} and systolic blood pressure during follow-up were associated with the renal outcome in REWIND, and then re-estimating the effect of dulaglutide on the renal outcome after adjusting for these two variables (appendix p 34). These analyses showed that the effect size of dulaglutide on the renal outcome was attenuated by up to 25·8% after accounting for its effect on HbA_{1c} and by up to 15·1% after accounting for its effect on systolic blood pressure.

Discussion

These exploratory analyses suggest that weekly injections of dulaglutide 1·5 mg for a median period of 5·4 years reduced the hazard of the composite renal outcome compared with placebo in middle-aged people with type 2 diabetes who had mean eGFR of 77 mL/min per 1·73 m² and baseline prevalence of albuminuria of 35·0%. On the basis of the observed absolute risk difference, our findings also suggest that one composite renal outcome event would be prevented for every 31 similar people with type 2 diabetes treated with dulaglutide for a median of 5·4 years. Although dulaglutide numerically reduced all three components of the composite renal outcome (the development of new macroalbuminuria, a sustained ≥30% decline in eGFR, or chronic renal replacement therapy), the largest effect was noted for the development of macroalbuminuria.

These findings are consistent with those from other cardiovascular outcomes trials of GLP-1 receptor agonists, in which statistically significant reductions in composite renal outcomes were mainly due to a robust effect on the development of macroalbuminuria.[9,10,12,21] Our findings did not confirm the results of a previous trial that reported a

beneficial effect of dulaglutide on the decline in eGFR in people with advanced renal insufficiency (who had a mean eGFR of 38 mL/min per 1·73 m²).[14] However, our sensitivity analyses suggested a reduced incidence of a 40% and 50% decline in eGFR with dulaglutide, supporting the possibility that dulaglutide might preserve renal function; this association merits further scrutiny.

These findings for dulaglutide add to what is already known regarding the effect of GLP-1 receptor agonists on renal disease. They suggest that treatment with dulaglutide modestly reduces progression of kidney disease and that the renal effect might persist for at least 5 years. Our findings also suggest that the effect of dulaglutide on HbA_{1c} and systolic blood pressure might account for a portion of its effect on the composite renal outcome and particularly its albuminuria component. This possibility is consistent with a meta-analysis of large outcomes trials of people with type 2 diabetes, which reported that glucose lowering reduced the hazard of renal outcomes by 20%, with the largest effect on macroalbuminuria.[3] It is also consistent with a large meta-analysis of trials in people with and without diabetes, which reported that blood pressure lowering mainly reduced albuminuria.[22,23]

The effect of dulaglutide on HbA_{1c} and systolic blood pressure clearly cannot account for all of its effect on the renal outcome. Accumulating evidence suggests that GLP-1 receptor agonists directly affect the kidney by reducing inflammation, reducing oxidative stress, and preserving endothelial function.[24] Indeed, the observed reduction in albuminuria might reflect a direct effect on renal endothelial cells, and by extension endothelial tissue throughout the body.[25] A theoretical possibility is based on experimental data and suggests that GLP-1 receptor agonist-mediated inhibition of sodium–hydrogen exchange in the proximal tubule might promote afferent arteriolar constriction and a short-term fall in eGFR due to tubuloglomerular feedback.[24] However, the absence of any effect of dulaglutide on the eGFR during the first year of therapy suggests that this is an unlikely mechanism.[26]

Strengths of this study include a study population that is representative of a large proportion of people with type 2 diabetes, including a high proportion of women, a wide range of baseline renal function, and an HbA_{1c} typical of the average person with type 2 diabetes.[27] Other strengths include the multicentre design; large sample size; long, extensive, and near-complete follow-up; and exploration of the possible explanatory effect of glycaemia and blood pressure. The major limitation is the exploratory nature of these analyses and the use of local measurement of albuminuria and serum creatinine for estimation of eGFR.

In addition to the reduced incidence of cardiovascular outcomes with dulaglutide that was reported in the REWIND trial,[13] these exploratory analyses suggest that about 5 years' exposure to dulaglutide might reduce progression of renal disease across a wide range of cardiovascular risk, renal function, and glycaemic control. Our findings also suggest that this reduction occurs for reasons that extend beyond the effect of dulaglutide on glucose and blood pressure and is independent of the use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. Irrespective of the reason, these analyses suggest that use of dulaglutide to lower glucose concentrations in people with type 2 diabetes is likely to confer additional renal benefits.

Contributors

HCG (REWIND Chair) prepared the first draft of the report, and together with HMC, GRD, RD, ML, PP, JP, FTB, 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 Cirius. 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 Cirius; honoraria for speaking from Sanofi; and consulting fees from Sanofi and Cirius. 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, FTB 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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