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 control1 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.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
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 agonist 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 HbA₁c 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 control 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.
Randomisation and masking

As described in detail elsewhere, 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. HbA1c measurements were taken at least every 12 months and were used by investigators to manage glucose concentrations according to local guidelines. 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 known causes), secondary outcomes (including the composite clinical microvascular outcome), and safety outcomes of REWIND have been reported elsewhere. 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, or the need for dialysis or renal transplantation.

Statistical analysis

Sample size calculations for the REWIND trial have been reported elsewhere. The REWIND statistical hierarchical testing strategy prespecified 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. 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 participants. Data are mean (SD), n (%), or median (IQR). SGLT2=sodium-glucose co-transporter-2. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. HbA1c=glycated haemoglobin A1c. eGFR=estimated glomerular filtration rate. UACR=urinary albumin-to-creatinine ratio. *UACR ≥3.39 mg/mmol. †UACR ≥33.9 mg/mmol. ‡UACR >33.9 mg/mmol.
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 each component of that outcome 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 \( \chi^2 \) 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 \( \text{HbA}_1 \text{c} \) 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 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 variables 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 \( 100 \times \left( \ln \text{HR}_{\text{adjusted}} - \ln \text{HR}_{\text{unadjusted}} \right) / \ln \text{HR}_{\text{unadjusted}} \). 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.

Figure 1: Cumulative incidence of renal outcomes

HR=hazard ratio. eGFR=estimated glomerular filtration rate.
Table 2: Effect of treatment allocation on renal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dulaglutide (n=4949)</th>
<th>Placebo (n=4952)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components of composite renal outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New macroalbuminuria</td>
<td>441 (8.9%)</td>
<td>176</td>
<td></td>
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<tr>
<td>Sustained decline in eGFR of ≥30%</td>
<td>453 (9.2%)</td>
<td>179</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal replacement therapy</td>
<td>16 (0.3%)</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious renal adverse event*</td>
<td>84 (1.7%)</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity analyses of renal effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained decline in eGFR of ≥40%</td>
<td>159 (3.4%)</td>
<td>0.66</td>
<td>237 (4.8%)</td>
<td>0.93</td>
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<td>Composite renal outcome with this decline</td>
<td>587 (11.9%)</td>
<td>2.36</td>
<td>751 (15.2%)</td>
<td>3.10</td>
</tr>
<tr>
<td>Sustained decline in eGFR of ≥50%</td>
<td>61 (1.2%)</td>
<td>0.24</td>
<td>108 (2.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Composite renal outcome with this decline</td>
<td>496 (10.0%)</td>
<td>1.99</td>
<td>649 (13.1%)</td>
<td>2.66</td>
</tr>
</tbody>
</table>

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

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 were similar between groups (table 1). Mean HbA1c, 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 had lower HbA1c, systolic blood pressure, and systolic and diastolic blood pressure outcomes (table 2).

In participants assigned to dulaglutide, the proportional change from baseline in geometric mean UACR was 0.96 (SE 0.02) in the dulaglutide group and 1.17 (SE 0.02) 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 -0.04, 95% CI -0.07 to -0.01; p<0.0001). The eGFR concomitantly decreased by 1.62 mL/min per 1.73 m² (SE 0.19) in the dulaglutide group and by 1.17 mL/min per 1.73 m² (SE 0.24) in the placebo group during the first year of therapy (p=0.0001), 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 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 HbA1c (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 0.75 (0.68–0.84) and 0.74 (0.66–0.84) for the respective composite renal outcomes (table 2).
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. Our findings did not confirm the results of a previous trial that reported a 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\(_\text{c}\) and systolic blood pressure were greater in the dulaglutide group than in the placebo group (between-group difference 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\(_\text{c}\) and lowering of systolic blood pressure 4 reduce 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. 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). 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 HbA₁c 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. 24 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 HbA₁c, 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 HbA₁c 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 theREWIND 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, MI, 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, DaCor, 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, DaCor, 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. MI 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, Biogen, Mundipharma, MSD, Novartis, Novo Nordisk, and Servier. MEI 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 Alkem. TTK 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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all listed in the appendix (pp 2–11). Their contributions, as well as those of ICON Clinical Research, which provided site management and collected the data, are gratefully acknowledged.

References
Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

APPENDIX

Dulaglutide and Renal Outcomes in Type 2 Diabetes: an Exploratory Analysis of the REWIND Randomised Controlled Trial

TABLE OF CONTENTS

Operations Committee 2
Steering Committee 2
Global Project Office 2
Independent Data Monitoring Committee (IDMC) 2
Site Investigators by Country 2-6
Site Coordinators by Country 7-11
Criteria for Adjudication of Reported Clinical Events 12-27
Data Sharing Policy 28-29
Table S1: Medications used at the last visit 30
Table S2: Effect of treatment allocation on continuous variables during follow-up 31
Table S3: Effect of dulaglutide on the renal composite outcome in key clinical Subgroups 32
Table S4: Renal and urinary serious adverse events 33
Table S5: Attenuation of the effect of dulaglutide on the renal outcome after accounting for its effect on HbA1c or blood pressure 34
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Criteria for Adjudication of Reported Clinical Events

Individual members of the CEC committees will perform adjudication based on definitions adapted from the October 2010 draft of the FDA task force Standardized Definitions for Endpoint Events in Cardiovascular Trials document. Definitions of acute and chronic pancreatitis, medullary thyroid carcinoma, and C-cell hyperplasia are based on clinical practice guidelines.

1. DEATH
   1.1. Definition of CV Death
CV death includes death due to myocardial infarction (MI), sudden cardiac death, death due to heart failure or cardiogenic shock, death due to stroke, and death due to other cardiovascular causes.

- Death due to Acute MI
Death due to Acute MI refers to a death by any mechanism (arrhythmia, heart failure, low output) within 30 days after an MI related to the immediate consequences of the MI, such as progressive heart failure (HF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., HF and arrhythmia free period of at least one week), they will be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an MI. The MI will be verified to the extent possible by the diagnostic criteria outlined for MI or by autopsy findings showing recent MI or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy will be considered as death resulting from an MI, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Death resulting from an emergent procedure to treat an MI such as a percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), or to treat an immediate complication resulting from an MI, will also be considered as a death due to MI.

Death resulting from a procedure to treat myocardial ischemia (angina) or death due to MI that occurs as a direct consequence of a CV investigation/procedure/operation will be considered as a death due to other CV causes.

- Sudden Cardiac Death
Sudden cardiac death refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths:

  a. Witnessed and instantaneous without new or worsening symptoms
  b. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms unless the symptoms suggest MI
  c. Witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
  d. Death after unsuccessful resuscitation from cardiac arrest
  e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
f. Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided)

A subject seen alive and clinically stable 12 to 24 hours prior to being found dead without any evidence or information of a specific cause of death will be classified as "sudden cardiac death." Typical scenarios include:

a. Subject was well the previous day but found dead in bed the next day

b. Subject found dead at home on the couch with the television on

Unwitnessed deaths for which there is no information beyond "Patient found dead at home" will be classified as "death due to other CV causes."

- **Death due to Heart Failure or Cardiogenic Shock**
  
  Death due to Heart Failure or Cardiogenic Shock refers to death occurring in the context of new or clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death and not following an MI. Deaths due to heart failure can have various etiologies, including one or more MIs (late effect), ischemic or non-ischemic cardiomyopathy, or valve disease.

  Death due to Heart Failure or Cardiogenic shock will include sudden death occurring during an admission for new or worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

  New or worsening signs and/or symptoms of HF include any of the following:

  a. New or increasing symptoms, and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure

  b. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration for hypoxia due to pulmonary edema

  c. Confinement to bed predominantly due to heart failure symptoms

  d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an MI, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

  e. Cardiogenic shock not occurring in the context of MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

  Cardiogenic shock will be defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

  - Oliguria (urine output < 30 mL/hour) or
  - Altered sensorium or
  - Cardiac index < 2.2 L/min/m²

  Cardiogenic shock may also be defined if SBP < 90 mm Hg and increases to >=90 mm Hg in less than 1 hour (with positive inotropic or vasopressor agents alone and/or with mechanical support.)
• **Death due to Stroke**
Death due to Stroke refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

• **Death due to Other Cardiovascular Causes**
Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories (e.g., dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, CV intervention [other than one related to an MI], aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization will be classified as CV deaths.

1.2. **Definition of Non-CV Death**
Non-CV death is defined as any death that is not thought to be due to a CV cause. The CEC will attempt to classify Non-CV Causes into one the following categories:

- Pulmonary
- Renal (includes renal organ failure)
- Gastrointestinal (includes hepatobiliary, pancreatic, GI organ failure)
- Primary Infection (not nosocomial infection or complication of other or protracted illness)
- Malignancy/Hematologic Disorder
- Complication of Non-CV Surgery
- Degenerative Neurologic\Non-Stroke or ICH (Parkinson's, Alzheimer's)
- Other, Non-CV

Death due to a gastrointestinal bleed will be considered a non-CV death.

1.3. **Definition of Undetermined Cause of Death**
Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be infrequent and should only apply to a minimal number of patients.

2. **MYOCARDIAL INFARCTION**
The term myocardial infarction (MI) will be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI will require the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

The totality of the clinical, electrocardiographic, and cardiac biomarker information will be considered to determine whether or not an MI has occurred. Specifically, timing and trends in cardiac biomarkers and
electrocardiographic information will be carefully analyzed. The adjudication of MI will also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2.1. Criteria for MI

• Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI will be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, HF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information will also be considered from myocardial and coronary imaging. The totality of the data may help differentiate MI from the background disease process.

• Biomarker Elevations

For cardiac biomarkers, sites should report the laboratories' upper reference limit (URL). If the 99th percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory will be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory will be used as the URL. Sites can also report both the 99th percentile of the URL and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK-MB, troponin, or CK will be required. The specific criteria will be referenced to the URL.

In patients who present acutely to hospitals which are not participating sites, and it is not practical to stipulate the use of a single biomarker or assay, the locally available results will be used as the basis for adjudication.

• Electrocardiogram (ECG) Changes

Electrocardiographic changes will used to support or confirm an MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

• Criteria for MI (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

  o ST elevation
    New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: 2: 0.2 mV in men (> 0.25 mV in men < 40 years) or 2: 0.15 mV in women in leads V2-V3 and/or 2: 0.1 mV in other leads.

  o ST depression and T-wave changes
    New horizontal or down-sloping ST depression 2: 0.05 mV in two contiguous leads and/or new T inversion 2: 0.1 mV in two contiguous leads.
The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for Pathological Q-wave**
  - Any Q-wave in leads V2-V3 2: 0.02 seconds or QS complex in leads V2 and V3
  - Q-wave 2: 0.03 seconds and 2: 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I,aVL, V6; V4-V6; II, III, and aVF). The same criteria will be used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

2.2. **Myocardial Infarction Subtypes**

MIs will be classified into the following subtypes as defined below:

- **Spontaneous MI:**
  1. Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:
     - Clinical presentation consistent with ischemia
     - ECG evidence of MI (new pathological Q waves)
     - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
     - Autopsy evidence of MI
  2. If biomarkers are elevated from a prior infarction, then a spontaneous MI will be defined as
     a. One of the following:
        - Clinical presentation consistent with ischemia
        - ECG evidence of MI (new pathological Q waves)
        - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
        - Autopsy evidence of MI
     b. Both of the following:
        - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI
        - >=20 % increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

- **PCI-Related MI**

PCI-related MI will be defined by any of the following criteria. Symptoms of cardiac ischemia will not be required.

1. Biomarker elevations within 48 hours of PCI:
• Troponin or CK-MB (preferred) >3 x URL and
• No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

Both of the following must be true:
• A minimum of 50% increase in the cardiac biomarker result
• Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

2. New pathological Q waves

3. Autopsy evidence of MI

Coronary Artery Bypass Grafting-Related Myocardial Infarction

CABG-related MI will be defined by the following criteria. Symptoms of cardiac ischemia will not be required.

1. Biomarker elevations within 72 hours of CABG:
• Troponin or CK-MB (preferred) >5 x URL and
• No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

Both of the following must be true:
• >=50% increase in the cardiac biomarker result
• Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

AND

2. One of the following:
• New pathological Q-waves persistent through 30 days
• New persistent non-rate-related LBBB
• Angiographically documented new graft or native coronary artery occlusion
• Other complication in the operating room resulting in loss of myocardium
• Imaging evidence of new loss of viable myocardium

OR

3. Autopsy evidence of MI
• **Silent MI**

Silent MI will be defined by the following:

1. No symptomatic or biomarker evidence of MI

AND one of the following

2. New pathological Q-waves as compared to baseline or most proximate/prior ECG recorded post randomization

OR

3. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause

2.3. **Clinical Classification of MI by the Universal MI Definition**

Each MI confirmed by the CEC to have met the definition of MI also will be classified using the following definitions:

• **Type 1**

Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

• **Type 2**

MI secondary to ischemia due to either increased oxygen demand or decreased supply, eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

• **Type 3**

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

• **Type 4a**

MI associated with PCI

• **Type 4b**

MI associated with stent thrombosis as documented by angiography or at autopsy

• **Type 5**

MI associated with CABG.

2.4. **Electrocardiographic Categorization of MI**

Events of MI confirmed by the CEC also will be classified based on electrocardiographic features into the following classifications:

• **ST-Elevation MI (STEMI)**

  o a -wave
o Non-Q wave

• Non-ST Elevation MI (NSTEMI)
  o Q-wave
  o Non-Q wave

• ECG not available or not interpretable

3. HOSPITALIZATION FOR UNSTABLE ANGINA
Unstable angina requiring hospitalization will be defined as:

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

   AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) within 24 hours of the most recent symptoms (or a date change if the time of admission/discharge is not available)

   AND

3. At least one of the following:
   a. New or worsening ST or T wave changes on ECG.
      o ST Elevation
         • New ST elevation at the J-point in two anatomically contiguous leads with the cut-off points: >=0.2 mV in men or >=0.15 mV in women in leads V2-V3 and/or >=0.1 mV in other leads
      o ST depression and T-wave changes
         • New horizontal or down-sloping ST depression >=0.05 mV in two contiguous leads; and/or T inversion >=0.1 mV in two contiguous leads.

It is recognized that lesser ECG abnormalities may represent an ischemia response and will be accepted under the category of abnormal ECG findings.

b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs

c. Angiographic evidence of >=70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs

d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay.
   This criterion would be fulfilled if the admission for myocardial ischemia led to transfer to
another institution for the revascularization procedure without interceding home discharge.

AND

4. No evidence of MI.

Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of -blockers, will be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy without any of the additional findings listed under category 3, will be insufficient alone to support classification as hospitalization for unstable angina.

4. **HEART FAILURE EVENT TYPES**

4.1. **Heart Failure Requiring Hospitalization**

Heart failure (HF) requiring hospitalization will be defined as an event that meets the following criteria:

a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour* stay (or a date change if the time of admission/discharge is not available).

AND

b. Clinical symptoms of heart failure including at least one of the following: New or worsening

- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- increasing fatigue/worsening exercise tolerance

AND

c. Physical signs of heart failure, including at least two of the following:

- Edema (greater than 2+ lower extremity)
- Pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress not occurring in the context of an MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure)
- Jugular venous distension
- Tachypnea (respiratory rate > 20 breaths/minute)
- Rapid weight gain
- S3 gallop
- Increasing abdominal distension or ascites
- Hepatojugular reflux
• Radiological evidence of worsening heart failure
• A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) $\geq 18$ mm Hg or a cardiac index $< 2.2$ U min/m$^2$

**AND**

d. Need for additional/increased therapy

1. Initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF and including at least one of the following:
   • Initiation of or a significant augmentation in oral therapy for the treatment of HF
   • Initiation of intravenous diuretic, inotrope, or vasodilator therapy
   • Uptitration of intravenous therapy, if already on therapy
   • Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of HF.

**AND**

e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms are identified.

Biomarker results (e.g., brain natriuretic peptide [BNP]) consistent with HF will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the URL, may also be supportive of the diagnosis of HF in selected cases (e.g., morbid obesity).

It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of HF requiring hospitalization, the diagnosis of HF would need to be the primary disease process accounting for the above signs and symptoms.

**4.2. Urgent Heart Failure Visit**

An Urgent Heart Failure Visit is defined as an event that meets all of the following:

1. The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
2. All signs and symptoms for HF hospitalization must be met as defined in above section
3. The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy which will not be sufficient.
5. REVASCULARIZATION PROCEDURES

Revascularization procedures will be defined as follows:

- **A coronary revascularization procedure** will be defined as a catheter based or open surgical procedure designed to improve myocardial blood flow. Insertion of a guidewire through a coronary guide catheter into a coronary artery or bypass graft for the purpose of PCI is considered a procedure.

- **A carotid revascularization procedure** will be defined as a catheter-based or open surgical procedure designed to improve carotid arterial blood flow. This procedure may include endarterectomy or stent placement. The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guidewire through a guide catheter into a peripheral artery.

- **A peripheral arterial revascularization procedure** will be defined as a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow. This procedure may include thrombectomy, embolectomy, atherectomy, dissection repair, angioplasty or stent placement. The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guidewire through a guide catheter into a peripheral artery.

5.1. Procedural Success/Failure

For any revascularization procedure, procedural success will be classified into one of the following categories:

**Success:**

- **Procedure Successful Based Upon Procedure Report and Medical Record** is a procedure that will be considered a complete success if the post-procedure visual residual stenosis is <30% with no decrement in flow. A procedure will be classified as a partial success if there is either a >50% residual stenosis by visual assessment or for coronary revascularization procedures, if at least TIMI Grade 2 Flow is not attained. For the procedure to be successful the patient must have been discharged to home and/or the hospitalization was not prolonged due to specific, procedure-related complications.

- **Procedure Successful Based Upon Medical Record, Absent Procedure Report** will apply if the patient was discharged to home and/or hospitalization was not prolonged due to specific procedure-related complications.

**Failure:**

- **Procedure a Failure Based Upon Procedure Report and Medical Record** is a procedure that will be classified a failure if there is a persistent total occlusion, if the lesion cannot be crossed, or if there is persistent abrupt closure. The procedure will also be classified as a failure if the patient's hospitalization was prolonged specifically due to procedure related complications.

- **Procedure a Failure Based Upon Medical Record, Absent Procedure Report** will apply if the patient's hospitalization was prolonged specifically due to procedure related complications.

**Procedure Could not be Classified as a Success or Failure due to Absence of Source Documentation Despite Efforts to Obtain Source Documents.**
6. CEREBROVASCULAR EVENT (STROKE)

6.1. TIA
TIA will be defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

6.2. Stroke
Stroke will be defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

6.3. Classification
A. Ischemic Stroke
Ischemic stroke will be defined as an acute episode of focal cerebral, spinal or retinal dysfunction caused by an infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke will be an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke
Hemorrhagic stroke will be defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a non-traumatic, intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke
Undetermined stroke will be defined as a stroke with insufficient information to allow categorization as A or B.

6.4. Stroke Disability
Stroke disability will be measured using the modified Rankin Scale and will be assessed at approximately 30 days following the stroke diagnosis.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

6.5. Additional Considerations
The distinction between a TIA and an Ischemic Stroke is the presence of infarction, not the transience of the symptoms. In addition to documentation of infarction, persistence of symptoms is an acceptable indicator of infarction.

7. PANCREATITIS
Events of pancreatitis will be classified as acute, chronic, or unknown.

7.1. Acute Pancreatitis
Acute pancreatitis (AP) will be defined as an event that meets 2 of the following 3 criteria.

1. Abdominal pain
   - Pain is generally located in the epigastric region
   - Pain may radiate to the back
   - Swift onset with pain reaching maximum intensity within 30 minutes. Pain varies in intensity, may be severe and persist for more than 24 hours without relief.
   - Pain is commonly associated with nausea and vomiting
   - Physical examination may reveal fever, tachycardia, and upper abdominal tenderness on palpation, associated with guarding. Rebound tenderness may be present.

2. Laboratory Criteria
   - Serum amylase and/or lipase > 3 x URL

3. CT, MRI, or other imaging modalities (eg, magnetic resonance cholangiopancreatography [MRCP], endoscopic ultrasound) showing findings consistent with inflammatory changes in the pancreas. Findings on imaging studies may include:
   - Enlargement of the pancreas with diffuse edema
   - Heterogeneity of pancreatic parenchyma
   - Peripancreatic stranding
   - Peripancreatic fluid collections
   - Pancreatic necrosis

7.2. Chronic Pancreatitis
Chronic pancreatitis (CP) is a chronic, irreversible inflammation (monocyte and lymphocyte) that leads to fibrosis with calcification. It is characterized by a clinical spectrum that encompasses pain, loss of exocrine pancreatic function, diabetes mellitus, and various complications usually involving organs adjacent to the pancreas. CP will require at least 1 of the following clinical criterions and must be accompanied by well-defined abnormalities in imaging findings. These criteria were adapted from Bornman et al. (BMJ 2001;322:660-663) and Buchler et al (BMC Gastroenterology 2009;9[93]).
• **Clinical Criteria:**
  
a. **Abdominal Pain**, including some or all of the following characteristics:
   - Severe, dull epigastric pain that may radiate to the back
   - May be associated with nausea and vomiting
   - May be associated with meals or independent of meals
   - May be intermittent but it is not fleeting and can persist for days or may be constant
   - Epigastric tenderness may be present on physical examination

b. **Attacks of AP,**
c. **Diarrhea,**
d. **Weight loss,**
e. **Steatorrhoea,**

**OR**

f. **Complications of CP such as one of the following:**
   - Bile duct obstruction/stenosis with cholestasis or jaundice
   - Duodenal obstruction/stenosis with clinical signs
   - Vascular obstruction/stenosis with clinical or morphological signs of portal/splenic vein hypertension
   - Pancreatic pseudocysts with clinical signs (compression of adjacent organs, infection, bleeding, etc)
   - Pancreatic fistula (internal or external)
   - Pancreatogenic ascites
   - Other rare complications related to organs in vicinity (ie, colonic stenosis, splenic pseudocyst, etc)

• **Imaging Criteria**
  - Plain abdominal x-ray showing pancreatic calcifications
  - CT, MRI, or other imaging modalities (eg, ERCP, MRCP, endoscopic ultrasound) show ductal and/or parenchymal changes consistent with chronic pancreatitis: diffuse calcification, enlarged/irregular pancreas, dilated pancreatic duct ± strictures, intrapancreatic cysts, pseudocysts, splenic vein thrombosis

Approximately 20% of patients have painless CP and present with signs and symptoms of pancreatic exocrine or endocrine insufficiency. Patients meeting these criteria will meet the definition of CP.
Diabetes mellitus is usually a criterion for the diagnosis of chronic pancreatitis; however, all patients enrolled in the REWIND trial must have type 2 diabetes and therefore this criterion was removed from the clinical criteria.

7.3. Unknown

Events that may meet the definition of pancreatitis but are unable to be classified as either AP or CP will be classified as unknown.

7.4. Severity of AP

The severity of AP will be classified as mild, moderate, severe, or critical using the criteria proposed by Petrov and Windsor (Am J Gastroenterol 2010;105:74-76). This classification is based on peri-pancreatic complications (absent, sterile, or infectious) and organ failure (absent, transient, persistent).

- **Mild**: no peri-pancreatic complication AND no organ failure
- **Moderate**: sterile peri-pancreatic complication OR transient organ failure
- **Severe**: infectious peri-pancreatic complication OR persistent organ failure
- **Critical**: infectious peri-pancreatic complication AND persistent organ failure

*Severity is graded on the basis of more severe local or systemic complication (e.g., sterile pancreatic necrosis without organ failure has to be graded as moderate; sterile pancreatic necrosis with persistent organ failure has to be graded as severe)*

8. THYROID EVENTS REQUIRING A BIOPSY OR THYROIDECTOMY

The CEC will adjudicate thyroid evaluations that result in a surgical biopsy of the thyroid gland and/or a thyroidectomy or a diagnosis of a thyroid malignancy or C-cell hyperplasia. The CEC will classify these events as C-cell hyperplasia, carcinoma in situ (microcarcinoma), medullary thyroid carcinoma, or other (i.e., papillary, follicular, and anaplastic).

To classify these events, the CEC will use all available data including physical examination, imaging study findings (e.g., ultrasound), laboratory data (e.g., calcitonin), and biopsy/surgical results (as reported by the local pathologist). Tissue samples will not be required in support of the adjudication process.

**C-cell hyperplasia**

Even though the pathological diagnosis of c cell hyperplasia is controversial (PW Biddinger and M Ray Pathology Annual. 28 PT 1:205-229, 1993), anatomically c-cell hyperplasia for this study will be defined as more than 50 c-cells per low power field (at 10 x magnification) (VA LiVols i et al. J Clin Endocrinol Metab 37:550, 1973).

**Medullary Thyroid Carcinoma**

Medullary carcinoma of the thyroid (MTC) will be defined as a distinct thyroid carcinoma that originates in the calcitonin producing parafollicular C cells of the thyroid gland. MTG usually runs a slow but progressive course which may include invasion of local neck structures and cervical lymph nodes. Calcitonin, and any other supporting laboratory results provided, will be reviewed and considered in the determination of MTC.
Medullary thyroid carcinoma (MTC) often appears to be multifocal but inhomogeneous and if detected early to be microscopic. The typical tumor histology has clusters of polyhedral neoplastic cells arranged in compartments separated by amyloid-containing stroma. This appearance with the absence of neoplastic follicles and papillary elements is the diagnostic feature which differentiates MTC from follicular cell tumors (CS Hill, et al., Medicine (Baltimore) 52:141-171, 1973).

The clinical staging system of the American Joint Committee on Cancer (AJCC) correlates survival to size of the primary tumor, presence or absence of lymph node metastases, and presence or absence of distance metastasis. Events of MTC will be classified according to stage based on the AJCC classification.

Stage O medullary thyroid cancer
   Clinically occult disease detected by provocative biochemical screening.

Stage I medullary thyroid cancer
   Tumor smaller than 2 cm.

Stage II medullary thyroid cancer
   Tumor larger than 2 cm but 4 cm or smaller with no metastases or larger than 4 cm with minimal extrathyroid extension.

Stage III medullary thyroid cancer
   Tumor of any size with metastases limited to the pretracheal, paratracheal or prelaryngeal/Delphian lymph nodes.

Stage IV medullary thyroid cancer
   Stage IVA (moderately advanced with or without lymph node metastases [for T4a] but without distant metastases).
   Stage IVB (very advanced with or without lymph node metastases but no distant metastases).
   Stage IVC (distant metastases.)
Data will be disclosed only upon request and approval of the proposed use of the data by a review committee. Membership in the review committee will be determined by the executive leadership of the study. Generally only those requests made by a journal's statistician regarding the data related to the results of the publication will be considered unless the review committee sees high merit in other requests. The following principles will apply to requests:

1. The review committee will have established criteria to review the request to ensure that patient privacy and rights, and PHRI data and research integrity can be maintained with the sharing of the data. This includes (but is not limited to) demonstrated competence related to data security and data analysis by the investigator requesting access. The review committee will also ensure that provision of data to external parties does not contravene any prior agreement with any other parties.

2. PHRI will make individual participant data available, including data dictionaries, within the requirements and/or restrictions of REB/IRB and subject to the conditions set forth in the consent forms of the study. Data provided will be limited to data which underlies the results in the main publication after de-identification. Any analyses and publications should be reviewed and approved by PHRI before publication to ensure that the analyses are accurate and that the publication is not misleading.

3. The study protocol and the statistical analysis plan for analysis of the primary results will be shared.

4. For those requests that originate from concerns expressed by the journal about the data or statistical analyses, the data will be available to the journal statisticians in a timely manner.

5. Data can be disclosed for all other requests from 2 years after the main paper is published plus 6 additional months for each year of study conduct. However, there will be a maximum of 7 years to the time limit restriction.

6. Data will be shared to achieve the objective in the approved proposal with no additional analysis permitted without approval. Only proposals for analyses that do not compete with ongoing analyses or analyses proposed by study investigators will be approved.

7. Data will be made available by one of the following mechanisms. 1) The Statistics Department at PHRI can perform the analysis in accordance with the SAP provided by the investigator and under his/her supervision or 2) Arrangement can be made to transfer the data to a secure location using a process that has been verified by the Director of Statistics at PHRI.

8. Every proposal must identify and provide funding sufficient to defray the cost of data preparation, storage, transfer and analysis for the organization incurring these costs (this may include studies not fully funded from external sources i.e. industry or peer review grants). On occasions where the new analyses proposed are of sufficient scientific interest to PHRI, then a collaborative agreement for joint analyses and publication can be developed and charges may be reduced.
9. The data will be provided for a specified time limit that can allow completion of the analyses that is proposed. At the end of the proposed analyses, the requesting party undertakes to return or destroy the data base provided and provide written documentation of this.

References
3. Supplemental Endorsers of Article listed in 2
<table>
<thead>
<tr>
<th></th>
<th>Dulaglutide (N=4949)</th>
<th>Placebo (N=4952)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had a Final Visit</td>
<td>4932</td>
<td>4935</td>
</tr>
<tr>
<td>Metformin – N (%)</td>
<td>3436 (69.7)</td>
<td>3594 (72.8)</td>
</tr>
<tr>
<td>Sulfonylurea – N (%)</td>
<td>1608 (32.6)</td>
<td>1860 (37.7)</td>
</tr>
<tr>
<td>Insulin – N (%)</td>
<td>1336 (27.1)</td>
<td>1770 (35.9)</td>
</tr>
<tr>
<td>SGLT2i – N (%)</td>
<td>259 (5.3)</td>
<td>361 (7.3)</td>
</tr>
<tr>
<td>GLP-1 RA – N (%)</td>
<td>28 (0.6)</td>
<td>45 (0.9)</td>
</tr>
<tr>
<td>Thiazolidinedione – N (%)</td>
<td>71 (1.4)</td>
<td>97 (2.0)</td>
</tr>
<tr>
<td>Statin – N (%)</td>
<td>3281 (66.5)</td>
<td>3328 (67.4)</td>
</tr>
<tr>
<td>ARB or ACEi – N (%)</td>
<td>3739 (75.8)</td>
<td>3829 (77.6)</td>
</tr>
<tr>
<td>ASA – N (%)</td>
<td>2481 (50.3)</td>
<td>2514 (50.9)</td>
</tr>
<tr>
<td>Beta Blocker – N (%)</td>
<td>2302 (46.7)</td>
<td>2332 (47.3)</td>
</tr>
</tbody>
</table>
Table S2: Effect of Treatment Allocation on Continuous Variables During Follow-up

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Dulaglutide</th>
<th>Placebo</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.46 (0.01)</td>
<td>0.16 (0.01)</td>
<td>-0.61 (-0.65, -0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-3.15 (0.13)</td>
<td>-1.44 (0.13)</td>
<td>-1.70 (-2.07, -1.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-4.32 (0.19)</td>
<td>-4.75 (0.19)</td>
<td>0.42 (-0.11, 0.96)</td>
<td>0.119</td>
</tr>
<tr>
<td>Urine ACR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.96 (1.02)</td>
<td>1.17 (1.02)</td>
<td>0.82 (0.78, 0.86)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Least square estimates (SE or 95% CI) are shown and the P value is the adjusted Tukey-Kramer value for the 2-group t-test; <sup>a</sup>within and between-treatment group mean differences are expressed as dulaglutide-placebo with their 95% CI; <sup>b</sup>within and between group proportional geometric mean differences are shown; BP – blood pressure; eGFR – estimated glomerular filtration rate; ACR – urine albumin:creatinine ratio
Table S3: Effect of Dulaglutide on the Renal Composite Outcome in Key Clinical Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Dulaglutide</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>HR (95%CI)</th>
<th>P (int)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (%)</td>
<td>Rate</td>
<td>Events (%)</td>
<td>Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Effect</td>
<td>848/4949</td>
<td>3.5</td>
<td>970/4952</td>
<td>4.1</td>
<td>0.85 (0.77, 0.93)</td>
<td>-</td>
</tr>
<tr>
<td>Age ≥ 66 y</td>
<td>394/2314</td>
<td>3.5</td>
<td>485/2350</td>
<td>4.4</td>
<td>0.79 (0.69, 0.90)</td>
<td>0.17</td>
</tr>
<tr>
<td>Age &lt; 66 y</td>
<td>454/2635</td>
<td>3.4</td>
<td>485/2602</td>
<td>3.8</td>
<td>0.90 (0.79, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>398/2306</td>
<td>3.5</td>
<td>433/2283</td>
<td>3.9</td>
<td>0.88 (0.77, 1.01)</td>
<td>0.39</td>
</tr>
<tr>
<td>Male</td>
<td>450/2643</td>
<td>3.5</td>
<td>537/2669</td>
<td>4.2</td>
<td>0.82 (0.72, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Diabetes &lt; 5 y</td>
<td>187/1227</td>
<td>3.1</td>
<td>199/1192</td>
<td>3.4</td>
<td>0.90 (0.73, 1.09)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes 5-9 y</td>
<td>247/1446</td>
<td>3.4</td>
<td>276/1476</td>
<td>3.8</td>
<td>0.89 (0.75, 1.06)</td>
<td></td>
</tr>
<tr>
<td>Diabetes ≥ 10 y</td>
<td>414/2276</td>
<td>3.7</td>
<td>495/2284</td>
<td>4.6</td>
<td>0.80 (0.70, 0.91)</td>
<td></td>
</tr>
<tr>
<td>HbA1c &gt; 7.2%</td>
<td>488/2610</td>
<td>3.8</td>
<td>562/2603</td>
<td>4.6</td>
<td>0.83 (0.74, 0.94)</td>
<td>0.78</td>
</tr>
<tr>
<td>HbA1c ≤ 7.2%</td>
<td>356/2329</td>
<td>3.1</td>
<td>404/2334</td>
<td>3.5</td>
<td>0.86 (0.75, 0.99)</td>
<td></td>
</tr>
</tbody>
</table>

Rate is expressed as n/100 person years; HR (95%CI) – hazard ratio and 95% confidence intervals; P (int) - P for the interaction of subgroup and allocation; y - years; CVD - cardiovascular disease
<table>
<thead>
<tr>
<th></th>
<th>Dulaglutide</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Rate</td>
<td>N (%)</td>
<td>Rate</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>156 (3.15%)</td>
<td>0.60</td>
<td>177 (3.57%)</td>
<td>0.69</td>
<td>0.24</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2 (0.04%)</td>
<td>0.01</td>
<td>7 (0.14%)</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>17 (0.34%)</td>
<td>0.07</td>
<td>16 (0.32%)</td>
<td>0.06</td>
<td>0.86</td>
</tr>
<tr>
<td>Renal colic</td>
<td>7 (0.14%)</td>
<td>0.03</td>
<td>6 (0.12%)</td>
<td>0.02</td>
<td>0.78</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16 (0.32%)</td>
<td>0.06</td>
<td>16 (0.32%)</td>
<td>0.06</td>
<td>0.99</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3 (0.06%)</td>
<td>0.01</td>
<td>9 (0.18%)</td>
<td>0.03</td>
<td>0.08</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>7 (0.14%)</td>
<td>0.03</td>
<td>6 (0.12%)</td>
<td>0.02</td>
<td>0.78</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>14 (0.28%)</td>
<td>0.05</td>
<td>17 (0.34%)</td>
<td>0.07</td>
<td>0.59</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>60 (1.21%)</td>
<td>0.23</td>
<td>67 (1.35%)</td>
<td>0.26</td>
<td>0.53</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>3 (0.06%)</td>
<td>0.01</td>
<td>6 (0.12%)</td>
<td>0.02</td>
<td>0.32</td>
</tr>
<tr>
<td>Ureterolithiasis</td>
<td>9 (0.18%)</td>
<td>0.03</td>
<td>9 (0.18%)</td>
<td>0.03</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Serious adverse events are listed here if they were reported more than 5 people in either group. Chi-square P values are reported.
Table S5: Attenuation of the Effect of Dulaglutide on the Renal Outcome After Accounting for its Effect on HbA1c or Blood Pressure

<table>
<thead>
<tr>
<th>Effect of dulaglutide on the variable(^a)</th>
<th>HbA1c (%)</th>
<th>Systolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiologic relationship to renal outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) per unit rise (updated mean)</td>
<td>-0.61 (-0.65, -0.58)</td>
<td>-1.70 (-2.07, -1.33)</td>
</tr>
<tr>
<td>HR (95% CI) per unit rise (change)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) of dulaglutide on the renal outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.079 (1.035, 1.126)</td>
<td>1.015 (1.011, 1.018)</td>
</tr>
<tr>
<td>Adjusted for updated mean(^b)</td>
<td>1.086 (1.048, 1.125)</td>
<td>1.015 (1.012, 1.018)</td>
</tr>
<tr>
<td>Adjusted for change from baseline(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of effect accounted for(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By updated mean (%)</td>
<td>0.847 (0.772, 0.929)</td>
<td>0.847 (0.772, 0.929)</td>
</tr>
<tr>
<td>By change from baseline (%)</td>
<td>0.879 (0.798, 0.968)</td>
<td>0.866 (0.790, 0.950)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.884 (0.804, 0.972)</td>
<td>0.868 (0.792, 0.952)</td>
</tr>
</tbody>
</table>

\(^a\)Least square estimates with 95% confidence intervals from the mixed model (from Table S2) are shown;\(^b\)Cox proportional Hazards model with treatment, baseline HbA1c or systolic BP value and updated mean as the covariates;\(^c\)Cox proportional Hazards model with treatment, baseline value and change from baseline of HbA1c or systolic BP as the covariates;\(^d\)estimated as 100*(ln HR unadjusted – ln HR adjusted) /ln HR unadjusted.