ORIGINAL ARTICLE

WILEY

Efficacy and safety outcomes of dulaglutide by baseline HbA1c: A post hoc analysis of the REWIND trial

Edward Franek MD[1] | Hertzel C. Gerstein MD, MSc[2] | Matthew C. Riddle MD[3] | Claudia Nicolay PhD[4] | Ana Hickey PhD[4] | Fady T. Botros PhD[4] | Li Shen Loo PhD[4]

[1]Mossakowski Medical Research Centre, Polish Academy of Sciences and Central Clinical Hospital MSWiA, Warsaw, Poland

[2]Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

[3]Department of Medicine, Oregon Health & Science University, Portland, Oregon

[4]Eli Lilly and Company, Indianapolis, Indiana

Correspondence
Li Shen Loo, PhD, Eli Lilly and Company, Indianapolis, IN 46285.
Email: loo_li_shen@lilly.com

Abstract

Aim: To assess cardiovascular, glycaemic, weight and safety outcomes of long-term treatment with dulaglutide 1.5 mg compared with placebo in patients with a baseline HbA1c of less than 7% versus 7% or higher.

Materials and Methods: Intention-to-treat analyses were performed on REWIND participants with a baseline HbA1c measurement, using Cox proportional hazards regression and mixed model for repeated measures. Subgroup analyses with factors for baseline HbA1c categories and their interaction with treatment group, as well as analyses within the HbA1c subgroups, were conducted. Additionally, sensitivity analyses were performed for baseline HbA1c subgroups of 6.5% or less and more than 6.5%.

Results: Of the 9876 eligible participants, 3921 and 5955 had a baseline HbA1c of less than 7% and 7% or higher, respectively. Mean baseline HbA1c was 6.3% and 8.0% and the mean duration of diabetes was 9.0 and 11.6 years in the respective subgroups. The less than 7% subgroup was slightly older and less frequently insulin-treated. There was no evidence of a differential dulaglutide treatment effect on body mass index (BMI) reduction, cardiovascular or safety outcomes of interest between the baseline HbA1c subgroups. Treatment-by-baseline HbA1c group interaction was significant for HbA1c change from baseline ($P < .001$), with a greater reduction in the subgroup with higher baseline HbA1c values. Sensitivity analyses by baseline HbA1c subgroups of 6.5% or less and more than 6.5% showed similar results.

Conclusions: The reduced incidence of cardiovascular events, and the reduction in BMI in participants treated with once-weekly dulaglutide, were independent of the baseline HbA1c level. Conversely, participants with a higher baseline HbA1c level had greater reductions in HbA1c. Dulaglutide has a positive benefit–risk profile and can be considered in patients with comparatively well-controlled HbA1c levels seeking optimal metabolic control and cardiovascular benefits.

KEYWORDS
cardiovascular disease, clinical trial, dulaglutide, glycaemic control, incretin therapy, type 2 diabetes

1 | INTRODUCTION

Several large prospective, multi-centre, randomized clinical trials have evaluated the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and found that the treatments were associated with glycaemic benefits, some weight loss, and limited short-term risks.[1] Overall, GLP-1 RA cardiovascular outcomes trials (CVOTs) showed CV safety or benefit, suggesting that drugs in this class are not associated with increased CV risk, and indeed some reduce CV risk (three-point major adverse CV events, CV mortality, or all-cause mortality risk), without altering the safety profile of the medication class.[2-4]

Several treatment guidelines for type 2 diabetes (T2D) recommend an HbA1c treatment target of less than 7% as an HbA1c goal for many non-pregnant adults without significant hypoglycaemia, few co-existing chronic illnesses, and intact cognitive and functional status.[5-8] Furthermore, the American Association of Clinical Endocrinologists and American College of Endocrinology statement supports an HbA1c target of 6.5% or less, provided that it can be achieved without adverse events such as hypoglycaemia.[9] Intensive glycaemic control reduces the risk of microvascular complications[8] and there is a growing body of evidence that it also reduces macrovascular events.

The Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial showed that adding once-weekly GLP-1 RA dulaglutide to the standard of care significantly reduced the risk of major adverse CV events in adults with T2D and either established cardiovascular disease (CVD) or multiple CV risk factors compared with placebo.[10] Unlike other GLP-1 RA CVOTs, REWIND included patients with moderate to high CVD risk, which may be more representative of the broader US adult population with T2D.[11] A prior post hoc analysis of the REWIND trial showed no differences in CV benefits and safety outcomes between older and younger subgroups (aged ≥65 and <65 years).[12] Additionally, of the GLP-1 RA CVOTs published to date, REWIND had the lowest mean baseline HbA1c of 7.3%[4,13] and did not have a lower HbA1c limit for the enrolment.[14] As REWIND had a comparatively large population of participants entering the trial with well-controlled HbA1c, the study provided the opportunity to analyse whether there is any differential response in patients with a baseline HbA1c below and above certain targets. The current post hoc analysis of the REWIND trial evaluated HbA1c, body mass index (BMI), CV and certain safety outcomes in patients with higher and lower baseline HbA1c treated with dulaglutide 1.5 mg versus placebo.

2 | METHODS

2.1 | Study design and patients

A full description of the REWIND study design and main outcomes has previously been published.[10,14] Briefly, REWIND was a multi-centre, global, randomized, double-blind, placebo-controlled clinical trial. Patients with T2D aged 50 years or older with established CVD, aged 55 years or older with subclinical CVD, or aged 60 years or older with two or more CV risk factors were included. Eligible participants

(N = 9901) were randomized 1:1 to receive a once-weekly subcutaneous injection of dulaglutide 1.5 mg or placebo in addition to the standard of care of their country during the median follow-up of 5.4 years. All participants provided written and informed consent and the trial was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. This study is a post hoc analysis of the REWIND data.

2.2 | Outcomes

The current analysis assessed the efficacy and safety outcomes in patients treated with dulaglutide 1.5 mg compared with placebo by baseline HbA1c subgroups of less than 7% and 7% or higher. HbA1c subgroups of 6.5% or less and more than 6.5% were used for sensitivity analysis. The efficacy outcomes evaluated were the incidence of major adverse cardiovascular events-3 (MACE-3; non-fatal myocardial infarction [MI], non-fatal stroke, or death from CV or unknown causes), non-fatal MI, non-fatal stroke, death from CV or unknown causes, all-cause mortality, hospitalization for heart failure, as well as change from baseline in HbA1c and change from baseline in BMI. The safety outcomes of interest analysed were permanent discontinuation of study drug for any reason, permanent discontinuation of study drug because of adverse events, severe hypoglycaemia, serious renal or urinary events, and serious gastrointestinal (GI) events. Detailed definitions for these efficacy and safety outcomes have previously been published.[10]

2.3 | Statistical analysis

Analyses were conducted in all patients receiving at least one dose of study medication and with a baseline HbA1c measurement. Baseline demographic and other characteristics were summarized within each baseline HbA1c subgroup. Continuous variables were summarized as means and standard deviations and compared between HbA1c subgroups with t-test or Wilcoxon rank sum test (if normality assumption did not hold). Categorical variables were summarized as counts and proportions and compared with chi-squared test or Fisher's exact test (in case of expected frequencies being too low).

For time-to-event outcomes, a Cox proportional hazards (CPH) regression analysis with fixed effects for treatment group, baseline HbA1c subgroup, and treatment by subgroup interaction, was conducted. In addition, CPH analyses were performed within baseline HbA1c subgroups, including only treatment as a fixed effect. Patients who did not experience the outcome of interest were censored at their last known follow-up date. For MACE-3, the treatment effect was also examined using a CPH regression interaction model where baseline HbA1c was entered as a continuous variable.

Continuous outcomes (change from baseline) were analysed by a mixed effects model for repeated measures. The initial model included fixed effects for treatment group, baseline HbA1c subgroup, visit

TABLE 1 Clinical and demographic characteristics at baseline for the overall intention-to-treat population and the <7% and ≥7% subgroups

Patient characteristics (ITT population)	Overall (N = 9876)	HbA1c < 7% (N = 3921)	HbA1c ≥ 7% (N = 5955)	P value
Age, y	66.2 (6.5)	66.7 (6.5)	65.9 (6.5)	<.001
Female	4581 (46.4)	1818 (46.4)	2763 (46.4)	.975
Race, White	7477 (75.7)	3077 (78.5)	4400 (73.9)	<.001
Current tobacco use	1401 (14.2)	563 (14.4)	838 (14.1)	.247
HbA1c, %	7.3 (1.1)	6.3 (0.5)	8.0 (0.7)	<.001
Diabetes duration, y	10.5 (7.2)	9.0 (6.9)	11.6 (7.3)	<.001
eGFR < 60 ml/min/1.73m^2	2195 (22.8)	875 (22.9)	1320 (22.8)	.568
Albuminuria‡	3473 (37.7)	1174 (31.9)	2299 (41.4)	<.001
Weight, kg	88.7 (18.5)	88.6 (18.5)	88.7 (18.5)	.572
BMI, kg/m^2	32.3 (5.7)	32.2 (5.7)	32.4 (5.8)	.236
Systolic blood pressure, mmHg	137.2 (16.8)	136.4 (16.6)	137.7 (16.9)	<.001
Diastolic blood pressure, mmHg	78.4 (9.8)	78.3 (9.8)	78.5 (9.9)	.353
Heart rate, beats per min	71.5 (10.9)	70.2 (10.7)	72.3 (10.9)	<.001
Total cholesterol, mmol/L	4.52 (1.16)	4.51 (1.14)	4.53 (1.18)	.368
LDL cholesterol, mmol/L	2.56 (0.98)	2.54 (0.95)	2.57 (0.99)	.436
HDL cholesterol, mmol/L	1.18 (0.34)	1.22 (0.36)	1.16 (0.33)	<.001
Triglycerides, mmol/L	1.87 (1.16)	1.76 (1.13)	1.93 (1.18)	<.001
Prior CVD*	3103 (31.4)	1271 (32.4)	1832 (30.8)	.084
Prior MI	1598 (16.2)	656 (16.7)	942 (15.8)	.059
Hypertension	9199 (93.1)	3665 (93.5)	5534 (92.9)	.354
Hyperlipidaemia	7833 (79.3)	3085 (78.7)	4748 (79.7)	.259
Heart failure	850 (8.6)	358 (9.1)	492 (8.3)	.316
Stroke	685 (6.9)	266 (6.8)	419 (7.0)	.513
Coronary artery disease	2815 (28.5)	1175 (30.0)	1640 (27.5)	.006

Note: Data are presented as mean (SD) or n (%).

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; ITT, intention-to-treat; LDL, low-density lipoprotein; MI, myocardial infarction; N, number of patients in subgroup of ITT population; n, number of patients with stated characteristic; SD, standard deviation; UACR, urine albumin to creatinine ratio.

*Prior CVD was defined as MI, ischaemic stroke, unstable angina with electrocardiogram changes, myocardial ischaemia on imaging or stress test, or coronary, carotid, or peripheral revascularization. ‡Albuminuria was defined as UACR ≥ 30 mg/g.

(month), treatment-by-visit interaction, corresponding two- and three-way interaction terms, and the patient as a random effect. Analyses were also performed within baseline HbA1c subgroups, using a model that included fixed effects for treatment group, visit (month), treatment-by-visit interaction, and the patient as a random effect.

Statistical tests were performed at a two-sided α of .05. In all subgroup analyses, an interaction P value of less than .05 was considered statistically significant. Analyses presented were exploratory and hence not controlled for type I error. Analyses were performed using SAS version 9.4.

3 | RESULTS

3.1 | Baseline characteristics and demographics

Of the 9901 participants in the REWIND study, 9876 were eligible for this analysis. Of these patients, 39.7% (3921) had a baseline HbA1c of less than 7% (dulaglutide N = 1972, placebo N = 1949) and 60.3% (5955) had a baseline HbA1c of 7% or higher (dulaglutide N = 2967, placebo N = 2988). Important differences and similarities were noted in the baseline characteristics of the subgroups (Table 1). Patients with higher HbA1c values had longer and more advanced diabetes; mean baseline HbA1c was 6.3% and 8.0% in the less than 7% and 7% or higher subgroups, respectively, whereas the mean duration of diabetes was 9.0 and 11.6 years, respectively. Mean age also significantly differed between the two subgroups (66.7 and 65.9 years in the <7% and ≥7% subgroups, respectively), while prior CVD did not significantly differ between the subgroups (32.4% vs. 30.8%, respectively). The proportion of patients taking baseline antihyperglycaemic concomitant medications was generally lower in the HbA1c less than 7% subgroup than in the 7% or higher subgroup (Table S2). A significantly higher proportion of patients with a baseline HbA1c of 7% or higher was on insulin compared with the less than 7% subgroup (30.1% vs. 14.4%, respectively; P < .001). CV medication usage was similar between the subgroups except for fibrates.
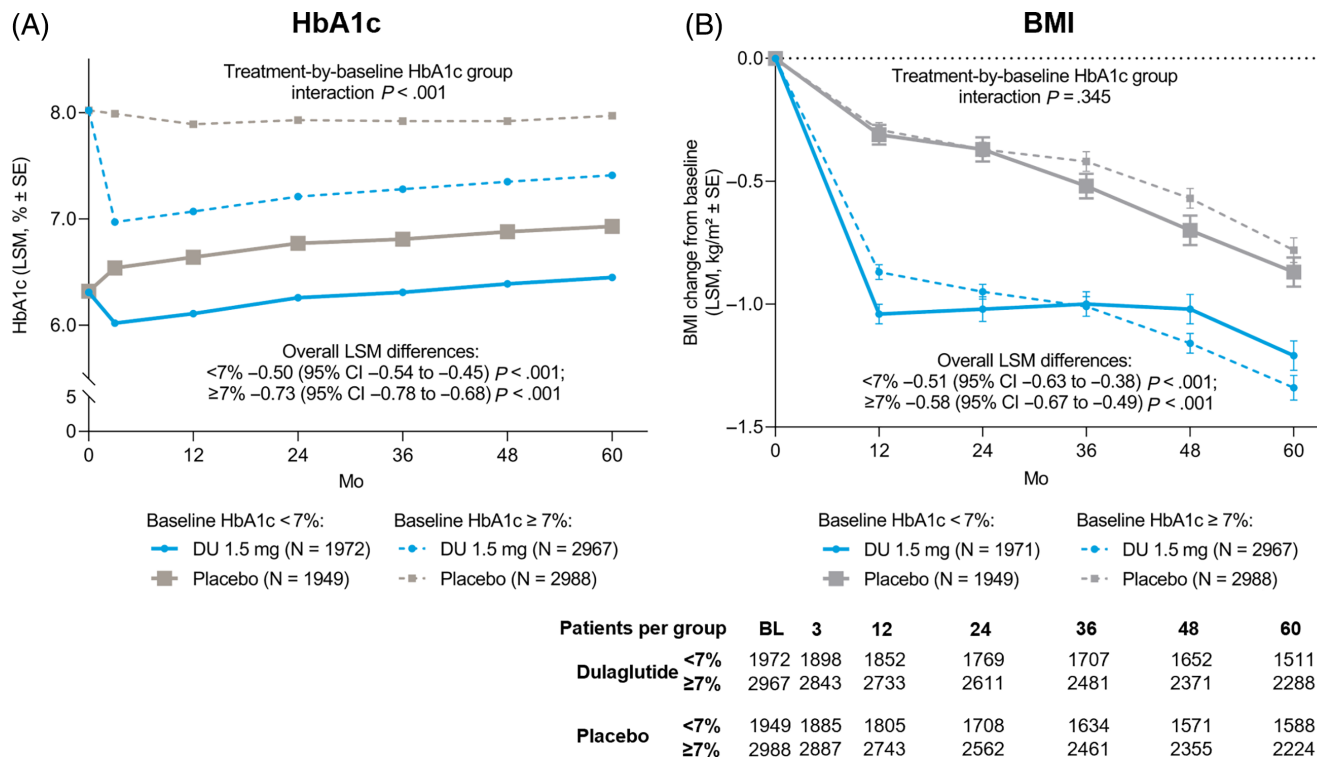
FIGURE 1 Mean HbA1c and body mass index (BMI) over 60 months of treatment by randomized treatment and higher or lower HbA1c group. Changes in A, HbA1c, and B, BMI, show that HbA1c values were significantly lower and BMI reduction was significantly greater in the baseline HbA1c <7% and ≥7% subgroups treated with dulaglutide (DU). Treatment-by-baseline HbA1c group interaction was significant for change from baseline in HbA1c (*P* < .001). Treatment-by-baseline HbA1c group interaction was not significant for change from baseline in BMI (*P* = .345). BL, baseline; LSM, least squares mean

When the groups were divided according to an HbA1c of 6.5% or less versus more than 6.5%, 24.1% (2382) had a baseline HbA1c of 6.5% or less and 75.9% (7494) had a baseline HbA1c of more than 6.5% (Table S1). The differences in baseline characteristics between the 6.5% or less and more than 6.5% subgroups were similar to those between the less than 7% and 7% or more subgroups. Mean baseline HbA1c was 6.0% and 7.8% in the 6.5% or less and more than 6.5% subgroups, respectively, while the mean duration of diabetes was 8.6 and 11.2 years, respectively. Overall, 32% of the 6.5% or less subgroup and 31.2% of the more than 6.5% subgroup had prior CVD. Antihyperglycaemic concomitant medication usage was generally lower in the HbA1c 6.5% or less subgroup than in the more than 6.5% subgroup, including patients on insulin. CV medication usage was similar between the subgroups except for fibrates.

3.2 | HbA1c change from baseline

Both the baseline HbA1c less than 7% and 7% or higher subgroups showed an immediate decline in HbA1c in patients treated with dulaglutide compared with those treated with placebo, followed by continued separation over 60 months (Figure 1A). There were significant differences in HbA1c change by baseline HbA1c subgroup in patients treated with dulaglutide versus placebo (interaction *P* < .001). The average least squares mean (LSM) difference in HbA1c for those with
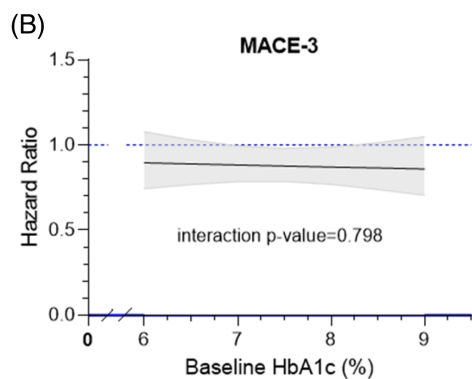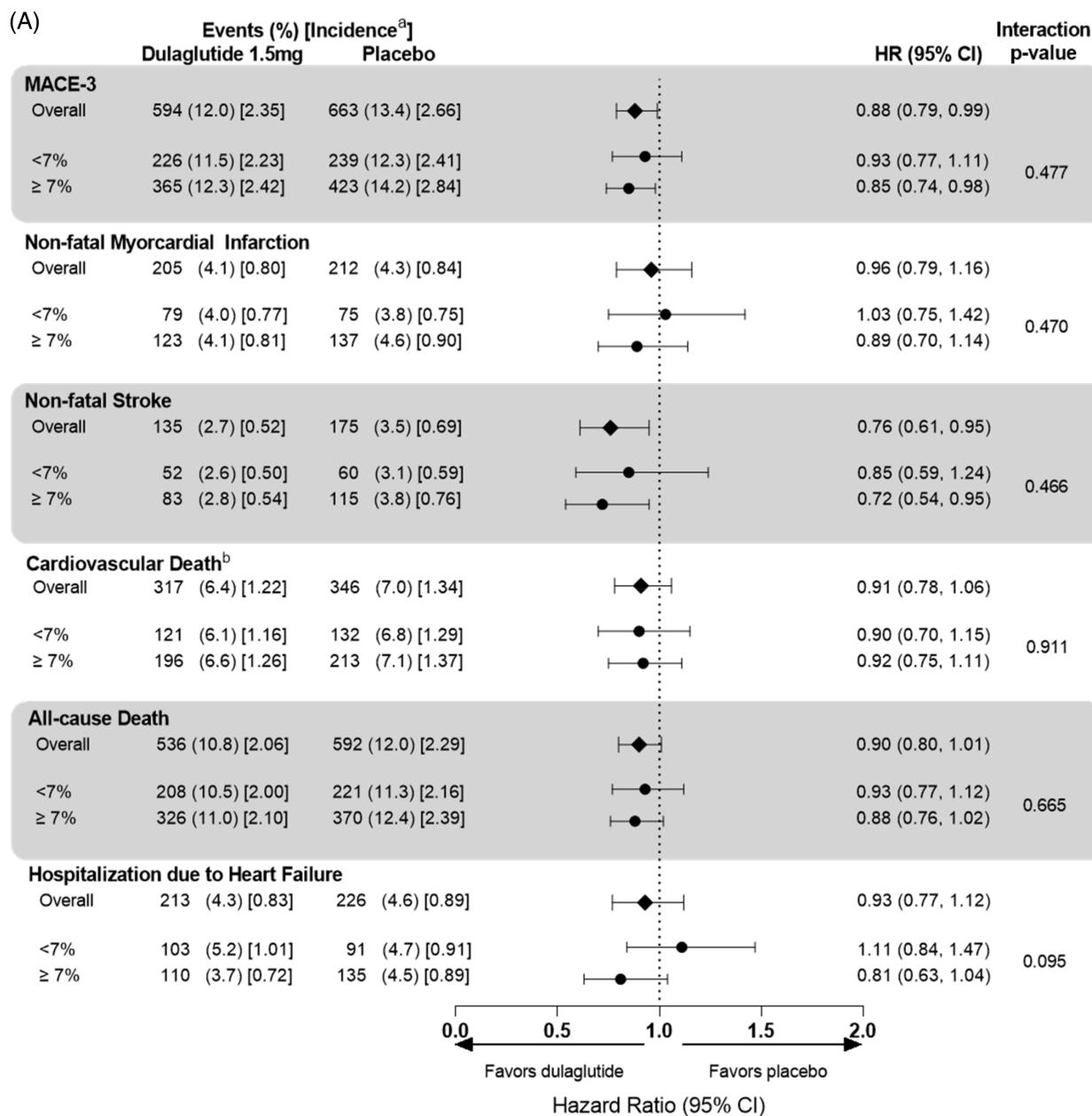
a baseline HbA1c of less than 7% was −0.5% (95% CI −0.54% to −0.45%; *P* < .001), and for those whose baseline HbA1c was 7% or more it was −0.73% (95% CI −0.78% to −0.68%; *P* < .001). Sensitivity analyses using baseline HbA1c subgroups of 6.5% or less and more than 6.5% provided consistent results (Figure S1A; interaction *P* < .001).

3.3 | BMI change from baseline

Consistent with the overall results with dulaglutide in the REWIND trial,[10] there was a difference in the BMI reduction between the dulaglutide and placebo groups. These differences in BMI were observed regardless of baseline HbA1c (Figure 1B; interaction *P* = .345). The average LSM difference in BMI change from baseline in the overall population was −0.55 kg/m² (95% CI −0.62 to −0.48; *P* < .001). Sensitivity analyses using baseline HbA1c subgroups of 6.5% or less and more than 6.5% provided consistent results (Figure S1B).
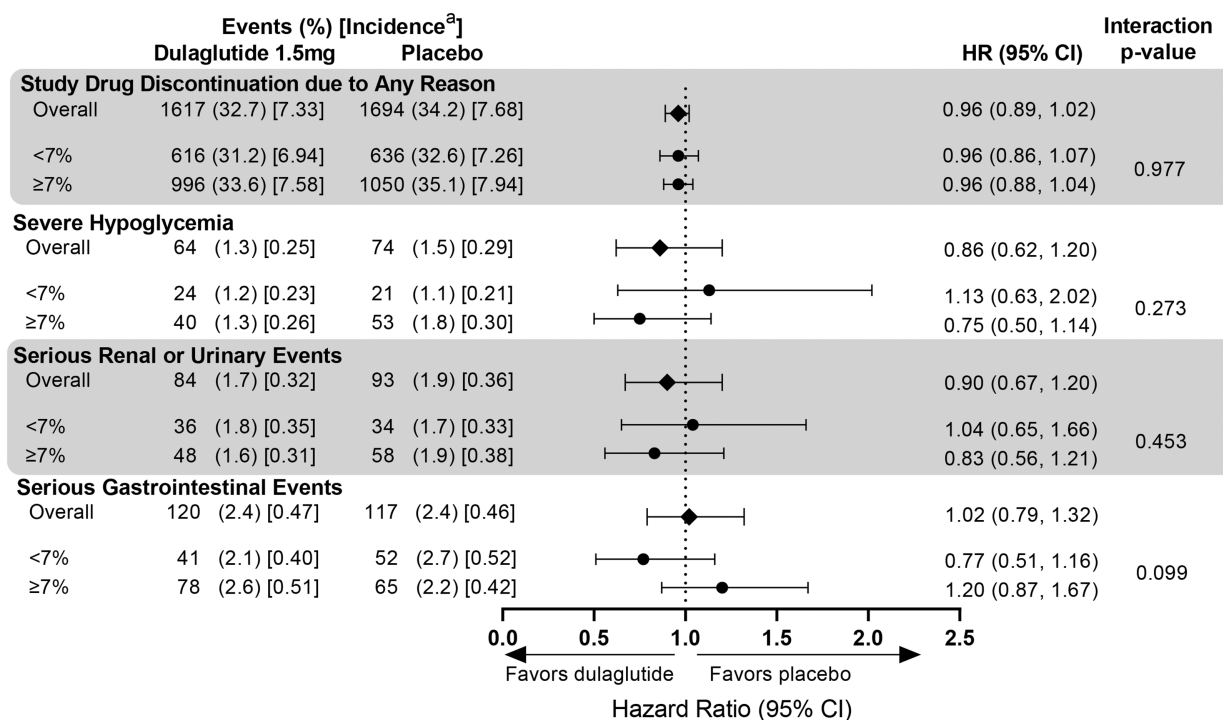
3.4 | CV and safety outcomes

For CV events, there was no evidence of a differential treatment effect between the baseline HbA1c subgroups (Figure 2A; interaction *P* values not significant). The treatment effect of dulaglutide versus

(A)

	Events (%) [Incidence[a]]		HR (95% CI)	Interaction p-value
	Dulaglutide 1.5mg	Placebo		
MACE-3				
Overall	594 (12.0) [2.35]	663 (13.4) [2.66]	0.88 (0.79, 0.99)	
<7%	226 (11.5) [2.23]	239 (12.3) [2.41]	0.93 (0.77, 1.11)	0.477
≥ 7%	365 (12.3) [2.42]	423 (14.2) [2.84]	0.85 (0.74, 0.98)	
Non-fatal Myorcardial Infarction				
Overall	205 (4.1) [0.80]	212 (4.3) [0.84]	0.96 (0.79, 1.16)	
<7%	79 (4.0) [0.77]	75 (3.8) [0.75]	1.03 (0.75, 1.42)	0.470
≥ 7%	123 (4.1) [0.81]	137 (4.6) [0.90]	0.89 (0.70, 1.14)	
Non-fatal Stroke				
Overall	135 (2.7) [0.52]	175 (3.5) [0.69]	0.76 (0.61, 0.95)	
<7%	52 (2.6) [0.50]	60 (3.1) [0.59]	0.85 (0.59, 1.24)	0.466
≥ 7%	83 (2.8) [0.54]	115 (3.8) [0.76]	0.72 (0.54, 0.95)	
Cardiovascular Death[b]				
Overall	317 (6.4) [1.22]	346 (7.0) [1.34]	0.91 (0.78, 1.06)	
<7%	121 (6.1) [1.16]	132 (6.8) [1.29]	0.90 (0.70, 1.15)	0.911
≥ 7%	196 (6.6) [1.26]	213 (7.1) [1.37]	0.92 (0.75, 1.11)	
All-cause Death				
Overall	536 (10.8) [2.06]	592 (12.0) [2.29]	0.90 (0.80, 1.01)	
<7%	208 (10.5) [2.00]	221 (11.3) [2.16]	0.93 (0.77, 1.12)	0.665
≥ 7%	326 (11.0) [2.10]	370 (12.4) [2.39]	0.88 (0.76, 1.02)	
Hospitalization due to Heart Failure				
Overall	213 (4.3) [0.83]	226 (4.6) [0.89]	0.93 (0.77, 1.12)	
<7%	103 (5.2) [1.01]	91 (4.7) [0.91]	1.11 (0.84, 1.47)	0.095
≥ 7%	110 (3.7) [0.72]	135 (4.5) [0.89]	0.81 (0.63, 1.04)	

Favors dulaglutide ← Hazard Ratio (95% CI) → Favors placebo
(scale 0.0 0.5 1.0 1.5 2.0)

(B)

MACE-3

interaction p-value=0.798

Hazard Ratio vs Baseline HbA1c (%)

FIGURE 2 Legend on next page.

placebo across a range of continuous baseline HbA1c values showed no interaction for MACE-3 (Figure 2B; P = .798). Similarly, there were no differences between the baseline HbA1c less than 7% and 7% or higher subgroups regarding the effect of dulaglutide treatment on safety events analysed in patients treated with dulaglutide versus placebo (Figure 3; interaction P values not significant). Consistent results

	Events (%) [Incidence^a]		HR (95% CI)	Interaction p-value
	Dulaglutide 1.5mg	Placebo		

FIGURE 3 Hazard ratios (HRs) for safety outcomes of interest by HbA1c subgroups. Analysis of discontinuations for any reason, discontinuations because of adverse events, severe hypoglycaemia events, serious renal or urinary events, and serious gastrointestinal events by overall patients, and baseline HbA1c <7% and ≥7% subgroups. Number of overall patients: dulaglutide = 4949; placebo = 4952. Number of patients with baseline HbA1c <7%: dulaglutide = 1972; placebo = 1949. Number of patients with baseline HbA1c ≥7%: dulaglutide = 2967; placebo = 2988. The overall population also contains 25 patients that could not be included in any HbA1c subgroup because of missing HbA1c at baseline. ^aNumber of patients per 100 person-years

were seen with sensitivity analysis performed using baseline HbA1c subgroups of 6.5% or less and more than 6.5% (Figures S2 and S3).

4 | DISCUSSION

This post hoc analysis of the REWIND CVOT showed that patients treated with once-weekly dulaglutide had a lower incidence of MACE-3 and other CV outcomes without an increased risk of severe hypoglycaemia or other adverse events (study drug discontinuations because of any reason, serious renal or urinary events, or serious GI events) in all patients, regardless of baseline HbA1c, when compared

with placebo. It also showed that patients with a higher baseline HbA1c experienced a greater reduction in HbA1c and a similar reduction in BMI compared with those with a lower baseline HbA1c.

The REWIND trial did not have a lower HbA1c limit for enrolment.[14] Once-weekly dulaglutide or placebo injections were added to the background antihyperglycaemic medication regimens of patients, and investigators were encouraged to manage patients' glucose levels and CV risk according to their best judgement as informed by local clinical practice guidelines. Patients treated with dulaglutide had HbA1c reductions in both baseline HbA1c of less than 7% and 7% or higher subgroups, with a greater decrease observed in the 7% or higher subgroup, which is consistent across the GLP-1 RA class.[15-18]

FIGURE 2 Hazard ratios (HRs) for cardiovascular events by HbA1c subgroups. A, There was no evidence of a differential treatment effect between the baseline HbA1c subgroups in major adverse cardiovascular events-3 (MACE-3), non-fatal myocardial infarction events, non-fatal stroke events, cardiovascular-related deaths, all-cause deaths, and hospitalizations because of heart failure events by overall patient groups, and baseline HbA1c <7% and ≥7% subgroups. Number of overall patients: dulaglutide = 4949; placebo = 4952. Number of patients with baseline HbA1c < 7%: dulaglutide = 1972; placebo = 1949. Number of patients with baseline HbA1c ≥ 7%: dulaglutide = 2967; placebo = 2988. The overall population also contains 25 patients that could not be included in any HbA1c subgroup because of missing HbA1c at baseline. ^aNumber of patients per 100 person-years. ^bIncludes deaths of unknown causes. B, Treatment effect of dulaglutide (N = 4939) compared with placebo (N = 4937) as a function of baseline HbA1c (continuous, [%]) for the primary outcome, MACE-3. The solid black line represents the estimated HR of the treatment effect. The grey shaded area represents the 95% CI around the treatment effects. The dotted horizontal line represents an HR of 1 (i.e. no difference between randomized groups). Estimated HR and 95% CI values are displayed for baseline HbA1c between the observed 10th and 90th percentiles

The sharp decline in HbA1c seen by 3 months in patients treated with dulaglutide is consistent with the AWARD studies.[19] The subsequent increase in HbA1c trajectory until 5 years suggests possible disease progression. The effect of dulaglutide treatment compared with placebo on HbA1c reductions was more pronounced in the baseline HbA1c 7% or higher subgroup than in the less than 7% subgroup, which could be accounted for by a greater treatment effect at higher baseline HbA1c levels.[5-9]

In dulaglutide-treated patients, the incidence of CV outcomes was reduced by a similar degree in patients whose baseline HbA1c was less than 7% and 7% or higher. Glucose concentrations that increase the risk of CVD have previously been studied and indicate that hyperglycaemia may be a risk factor for CVD. From a large, randomized, controlled trial perspective, the UKPDS reported a sustained protective CV effect of intensive glycaemic control on MI and death from any cause during the 10 years of follow-up.[22] Several other prospective studies, including the ACCORD, VADT, and ADVANCE trials, did not observe a macrovascular benefit with long-term intensive glycaemic control, and ACCORD reported an increased mortality risk with an HbA1c treatment target of less than 6%.[23-25] In light of these previous findings, the consistent benefit–risk profile observed with dulaglutide treatment across different levels of HbA1c despite significant glucose lowering is reassuring. Differences in the results between REWIND and these previous trials may be explained by the fact that most members of the GLP-1 RA and sodium-glucose co-transporter-2 inhibitor (SGLT-2i) classes were not approved at the time of the ACCORD, VADT, and ADVANCE studies,[8] and those that were, were not widely used. With the increasing use of GLP-1 RA and SGLT2-i therapies with proven CV benefit and lower hypoglycaemia risk, these therapies may be considered for intensive glycaemic control. In addition, this study supports the 2022 American Diabetes Association guidelines, which state that for patients with T2D at risk of or with established atherosclerotic CVD, a GLP-1 RA and/or a SGLT2-i is recommended to reduce the risk of major CV events, independent of HbA1c.[26] The mechanisms underpinning the CV benefits of the GLP-1 RA class are not clear, however, there are several possible explanations. GLP-1 RAs may directly improve CV outcomes by increasing endothelial function, reducing vascular inflammation, and improving smooth muscle and mitochondrial function.[10,27] Indirectly, the improved CV outcomes may be a consequence of reduced adipose tissue, improved blood pressure, glucose regulation or improved lipid profile, with GLP-1 RA treatment.[10,27] Whether GLP-1 RAs can reduce CV outcomes in patients without diabetes remains unknown and warrants further research.

The analyses reported here have several strengths. The REWIND trial had a large patient cohort (N = 9901) and a long follow-up period (median 5.4 years). Additionally, REWIND had the largest enrolment of patients with CV risk factors, as opposed to established CVD, of any GLP-1 RA CVOT to date, which may be more reflective of the general population.[10] It also contained a comparatively high proportion of patients with a near-normal HbA1c level at baseline. The main limitation of these analyses is that they are post hoc and do not show cause and effect. The REWIND study was not designed to achieve or maintain specific HbA1c treatment goals. Investigators were not blinded to patients' HbA1c values during the trial and managed patients' glucose levels and CV risk according to their best judgement as informed by local clinical practice guidelines. The standard of care practice may differ across sites and patients.

In conclusion, our post hoc analysis indicates that dulaglutide-treated patients had a lower incidence of CV events with HbA1c and BMI reductions, and without compromising safety outcomes of interest in patients with T2D, regardless of HbA1c status compared with placebo. These observations support consideration of this GLP-1 RA even in comparatively well-controlled patients with T2D seeking CV benefits, as well as optimal metabolic control.

AUTHOR CONTRIBUTION

Contributions were made as follows: EF, HCG, MCR, FTB, LSL conceived and designed the work; CN performed the analysis; EF, HCG, MCR, CN, AH, FTB, LSL analysed and/or interpreted the data; AH drafted the manuscript; EF, HCG, MCR, CN, FTB, and LSL critically revised the manuscript. All authors participated sufficiently in the work to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors provided final approval of the version to be published.

CONFLICT OF INTEREST

EF has acted as an advisor to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Polfa Tarchomin, and reports honoraria for speaking from AstraZeneca, Bioton, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Polfa Tarchomin, Sanofi, and Servier. HCG holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly and Company, AstraZeneca, Merck, Novo Nordisk, and Sanofi; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, and Sanofi; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck, Novo Nordisk, Janssen, Sanofi, and Kowa. MCR reports grants to his institution from Eli Lilly and Company, AstraZeneca, and Novo Nordisk; honoraria for consulting from Adocia, DalCor, GlaxoSmithKline, and Theracos; and honoraria for speaking from Sanofi. LSL, CN, AH, and FTB are employees and stockholders of Eli Lilly and Company.

PEER REVIEW

DATA AVAILABILITY STATEMENT

ORCID

Hertzel C. Gerstein https://orcid.org/0000-0001-8072-2836
Matthew C. Riddle https://orcid.org/0000-0003-1169-3036
Fady T. Botros https://orcid.org/0000-0003-1980-4458
Li Shen Loo https://orcid.org/0000-0002-7907-0209

REFERENCES

1. Bailey CJ, Tahrani AA, Barnett AH. Future glucose-lowering drugs for type 2 diabetes. *Lancet Diabetes Endocrinol.* 2016;4(4):350-359.
2. Arnold SV, Inzucchi SE, Tang F, et al. Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: an NCDR research to practice project. *Eur J Prev Cardiol.* 2017;24(15):1637-1645.
3. Ahmad NS, Islahudin F, Paraidathathu T. Factors associated with good glycemic control among patients with type 2 diabetes mellitus. *J Diabetes Investig.* 2014;5(5):563-569.
4. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9(10):653-662.
5. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J.* 2020;41(2):255-323.
6. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2020;43(2):487-493.
7. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation.* 2019;140(11):e596-e646.
8. American Diabetes Association. 6Glycemic targets: standards of medical care in diabetes-2021. *Diabetes Care.* 2021;44(Suppl. 1):S73-S84.
9. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. *Endocr Pract.* 2020;26(1):107-139.
10. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019;394(10193):121-130.
11. Boye KS, Riddle MC, Garcia-Perez RML, Lage MJ, Riesmeyer JS, Lakshmanan MC. Generalizability of glucagon-like peptide-1 receptor agonist cardiovascular outcome trials to the overall type 2 diabetes population in the United States. *Diabetes Obes Metab.* 2019;21(6):1299-1304.
12. Riddle MC, Gerstein HC, Xavier D, et al. Efficacy and safety of dulaglutide in older patients: a post hoc analysis of the REWIND trial. *J Clin Endocrinol Metab.* 2021;106(5):1345-1351.
13. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* 2019;7(10):776-785.
14. Gerstein HC, Colhoun HM, Dagenais GR, et al. Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. *Diabetes Obes Metab.* 2018;20(1):42-49.
15. Tsoukas G, Bain S, Araki E, et al. Semaglutide reduces HbA1c across baseline HbA1c subgroups across SUSTAIN 1–5 clinical trials. *Can J Diabetes.* 2017;41(5):S50.
16. Komatsu M, Watada H, Kaneko S, Ross Agner BF, Nishida T, Kaku K. Efficacy and safety of the fixed-ratio combination of insulin degludec and liraglutide by baseline glycated hemoglobin, body mass index and age in Japanese individuals with type 2 diabetes: a subgroup analysis of two phase III trials. *J Diabetes Investig.* 2021;12(9):1610-1618.
17. Gallwitz B, Dagogo-Jack S, Thieu V, et al. Effect of once-weekly dulaglutide on glycated haemoglobin (HbA1c) and fasting blood glucose in patient subpopulations by gender, duration of diabetes and baseline HbA1c. *Diabetes Obes Metab.* 2018;20(2):409-418.
18. Pantalone KM, Patel H, Yu M, Fernández Landó L. Dulaglutide 1.5 mg as an add-on option for patients uncontrolled on insulin: subgroup analysis by age, duration of diabetes and baseline glycated haemoglobin concentration. *Diabetes Obes Metab.* 2018;20(6):1461-1469.
19. Patel H, Munir K, Sutherland S, Karanikas CA, Konig M. Efficacy of dulaglutide as a first injectable option for patients with type 2 diabetes: a post-hoc pooled analysis. *Diabetes Ther.* 2019;10(6):2321-2330.
20. Balkau B, Bertrais S, Ducimetiere P, Eschwege E. Is there a glycemic threshold for mortality risk? *Diabetes Care.* 1999;22(5):696-699.
21. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care.* 1999;22(2):233-240.
22. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359(15):1577-1589.
23. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360:129-139.
24. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358(24):2545-2559.
25. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358(24):2560-2572.
26. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical Care in Diabetes—2022. *Diabetes Care.* 2021;45(Supplement_1):S144-S174.

27. Berndt J, Ooi SL, Pak SC. What is the mechanism driving the reduction of cardiovascular events from glucagon-like peptide-1 receptor agonists? A mini review. *Molecules*. 2021;26(16):4822.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.