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Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin

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Objective Recent European Guidelines for Diabetes, Prediabetes and Cardiovascular Diseases introduced a shift in managing patients with type 2 diabetes at high risk for or established cardiovascular (CV) disease by recommending GLP-1 receptor agonists and SGLT-2 inhibitors as initial glucose-lowering therapy. This is questioned since outcome trials of these drug classes had metformin as background therapy. In this *post hoc* analysis, the effect of dulaglutide on CV events was investigated according to the baseline metformin therapy by means of a subgroup analysis of the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial.

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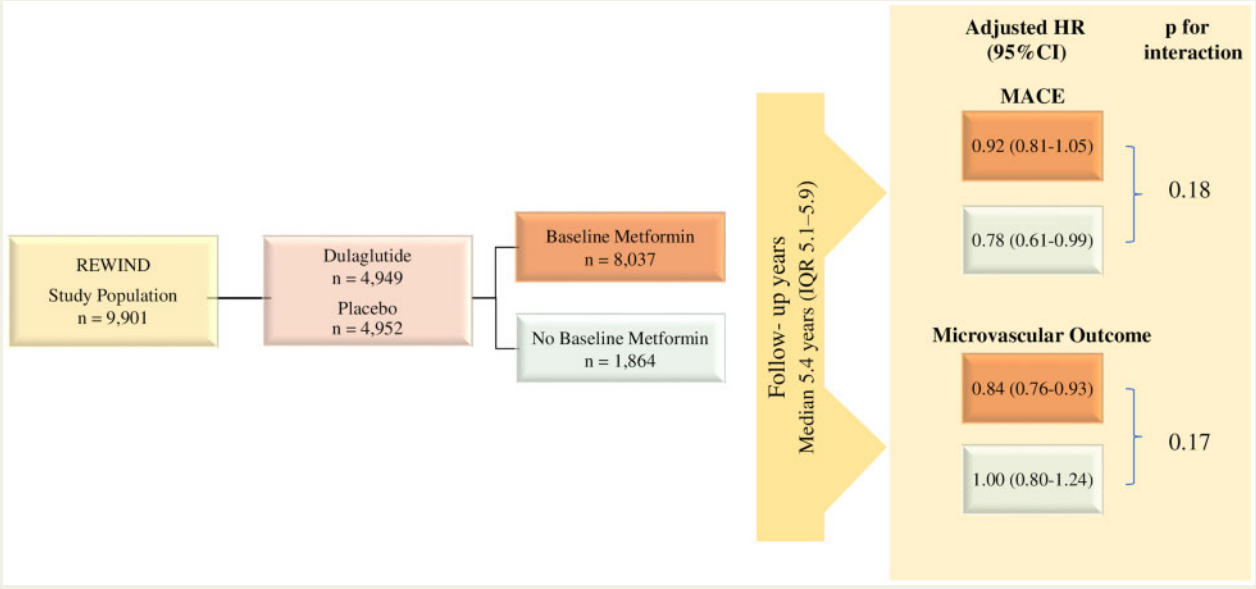
Research design and methods Patients in REWIND ($n = 9901$; women: 46.3%; mean age: 66.2 years) had type 2 diabetes and either a previous CV event (31%) or high CV risk (69%). They were randomized (1:1) to sc. dulaglutide (1.5 mg/weekly) or placebo in addition to standard of care. The primary outcome was the first of a composite of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular or unknown causes. Key secondary outcomes included a microvascular composite endpoint, all-cause death, and heart failure. The effect of dulaglutide in patients with and without baseline metformin was evaluated by a Cox regression hazard model with baseline metformin, dulaglutide assignment, and their interaction as independent variables. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by a Cox regression model with adjustments for factors differing at baseline between people with vs. without metformin, identified using the backward selection.

Results Compared to patients with metformin at baseline ($n = 8037$; 81%), those without metformin ($n = 1864$; 19%) were older and slightly less obese and had higher proportions of women, prior CV events, heart failure, and renal disease. The primary outcome occurred in 976 (12%) participants with baseline metformin and in 281 (15%) without. There was no significant difference in the effect of dulaglutide on the primary outcome in patients with vs. without metformin at baseline [HR 0.92 (CI 0.81–1.05) vs. 0.78 (CI 0.61–0.99); interaction $P = 0.18$]. Findings for key secondary outcomes were similar in patients with and without baseline metformin.

Conclusion This analysis suggests that the cardioprotective effect of dulaglutide is unaffected by the baseline use of metformin therapy.

Graphical Abstract



Keywords Cardiovascular disease • GLP-1-based therapy • Metformin • Mortality • Morbidity

Introduction

Type 2 diabetes is an independent risk factor for cardiovascular morbidity and mortality, despite the use of therapies addressing traditional cardiovascular risk factors.[1] Cardiovascular outcome trials (CVOTs) reported that several drugs belonging to the classes of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors reduced cardiovascular events in people who were also taking other cardioprotective medications. This resulted in recent European guideline recommendations

to use either of these agents as first-line glucose-lowering therapy in people with type 2 diabetes at high risk for or with established cardiovascular disease (CVD).[2,3]

The high prevalence of concomitant metformin use in participants in the outcome trials on GLP-1 RAs and SGLT-2 inhibitors has fuelled uncertainty regarding whether the cardiovascular benefits of these agents occur in both the presence and absence of metformin.[4–11] Therefore, whether the proven cardiovascular benefits of these new anti-hyperglycaemic drugs require concurrent metformin therapy remains unknown.[2,12,13]

In the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, the GLP-1 RA dulaglutide reduced the risk of major adverse cardiovascular events (MACE, comprising non-fatal myocardial infarction or stroke and cardiovascular death) compared to placebo in people with type 2 diabetes and established CVD or multiple cardiovascular risk factors.[11] A sizeable proportion of the REWIND participants were without metformin therapy at the time of randomization, equally in the dulaglutide group and in the placebo group.[11,14] Analyses of the cardiovascular effects of dulaglutide in the presence and absence of baseline metformin treatment may help clinicians choose the optimal first-line type 2 diabetes glucose-lowering treatment for patients at high cardiovascular risk, both with and without established CVD.

This *post hoc* analysis of the REWIND trial tests the hypothesis that the effect of dulaglutide on cardiovascular events is unaffected by the use of baseline metformin therapy.

Methods

Participants

The REWIND trial (ClinicalTrials.gov number: NCT01394952) was a multicentre, randomized, double-blind, placebo-controlled trial, conducted at 371 sites in 24 countries as previously described in detail.[14] Eligible patients were ≥50 years old with type 2 diabetes, HbA_{1c} ≤9.5% (≤80 mmol/mol), and BMI ≥23 kg/m^2 and were on stable treatment for at least 3 months with 0–2 glucose-lowering drugs, with or without basal insulin. The participants had either suffered a previous cardiovascular event or had multiple cardiovascular risk factors.[14] Exclusion criteria were an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, a history of cancer within 5 years prior to inclusion, any episode of severe hypoglycaemia in the year prior to inclusion, a life expectancy below 1 year, a coronary or cerebrovascular event within the previous 2 months or planned revascularization.

Study design

The participants were randomly assigned to 1.5 mg of weekly subcutaneous dulaglutide or to the same volume of placebo.[14] They underwent scheduled visits after 2 weeks, 3 and 6 months and subsequently every 3 months for drug dispensing and every 6 months for a more detailed assessment.[11,14] The investigators were encouraged to promote a healthy lifestyle and defined targets for each cardiovascular risk factor, and they could add any glucose-lowering medication, apart from another GLP-1 RA or pramlintide, at their discretion, according to local guidelines.

Outcomes

The primary endpoint was the first of a composite of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular or unknown causes (3-point major adverse cardiovascular outcomes, MACE). Three key secondary outcomes were analysed: (i) a composite clinical microvascular outcome, including retinopathy due to diabetes (defined as need for photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy) or renal disease (defined as development of a urinary albumin-to-creatinine ratio of >33.9 mg/mmol in those with a lower baseline concentration, a sustained 30% or greater decline in eGFR based on two consecutive eGFR assessments or need for chronic renal replacement therapy); (ii) all-cause death; and (iii) heart failure requiring either hospital admission or an urgent visit requiring therapy.

Ethics

The study complies with the Declaration of Helsinki, and the REWIND protocol was approved by research ethics boards at each site. All participants provided written informed consent. Data monitoring was carried out by an independent committee every 6 months.[14]

Data management and statistical analyses

The characteristics of participants according to reported baseline metformin were summarized; categorical variables are reported as count and percentages with the corresponding odds ratios (ORs, i.e. the odds of being on metformin in the presence vs. the absence of the variable) while continuous variables are reported as mean and standard deviation with the corresponding ORs (i.e. the odds of being on metformin for every unit increase in the value of the continuous variable). Logistic regression was used to assess the univariable relationship between the baseline characteristics of interest and baseline metformin use. A multivariable logistic regression model was constructed considering all of the univariable predictors of baseline metformin with a *P*-value of <0.05 using backward elimination method with the alpha-level of 0.05.

The estimated effect of dulaglutide on the study outcomes in participants with and without baseline metformin use was evaluated according to the intention-to-treat principle and included all outcomes occurring on or after randomization in the analysis. Kaplan–Meier estimates were used to generate cumulative incidence risks and Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) in each of subgroups of baseline metformin use. The interaction between dulaglutide and metformin use at baseline was assessed by including the subgroup and interaction term in the Cox model. The effect of dulaglutide on the primary outcome was also evaluated by means of an analysis of three subgroups in relation to glucose-lowering therapy at baseline: drug-naive patients (neither on metformin nor on any other glucose drugs); patients on any glucose-lowering drug except metformin; and patients on metformin with or without any other glucose-lowering drug.

In addition, the Cox models were adjusted for the baseline characteristics identified in the multivariable logistic regression model.

To investigate whether the use of metformin during follow-up influenced the effect of dulaglutide on the four major outcomes (MACE, all-cause death, microvascular, and heart failure), the hazard of dulaglutide was re-estimated after adjusting for baseline metformin use and metformin use as a time-varying covariate (i.e. at the last visit before either the outcome or censorship).

Results

Patient characteristics

A total of 9901 participants were recruited between August 2011 and August 2014, of whom 4949 were randomized to dulaglutide

Table 1 Baseline characteristics of patients with and without metformin treatment at baseline

	Overall	Metformin	No metformin	OR (95% CI)[a]	*P*-value[a]
Randomized, *n*	9901	8037	1864		
Age (years), mean (SD)	66.2 (6.53)	65.8 (6.34)	67.8 (7.05)	0.954 (0.947–0.961)	<0.0001
Females, *n* (%)	4589 (46.3)	3675 (45.7)	914 (49.0)	0.876 (0.792–0.969)	0.0099
White ethnicity, *n* (%)	7498 (75.7)	6065 (75.5)	1433 (76.9)	0.925 (0.821–1.042)	0.1995
Current tobacco use, *n* (%)	1407 (14.2)	1157 (14.4)	250 (13.4)	1.086 (0.937–1.258)	0.2712
Cardiovascular event, *n* (%)	2035 (20.6)	1585 (19.7)	450 (24.1)	0.777 (0.689–0.875)	<0.0001
Hypertension, *n* (%)	9224 (93.2)	7474 (93.0)	1750 (93.9)	0.865 (0.702–1.066)	0.1730
Prior heart failure, *n* (%)	853 (8.6)	620 (7.7)	233 (12.5)	0.586 (0.499–0.688)	<0.0001
Diabetes duration (years), mean (SD)	10.5 (7.22)	10.6 (7.03)	10.2 (8.01)	1.009 (1.002–1.016)	0.0163
Retinopathy due to diabetes, *n* (%)	891 (9.0)	720 (9.0)	171 (9.2)	0.979 (0.822–1.167)	0.8153
HbA_{1c} (%), mean (SD); mean (mmol/mol)	7.34 (1.05); 57	7.35 (1.04); 57	7.30 (1.10); 56	1.054 (1.004–1.106)	0.0321
eGFR < 60 (mL/min/1.73 m^2), *n* (%)	2199 (22.2)	1555 (19.3)	644 (34.5)	0.453 (0.405–0.506)	<0.0001
Albuminuria, *n* (%)	3467 (35.0)	2786 (34.7)	681 (36.5)	0.896 (0.804–0.997)	0.0440
Sulfonylurea, *n* (%)	4552 (46.0)	3723 (46.3)	829 (44.5)	1.077 (0.974–1.192)	0.1490
Insulin, *n* (%)	2363 (23.9)	1800 (22.4)	563 (30.2)	0.667 (0.596–0.746)	<0.0001
DPP4i, *n* (%)	564 (5.7)	456 (5.7)	108 (5.8)	0.978 (0.788–1.214)	0.8391
Thiazolidinedione, *n* (%)	168 (1.7)	97 (1.2)	71 (3.8)	0.309 (0.226–0.421)	<0.0001
Other glucose-lowering drugs, *n* (%)	32 (0.3)	0 (0.0)	32 (1.7)	0.000 (0.000–1E149)	0.9331
Body mass index (kg/m^2), mean (SD)	32.3 (5.74)	32.4 (5.73)	31.8 (5.77)	1.019 (1.010–1.028)	<0.0001
Systolic BP (mm Hg), mean (SD)	137 (16.8)	137 (16.8)	137 (16.9)	1.002 (0.999–1.005)	0.2322
Diastolic BP (mm Hg), mean (SD)	78.4 (9.83)	78.7 (9.75)	77.5 (10.1)	1.013 (1.007–1.018)	<0.0001
Heart rate (beats/min), mean (SD)	71.5 (10.9)	71.7 (10.8)	70.4 (11.1)	1.011 (1.007–1.016)	<0.0001
LDL cholesterol (mmol/L), mean (SD)	2.56 (0.98)	2.52 (0.97)	2.72 (0.97)	0.815 (0.774–0.857)	<0.0001
Triglycerides (mmol/L), median (IQR)	1.60 (1.17–2.22)	1.60 (1.18–2.22)	1.57 (1.17–2.20)	1.014 (0.970–1.061)	0.5328
ACEi/ARB, *n* (%)	8068 (81.5)	6593 (82.0)	1475 (79.1)	1.204 (1.062–1.365)	0.0037
Beta-blocker, *n* (%)	4512 (45.6)	3652 (45.4)	860 (46.1)	0.972 (0.879–1.076)	0.5856
Statin, *n* (%)	6547 (66.1)	5395 (67.1)	1152 (61.8)	1.262 (1.137–1.401)	<0.0001
Fibrate, *n* (%)	898 (9.1)	730 (9.1)	168 (9.0)	1.009 (0.846–1.202)	0.9245

ACEi/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; BP, blood pressure; CI, confidence interval; DPP4i, Dipeptidyl Peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; IQR, interquartile range; OR, odds ratio; SD, standard deviation.
[a]Categorical variables are reported as count and percentages with the corresponding ORs (i.e. the odds of being on metformin in the presence vs. the absence of the variable) while continuous variables are reported as mean and standard deviation with the corresponding ORs (i.e. the odds of being on metformin for every unit increase in the value of the continuous variable).

and 4952 to placebo. At baseline, 8037 (81%) of the participants were prescribed metformin and 1864 (19%) were without metformin therapy, with similar proportions in the dulaglutide and placebo groups (*Take home figure*).

Patients' characteristics are presented in *Table 1*. Compared to patients with baseline metformin those without such treatment included a higher proportion of female participants (49% vs. 45.7%) and they were older (67.8 years old vs. 65.8), slightly less obese (BMI 31.8 vs. 32.4 kg/m^2), with a higher proportion of previous cardiovascular events (24.1% vs. 19.7%), heart failure (12.5% vs. 7.7%), and renal disease (eGFR <60 mL/min/1.73 m^2 in 34.5% vs. 19.3%). Moreover, they had higher use of insulin (30.2% vs. 22.4%) and thiazolidinediones (3.8% vs. 1.2%) but a lower use of statins (61.8% vs. 67.1%) and renin-angiotensin system inhibitors (79.1% vs. 82.0%). The independent determinants of baseline metformin use included age, previous cardiovascular events, heart failure, diabetes duration, eGFR <60, insulin use, thiazolidinedione use, BMI, diastolic blood pressure, heart rate, LDL cholesterol, renin-angiotensin aldosterone system inhibitors use, and use of statins.

Outcome

During a median follow-up of 5.4 years (interquartile range 5.1–5.9), the primary outcome occurred in 976 (12%) participants with baseline metformin and 281 (15%) without metformin. As noted in *Table 2*, dulaglutide reduced the risk of the primary endpoint (MACE) with an HR of 0.88 (95% CI 0.79–0.99) in the entire REWIND cohort, with similar effects noted in participants who were and were not taking metformin at baseline (interaction $P = 0.26$). There were also similar effects according to baseline metformin use for the microvascular endpoint (interaction $P = 0.12$), all-cause death (interaction $P = 0.81$), and heart failure (interaction $P = 0.85$). Additional analyses confirmed the absence of any interaction between baseline metformin use and dulaglutide's effect on the components of MACE (Supplementary material online, *Table S1*), and between subgroups defined by the

Table 2 Number, proportions, and annual incidence of events for each outcome in the total cohort and in the dulaglutide and placebo groups, respectively, in patients with and without metformin at baseline

	Dulaglutide			Placebo			HR (95% CI)	*P*-value for interaction[a]
	Subgroup, *n*	*n* (%)	%/year	Subgroup, *n*	*n* (%)	%/year		
MACE	4949	594 (12.00)	2.35	4952	663 (13.39)	2.66	0.882 (0.789–0.985)	0.2598
Baseline metformin	4022	470 (11.70)	2.28	4015	506 (12.60)	2.49	0.913 (0.805–1.035)	
No baseline metformin	927	124 (13.38)	2.67	937	157 (16.76)	3.40	0.782 (0.618–0.989)	
Microvascular	4949	910 (18.39)	3.76	4952	1019 (20.58)	4.31	0.869 (0.795–0.950)	0.1168
Baseline metformin	4022	734 (18.25)	3.72	4015	847 (21.10)	4.40	0.840 (0.761–0.927)	
No baseline metformin	927	176 (18.99)	3.97	937	172 (18.36)	3.90	1.012 (0.820–1.248)	
All-cause mortality	4949	536 (10.83)	2.06	4952	592 (11.95)	2.29	0.897 (0.798–1.008)	0.8115
Baseline metformin	4022	413 (10.27)	1.95	4015	452 (11.26)	2.15	0.904 (0.791–1.033)	
No baseline metformin	927	123 (13.27)	2.57	937	140 (14.94)	2.93	0.874 (0.686–1.114)	
Heart failure	4949	213 (4.30)	0.83	4952	226 (4.56)	0.89	0.931 (0.772–1.123)	0.8452
Baseline metformin	4022	162 (4.03)	0.77	4015	170 (4.23)	0.82	0.942 (0.759–1.168)	
No baseline metformin	927	51 (5.50)	1.08	937	56 (5.98)	1.20	0.901 (0.617–1.317)	

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.
[a]Unadjusted *P*-value for interaction from Cox proportional hazards regression models.

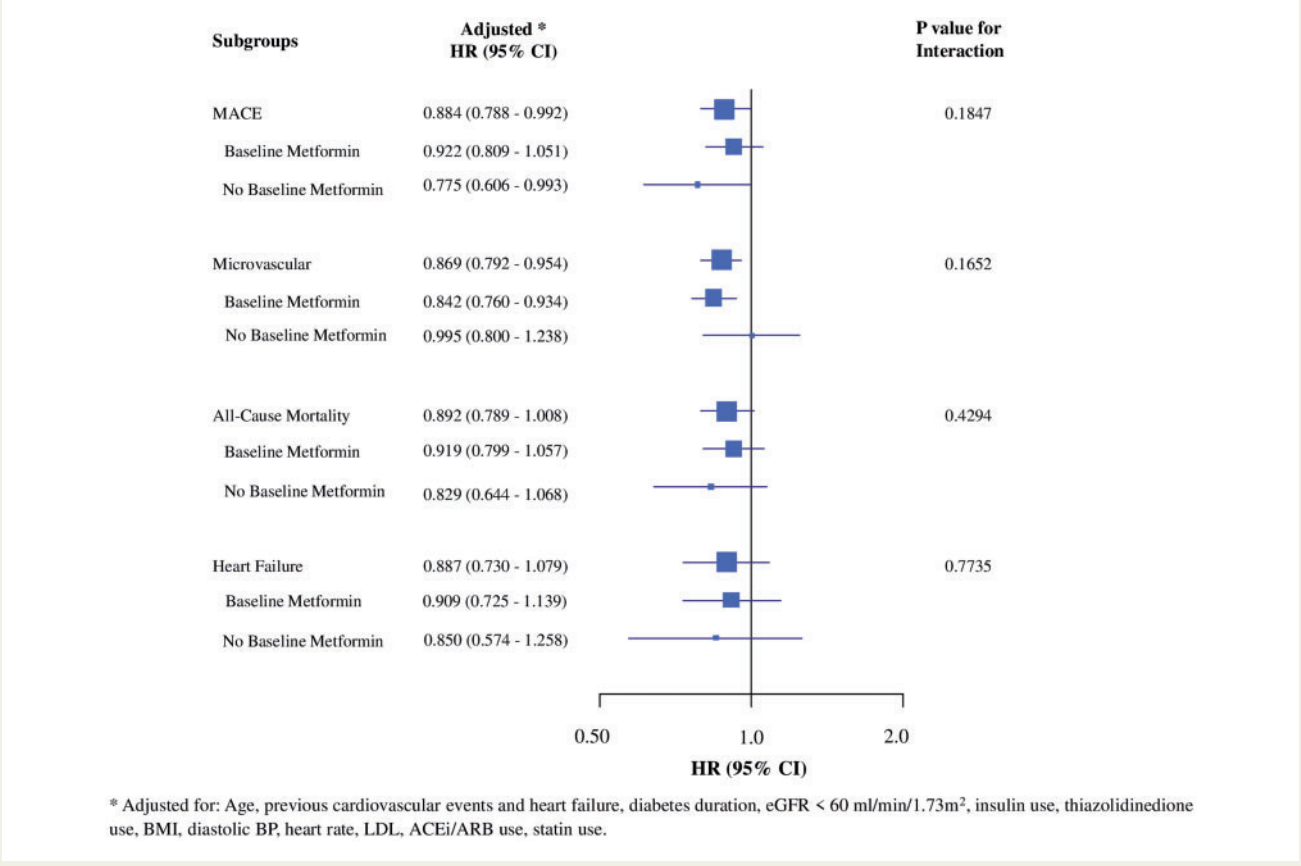


Figure 1 Cardiovascular outcomes, composite microvascular outcome, all-cause death and heart failure in participants by use of metformin at baseline, after adjusting for the independent determinants of metformin use. The size of each box is proportional to the number of events. ACEi/ARB, ACE inhibitors/angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular events.

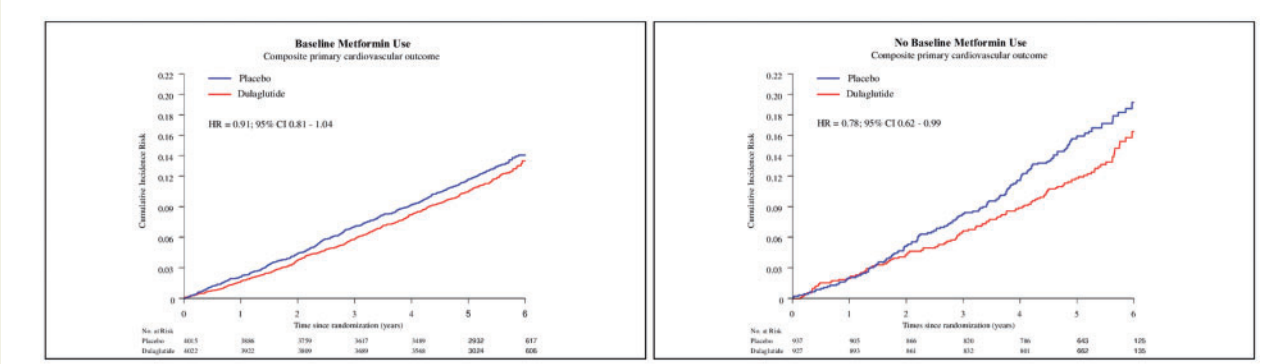
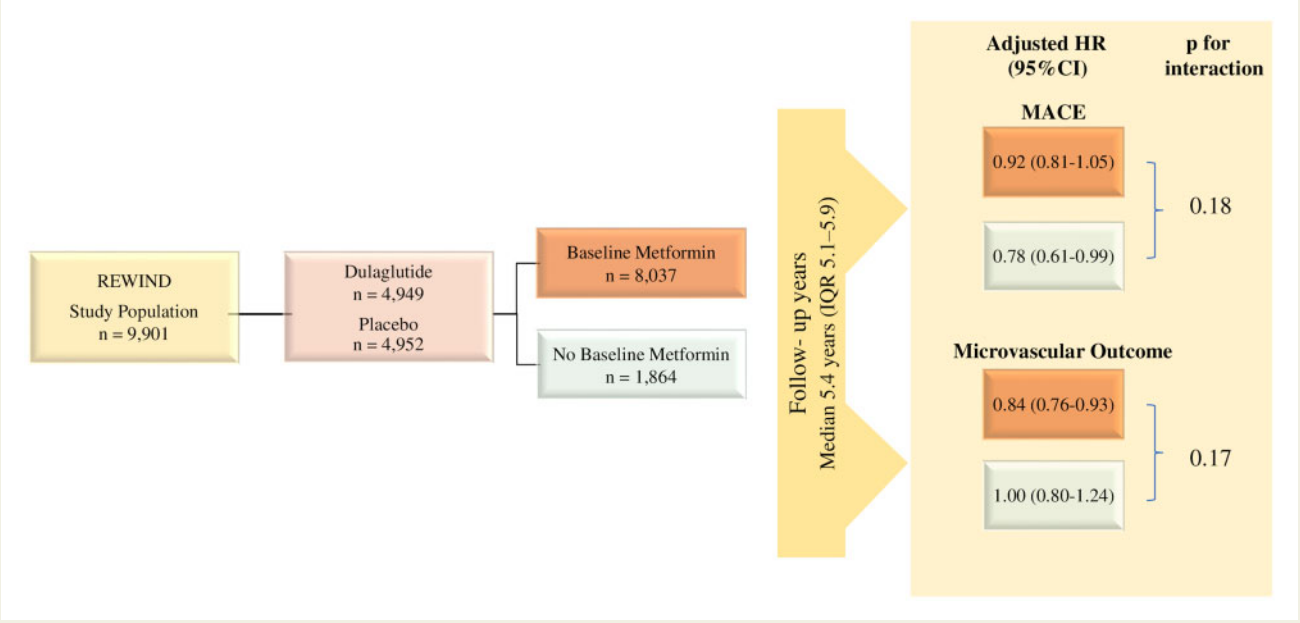


Figure 2 Kaplan–Meier curves showing the cumulative incidence of the primary outcome in participants with baseline metformin (*A*) and without baseline metformin use (*B*). CI, confidence interval; HR, hazard ratio.



Take home figure In this *post hoc* analysis of the REWIND trial, the cardiovascular protective effect of glucagon-like peptide 1 receptor agonist Dulaglutide was unaffected by baseline metformin therapy in patients with type 2 diabetes at high cardiovascular risk or with established cardiovascular disease. CI, confidence interval; HR, hazard ratio; IQR, interquartile range; MACE, major adverse cardiovascular events.

type of glucose-lowering therapy (Supplementary material online, *Table S2*) and dulaglutide (interaction $P = 0.53$).

Individuals who were taking baseline metformin differed from those not on baseline metformin in several ways (*Table 1*). The effect of dulaglutide in the presence and absence of metformin was therefore also assessed after accounting for the independent determinants of metformin use listed above. As noted in *Figure 1*, the absence of any significant interaction (all interaction *P*-values >0.1) provides no support for any differential effect of dulaglutide according to the baseline metformin use. In particular, there was no significant difference in the effect of dulaglutide on the primary outcome in patients with or without metformin at baseline [adjusted HR 0.92 (CI 0.81–1.05) vs. 0.78 (CI 0.61–0.99), respectively; interaction $P = 0.18$]. The risk for the composite microvascular endpoint, all-cause death and heart failure was similar in patients treated with dulaglutide, irrespective of use of baseline metformin both before and after adjusting for the independent determinants of metformin use (all interaction $P > 0.1$).

Kaplan–Meier curves for the primary MACE outcome in people with baseline metformin are shown in *Figure 2A*, whereas the corresponding curves for people without baseline metformin are shown in *Figure 2B*.

The effect of dulaglutide on the study outcomes was not influenced by the post-randomization use of metformin (Supplementary material online, *Table S3*).

Discussion

This *post hoc* analysis shows that the cardiovascular and microvascular outcomes within the REWIND trial were similar in people who were and were not taking metformin at baseline. Indeed, the absence of any evidence of interaction between dulaglutide use and metformin means that the best estimate of the effect of the intervention on these outcomes is the overall effect (e.g. HR 0.88 for MACE). This finding and the absence of an interaction after adjusting for the independent determinants of metformin use at baseline and the absence of any interaction with respect to the other key outcomes provide further support for the hypothesis that on these outcomes are consistent regardless of baseline metformin therapy. Two additional analyses further strengthened the present findings. The first showed the absence of interaction when subgrouping the participants in those who were drug naive, those who received any glucose-lowering therapy except metformin, and those taking metformin. The second one showed that post-randomization changes in metformin use did not impact the effect of dulaglutide on study outcomes.

Considering the lack of a CVOT investigating the effect of metformin vs. placebo on MACE, a subgroup analysis of a superiority randomized controlled trial represents a reasonable tool to assess the influence of metformin therapy on the effect of novel anti-hyperglycaemic agents and to investigate whether such agents maintain their cardioprotective benefit in patients who, by some reason, are not prescribed metformin.[11,14–16] In REWIND, the large dataset, the broad inclusion criteria comprising both people at risk for and with established CVD and the superiority trial nature allow insight in the cardiovascular risk reduction in a heterogeneous group of patients with type 2 diabetes. In accordance with the present results, a recent *post hoc* analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial identified no clear heterogeneity in the cardiovascular efficacy of the GLP-1 RA liraglutide in relation to the background use of metformin.[17] Similarly, participants with and without metformin at baseline in the Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and established CVD (Harmony Outcomes) trial had a consistent beneficial effect of the GLP-1 RA albiglutide on the primary composite cardiovascular outcome. This last report was, however, limited to a description of the primary outcome in prespecified subgroups, i.e. without any descriptions of or adjustments for dissimilarities in patients with and without baseline metformin.[10]

The mechanisms responsible for the cardiovascular benefits of GLP-1 RAs have not been fully elucidated.[18] Effects on glycaemic control, weight, lipid profile, blood pressure control, platelet function, and endothelial changes leading to improved myocardial perfusion have been shown.[19–21] Nevertheless, to assess the specific contribution of each action to the decrease in cardiovascular risk and to compare it to the respective metformin action would be impossible given the nature of the REWIND trial. Therefore, analyses like the present might be the most clinically insightful, while further mechanistic speculation on the present results would be inadequate.[15,18]

This study has some limitations. First, the study population is a selected trial cohort of people with type 2 diabetes at high cardiovascular risk or with established CVD that may not be fully representative of a wider population of such patients. However, to assess the generalizability of different CVOTs results, a recent analysis compared the key characteristics of participants of GLP-1 RAs CVOTs to a reference American population who matched the specific entry criteria: encouragingly, the REWIND population resulted as the most representative.[22] Second, REWIND was not specifically designed to assess difference between groups according to baseline therapy; therefore, these results should be considered indicative rather than proof of evidence. This is, at least partly, addressed by the absence of any interaction, even after adjusting for independent determinants of metformin use at baseline. The consistent results found for the secondary outcomes should also be interpreted as quality indicators of such sensitivity. Nevertheless, it is possible that other baseline characteristics were not included in the models. A third limitation is the relatively small proportion of participants without metformin at baseline, 19%, to a certain extent decreasing the power of the present analysis. A final limitation was that the possible effect of the other glucose-lowering medications taken by study participants was not characterized.

In conclusion, the present data favour the hypothesis that the benefit of the GLP-1 receptor agonist dulaglutide is unaffected by the use of baseline metformin in a population of patients with type 2 diabetes at high cardiovascular risk or with established CVD.

Data availability

The data sharing policy for this work is detailed in Appendix 1.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

G.F., H.C.G., and L.R. agreed to be accountable for all aspects of work ensuring integrity and gave final approval of publication. G.F., H.C.G., L.D., and L.R. contributed to conception, design, data acquisition and analyses, and interpretation of data. G.F. drafted the first manuscript that was critically reviewed by H.C.G., L.D., and L.R. Every other author led the trial overall or in their respective countries and every author critically reviewed and revised the article prior to submission.

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Guarantor's statement

Prof. Lars Rydén is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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