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Effect of expanded dulaglutide weekly doses (3.0 mg and 4.5 mg) on cardiovascular disease risk factors in participants with type 2 diabetes at increased cardiovascular disease risk: a post hoc analysis of the AWARD-11 study

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Abstract

Aims: This post hoc analysis investigated the effect of dulaglutide on cardiovascular disease (CVD) risk factors in subgroups of participants at increased CVD risk in the AWARD-11 study.

Methods: Participants who received once weekly dulaglutide 1.5, 3.0 or 4.5 mg for 52 weeks were categorized according to their baseline Framingham CVD risk category [low (N = 295), medium (N = 481) and high (N = 1054) risk], as well as their baseline CVD risk according to the REWIND study eligibility criteria (N = 953). Serum lipids and vital signs were assessed at baseline and at 52 weeks. Data were analysed as least squares mean percentage change from baseline for lipids and least squares mean change from baseline for vital signs.

Results: Demographic and baseline clinical characteristics were balanced across doses within the CVD risk groups. In the high Framingham CVD risk and REWIND-like groups, dulaglutide resulted in dose-related decreases in total cholesterol (≤6.0%), non-high-density lipoprotein cholesterol (≤8.8%), very-low-density lipoprotein cholesterol (≤19.4%) and triglycerides (≤21.5%), with little change in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. Systolic and diastolic blood pressure decreased up to 5.6 mmHg and 1.6 mmHg, respectively, and heart rate increased up to 2 beats/min.

Conclusions: This post hoc analysis suggests the magnitude of the favourable effects of dulaglutide 3.0 mg and 4.5 mg on several cardiometabolic CVD risk factors was similar to, if not greater than, those of dulaglutide 1.5 mg among participants with type 2 diabetes and increased CVD risk.

ClinicalTrials.gov Identifier: NCT03495102.

1 | INTRODUCTION

Dulaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that showed improvement in glycaemic control in people with type 2 diabetes (T2D).[1] It was initially approved for the treatment of T2D at once weekly doses of 0.75 and 1.5 mg.[1]

The REWIND study showed that the addition of dulaglutide 1.5 mg once weekly to existing antihyperglycaemic regimens

significantly decreased major adverse cardiovascular events (MACE) over a median of 5.4 years in participants with T2D and a wide range of glycaemic control.[2] These findings were consistent with those of cardiovascular disease (CVD) outcome trials of other GLP-1 RAs.[3] Of note, unique to these studies, REWIND enrolled middle-aged and older participants with either established CVD or cardiovascular (CV) risk factors only, with the majority of participants having CV risk factors without established CVD.[2,3]

The mechanism through which dulaglutide and other GLP-1 RAs reduce CV risk is unclear but probably multifactorial. Proposed mechanisms include (a) indirect effects resulting from improved glycaemic control and body weight and (b) direct effects on the vasculature (including the endothelium, smooth muscle, inflammation processes and the accumulation of atherogenic lipids), metabolism and the myocardium.[4-6] In glycaemic control studies of participants with T2D, as well as in REWIND, the effects of dulaglutide on established CV risk factors were similar to those established for other GLP-1 RAs,[7,8] including modest reductions in systolic blood pressure, improvements in specific serum lipids [particularly total cholesterol (total-C), very-low-density lipoprotein cholesterol (VLDL-C) and triglycerides] and reduced body weight.[1,2]

The AWARD-11 study investigated dulaglutide at higher doses of 3.0 and 4.5 mg once weekly in participants with T2D inadequately controlled with metformin and showed clinically relevant, dose-related reductions in glycated haemoglobin (HbA1c) and body weight with a similar safety profile to that of the 1.5 mg dose.[9,10] Based on these data, the 3.0 mg and 4.5 mg doses of dulaglutide have been approved, expanding the dosing options available for improving glycaemic control in people with T2D. The effect of the 3.0 and 4.5 mg doses of dulaglutide on the risk of MACE has not been tested in a CV outcomes trial. However, characterizing the effect of 3.0 and 4.5 mg dulaglutide on established CV risk factors, particularly in people with or at higher risk for CVD, can provide insights on the potential impact of higher doses on CV risk.

The objectives of this post hoc analysis of the AWARD-11 study were (a) to characterize the baseline CVD risk profile of the study population using two approaches, i.e. calculation of baseline Framingham CV risk score[11] and identification of a REWIND-like higher CVD risk subset by applying REWIND entry criteria to AWARD-11[2] and (b) to analyse the effects of dulaglutide 1.5, 3.0 and 4.5 mg on serum lipids, vital signs, body weight and glycaemic control (HbA1c) in subgroups of participants at higher baseline CVD risk defined using these two approaches relative to the overall study population through 52 weeks. We hypothesized that the effects of dulaglutide dose escalation on CVD risk factors would be favourable, and potentially greater, among participants at higher baseline CVD risk compared with the overall study population.

2 | METHODS

2.1 | Study design

Details of the study design and outcomes for the AWARD-11 study have been published previously.[10] In brief, participants with T2D ≥6 months, HbA1c between ≥7.5% and ≤11%, body mass index ≥25 kg/m^2, and who were insulin- and GLP-1 RA-naïve and taking metformin for ≥3 months were randomized 1:1:1 to dulaglutide 1.5 mg, 3.0 mg or 4.5 mg once weekly subcutaneous injection for 52 weeks.[10]

The study was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, and the International Conference on Harmonization Good Clinical Practices Guidelines. The protocol was approved by local institutional review boards. All participants provided written informed consent.

This study is registered with ClinicalTrials.gov, number NCT03495102.

In the previously published primary analysis of AWARD-11, HbA1c and body weight were primary and secondary efficacy measures, respectively.[10] Fasting serum lipids and blood pressure were collected as exploratory efficacy measures and are described in further detail in Appendix S1.

2.2 | Cardiovascular disease risk categorization

A history of CVD and CVD risk factors was collected at baseline through medical history and specific questions about previous CVD events, revascularization procedures and presence of dyslipidaemia or hypertension. The uses of antihypertensive and lipid-lowering medications were collected at each clinic visit. If used, antihypertensive medication was to be kept stable throughout the study to allow assessments of the effect of dulaglutide on blood pressure. Changes in concomitant medications were documented.

Baseline CVD risk was calculated for each participant without established CVD using the general Framingham CVD multivariate risk algorithm.[10] This algorithm estimates the 10-year probability of experiencing a CVD event based on age, levels of high-density lipoprotein cholesterol (HDL-C) and total-C, systolic blood pressure, smoking status and diabetes status (yes for all participants in this study).[11] Participants were categorized into the following Framingham CVD risk groups: high risk (Framingham 10-year probability >20%), intermediate risk (Framingham 10-year probability ≥10% to ≤20%) and low risk (Framingham 10-year probability <10%). Participants with established CVD (defined as a history of at least 1 of the following: myocardial infarction, coronary revascularization, hospitalization for unstable angina or heart failure, stroke or transient ischaemic attack, peripheral arterial disease, lower extremity or carotid artery revascularization, or documented coronary artery disease) were categorized in the high CV risk Framingham category.

The baseline CVD risk profile of the AWARD-11 study was also assessed by retrospectively applying REWIND study inclusion criteria relevant to CVD risk,[2,12] with modifications as necessary if required data were not available. The criteria for including participants in this "REWIND-like" group are summarized in Appendix S2 and Table S1.

2.3 | Statistical analysis

The safety population was used for this post hoc analysis, defined as all participants who were randomized and received at least one dose of study medication for the assigned treatment group. Changes from baseline in serum lipids on the log scale were analysed and then converted to percentage change from baseline using a mixed model repeated measures (MMRM) analysis. Vital signs (systolic blood pressure, diastolic blood pressure and heart rate), HbA1c and body weight were analysed as least squares mean change from baseline using the MMRM analysis.

The MMRM analysis was performed for each Framingham CVD risk group category and the REWIND-like group (subgroup analysis) and included factors for treatment, pooled country, baseline HbA1c strata, visit and treatment-by-visit interaction, with the baseline measure used as a covariate. A separate overall MMRM analysis was performed among all participants to assess the interaction terms between treatment and Framingham CVD risk category for each outcome (full model).

The MMRM analysis was conducted with treatment, pooled country, baseline HbA1c strata, visit, subgroup, treatment-by-visit, treatment-by-subgroup, visit-by-subgroup and treatment-by-visit-by-subgroup as fixed effects and baseline measurement as a covariate. The MMRM analysis excluded observations after either premature discontinuation of dulaglutide treatment or initiation of any new antihyperglycaemic medication for more than 14 days. Comparisons were made within treatment, and pairwise comparisons were made between dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg. Nominal *p*-values were reported for guidance on significance of the treatment effect estimate (set at $p < .05$). $p < .1$ is considered suggestive of the marginal effect of the Framingham CVD risk categories on the outcome and the interaction effect between the CVD risk category and treatment groups. There was no statistical hypothesis testing planned for this study, and multiple comparison adjustment for *p*-values was not performed. All data were analysed with SAS version 9.4.

3 | RESULTS

3.1 | Cardiovascular disease risk profile of the study population

Of the 1842 participants randomized in the safety population, 276 (15.0%) had a history of CVD and were thus included in the high Framingham CVD risk group. Of the remaining 1566 patients, 1554

TABLE 1 Demographic and baseline clinical characteristics

			Framingham risk category		
	Overall N = 1842	REWIND-like N = 953	High risk N = 1054	Medium risk N = 481	Low risk N = 295
Age, years; mean	57.1	64.4	61.3	54.9	45.6
Sex					
Female	898 (48.8)	469 (49.2)	362 (34.3)	307 (63.8)	219 (74.2)
Male	944 (51.2)	484 (50.8)	692 (65.7)	174 (36.2)	76 (25.8)
White	1580 (85.8)	856 (89.8)	947 (89.8)	403 (83.8)	221 (74.9)
Weight, kg; mean	95.7	93.5	97.0	93.9	94.4
Body mass index, kg/m^2; mean	34.2	33.9	34.0	34.1	35.1
HbA1c, %; mean	8.6	8.5	8.6	8.7	8.8
Previous CVD	276 (15.0)	276 (29.0)	276 (26.2)	0	0
Documented CAD	162 (8.9)	157 (16.5)	164 (15.6)	0	0
Hypertension	1284 (69.7)	794 (83.3)	872 (82.7)	315 (65.5)	91 (30.8)
Dyslipidaemia	1227 (66.6)	719 (75.4)	777 (73.7)	308 (64.4)	295 (45.4)
Antihypertensive medication	1302 (70.7)	812 (85.2)	890 (84.4)	314 (65.3)	93 (31.5)
ACE inhibitor or ARB	1137 (61.7)	703 (73.8)	778 (73.8)	277 (57.6)	77 (26.1)
Lipid-lowering medication	1013 (55.0)	625 (65.6)	667 (63.3)	245 (50.9)	98 (33.2)
HMG-CoA reductase inhibitor	924 (50.2)	573 (60.1)	602 (57.1)	229 (47.6)	89 (30.2)
Fibrate	178 (9.6)	105 (11.0)	122 (11.6)	36 (7.5)	19 (6.4)

Notes: Data are presented as n (%) unless otherwise indicated. Previous CVD defined as having a history of at least one of the following: myocardial infarction, coronary revascularization, hospitalization for unstable angina or heart failure, stroke or transient ischaemic attack, peripheral arterial disease, lower extremity or carotid artery revascularization, or documented coronary artery disease.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

(99.2%) had sufficient information collected at baseline to calculate a Framingham CVD risk score (Table S2). Overall, in total, 1054 participants (57.6%) were categorized into the high Framingham CVD risk group; 778 (42.2%) due to a Framingham 10-year risk probability of >20% and 276 (15.0%) due to having a history of established CVD (Table S2). In total, 481 participants (26.1%) were categorized as medium CVD risk and 295 (16.0%) were categoried as low CVD risk (Table S2). The number of participants receiving each of the three dulaglutide doses was generally balanced across the Framingham CVD risk groups (Table S2).

Applying REWIND eligibility criteria related to CVD risk to the AWARD-11 study population, 953 participants (51.7%) were

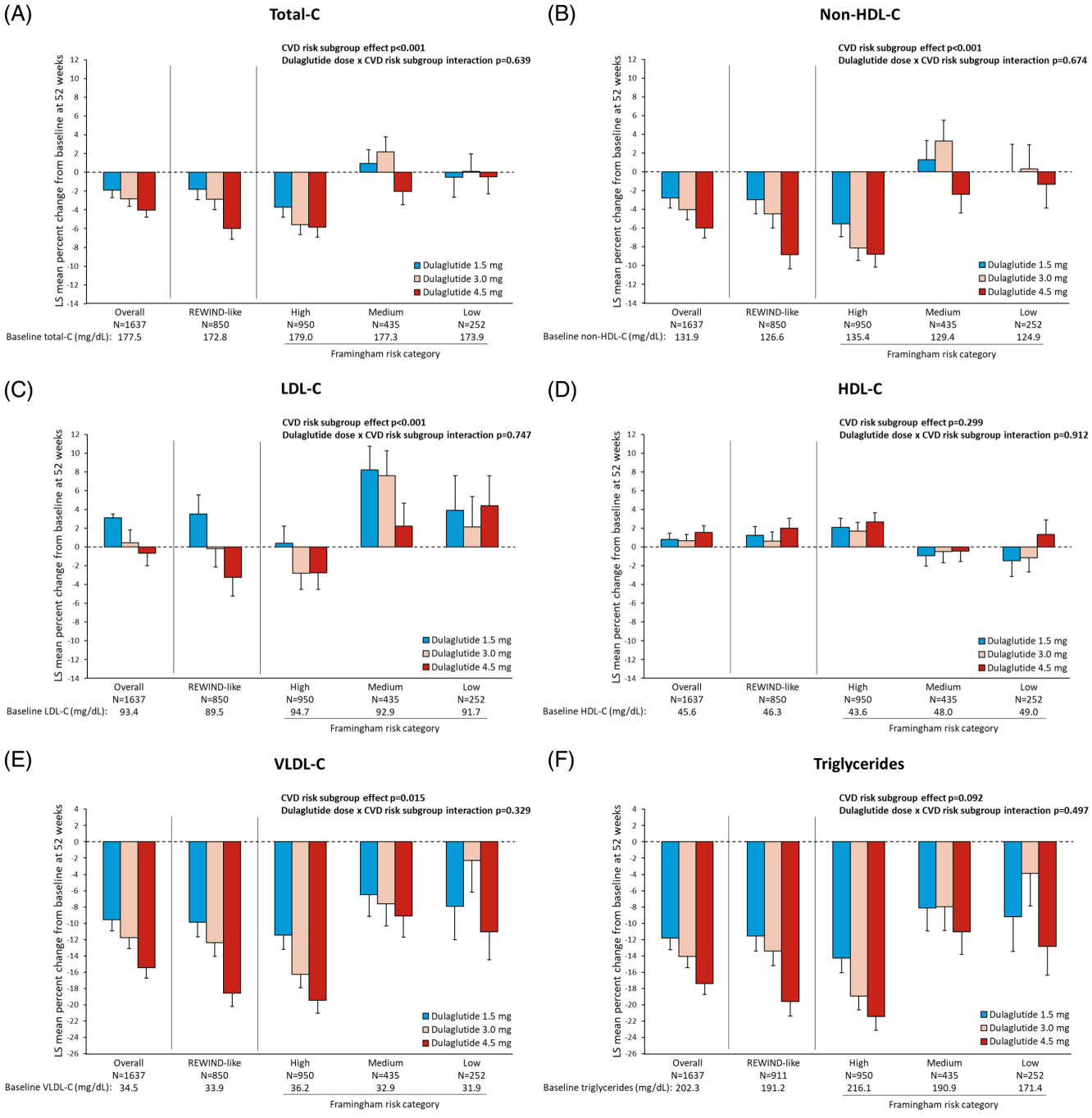

FIGURE 1 Least squares mean percentage change from baseline to 52 weeks in A, total-C, B, non-HDL-C, C, LDL-C, D, HDL-C, E, VLDL-C and F, triglycerides. Error bars represent standard error. Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares; non-HDL-C, non-high-density lipoprotein cholesterol; total-C, total cholesterol; VLDL-C, very-low-density lipoprotein cholesterol

categorized into the REWIND-like group (Table S2). Most participants [n = 761 (79.9%)] meeting criteria for the REWIND-like group were also included in the high CVD risk Framingham group (Table S2).

3.2 | Baseline characteristics by cardiovascular disease risk group

Participants in the high Framingham CVD risk group were generally older, a higher proportion were male, and they had higher blood pressure and less favourable lipid profiles compared with participants in the medium and low Framingham CVD risk groups (Table 1). The use of antihypertensive medications (84.4% of participants) and lipid-lowering medications (63.3% of participants) was highest in the high CVD risk Framingham group, with no clinically relevant differences across dulaglutide doses (Table S3). When compared with the medium and low Framingham CVD risk groups, participants in the REWIND-like group had higher blood pressure and poorer lipid profiles, and a high proportion of those participants were receiving antihypertensive medications (85.2%) and lipid-lowering medications (65.6%) at baseline (Table 1). Baseline characteristics and use of antihypertensive and lipid-lowering therapy was generally balanced across the three dulaglutide doses within each CVD risk group (Table S3).

3.3 | Serum lipids and triglycerides

In the overall study population at 52 weeks, dulaglutide 1.5, 3.0 and 4.5 mg resulted in dose-related least squares mean percentage reductions from baseline in total-C, non-high-density lipoprotein cholesterol (non-HDL-C), VLDL-C and triglycerides, with smaller mean percentage changes in low-density lipoprotein cholesterol (LDL-C) and HDL-C (Figure 1). The dose-related reductions from baseline in total-C, non-HDL-C, VLDL-C and triglycerides were generally numerically greater in the high CVD risk Framingham and REWIND-like groups compared with the medium and low CVD risk Framingham groups, regardless of dulaglutide dose. In contrast, among participants in the medium and

TABLE 2 Least squares mean change from baseline to 52 weeks in blood pressure and heart rate

			Framingham risk category				
	Overall N = 1842	REWIND-like N = 867	High risk N = 962	Medium risk N = 436	Low risk N = 252	CVD risk group *p*-value	Treatment-by-CVD risk group *p*-value
Systolic BP, mmHg						<.001	
Mean baseline	131.8	134.5	136.7	129.1	118.5		.259
Dulaglutide 1.5 mg	−3.2 (0.5)	−4.6 (0.7)	−5.5 (0.7)	−1.9 (0.9)	2.7 (1.2)		
Dulaglutide 3.0 mg	−3.6 (0.5)	−4.9 (0.7)	−5.6 (0.7)	−2.4 (0.9)	2.1 (1.1)		
Dulaglutide 4.5 mg	−4.1 (0.5)	−4.6 (0.7)	−5.1 (0.7)	−3.3 (0.9)	−1.0 (1.1)		
Diastolic BP, mmHg						.781	
Mean baseline	78.7	77.8	79.9	78.4	75.4		.904
Dulaglutide 1.5 mg	−1.1 (0.3)	−1.3 (0.4)	−1.6 (0.4)	−1.4 (0.6)	0.9 (0.9)		
Dulaglutide 3.0 mg	−1.0 (0.3)	−1.2 (0.4)	−1.5 (0.4)	−0.8 (0.6)	0.7 (0.8)		
Dulaglutide 4.5 mg	−1.1 (0.3)	−1.4 (0.5)	−1.6 (0.4)	−1.2 (0.6)	0.3 (0.8)		
Heart rate, bpm						.018	
Mean baseline	75.5	74.0	74.7	76.3	76.8		.249
Dulaglutide 1.5 mg	1.0 (0.3)	2.0 (0.5)	1.4 (0.4)	0.6 (0.6)	−0.2 (0.9)		
Dulaglutide 3.0 mg	1.9 (0.3)	1.8 (0.5)	2.4 (0.4)	0.3 (0.7)	2.2 (0.8)		
Dulaglutide 4.5 mg	1.9 (0.3)	2.0 (0.5)	1.9 (0.4)	1.3 (0.6)	2.8 (0.8)		

Notes: Data are presented as least squares mean change from baseline (standard error) unless otherwise indicated.
Abbreviations: BP, blood pressure; bpm, beats/min; CVD, cardiovascular disease.

low Framingham CVD risk groups, mean percentage changes in total-C, non-HDL-C, VLDL-C and triglycerides were generally smaller and more variable across dose groups, and LDL-C tended to increase from baseline, with little change in HDL-C in either group regardless of dose.

Results from the full model suggested that Framingham CVD risk category had an impact on overall percentage change from baseline in total-C ($p < .001$), non-HDL-C ($p < .001$), VLDL-C ($p = .015$), LDL-C ($p < .001$) and triglycerides ($p = .092$), but not HDL-C ($p = .299$). Dulaglutide dose effect-by-CVD risk group interaction was not significant for any of the serum lipids ($p_{interaction} \geq .165$).

3.4 | Blood pressure and heart rate

In the overall study population at 52 weeks, dulaglutide 1.5, 3.0 and 4.5 mg resulted in least squares mean reductions from baseline in both systolic blood pressure (3.2, 3.6 and 4.1 mmHg, respectively) and diastolic blood pressure (1.1, 1.0 and 1.1 mmHg, respectively), with a similar magnitude of effect for each dulaglutide dose. Dulaglutide 1.5 mg, 3.0 mg and 4.5 mg also resulted in least squares mean increases from baseline in heart rate (1.0, 1.9 and 1.9 bpm, respectively), with a similar magnitude of effect for each dulaglutide dose. Least squares mean changes from baseline in systolic blood pressure, diastolic blood pressure and heart rate at 52 weeks are summarized in Table 2, and time course data are shown in Figures S1–S3.

The reductions from baseline in systolic blood pressure were generally numerically greater in the high CVD risk Framingham and REWIND-like groups compared with the medium and low CVD risk Framingham groups, regardless of dulaglutide dose (Table 2 and Figure S1). The *p*-value for the effect of Framingham CVD risk category on change in systolic blood pressure was <.001, whereas the interaction effect for dulaglutide dose-by-Framingham CVD risk group was $p = .259$ for systolic blood pressure.

The reductions from baseline in diastolic blood pressure observed in the overall study population were small (<2 mmHg) and consistent among the Framingham CVD risk and REWIND-like groups, regardless of dulaglutide dose ($p = .781$ for CVD risk group effect) (Table 2 and Figure S2).

The increases from baseline in heart rate observed in the overall study population were consistent among the Framingham CVD risk and REWIND-like groups, regardless of dulaglutide dose (Table 2 and Figure S3). Although the *p*-value for effect of the Framingham CVD risk group on the change in heart rate was .018, the differences among the Framingham CVD risk groups were small and not considered clinically relevant. The *p*-value for interaction effect of dulaglutide dose-by-Framingham CVD risk group for change in heart rate was .249.

3.5 | Body weight and glycated haemoglobin

In the overall study population at 52 weeks, dulaglutide 1.5, 3.0 and 4.5 mg resulted in least squares mean reductions from baseline in body weight (Figure 2A) that were similar across Framingham CVD risk groups, as well as in the REWIND-like group (Figure 2A). Similar patterns of HbA1c reductions from baseline were observed across Framingham CVD risk groups and the REWIND-like group (Figure 2B). The Framingham CVD risk group effect had *p*-values of .899 and .859 for body weight and HbA1c, respectively, and the interaction effect of dulaglutide dose-by-Framingham CVD risk group had *p*-values of .625 and .364 for body weight and HbA1c, respectively.

3.6 | Shifts from baseline in Framingham cardiovascular disease risk group

Excluding participants with established CVD or with missing CVD risk categories, the proportion of participants in the same Framingham CVD risk group at 52 weeks compared with baseline was 80.7% for participants at high CVD risk, 64.8% for participants at medium CVD risk and 82.5% for participants at low CVD risk (Figure S4). Differences across dulaglutide doses in the proportion of participants staying in the same or shifting Framingham CVD risk groups at 52 weeks were generally small. However, a lower proportion of

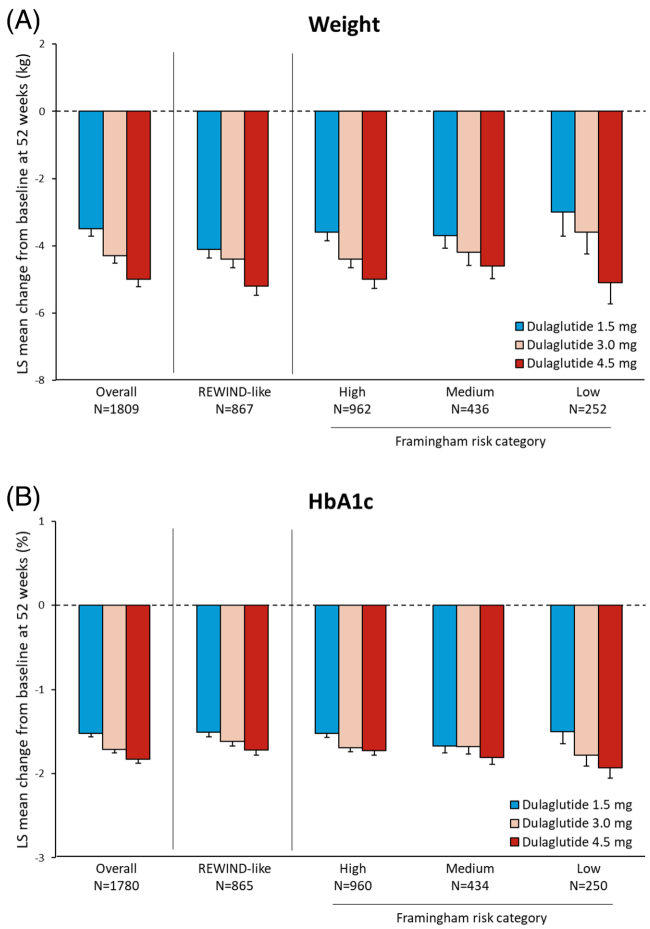

FIGURE 2 Least squares mean change from baseline to 52 weeks in A, body weight and B, HbA1c". Error bars represent standard error. Abbreviations: HbA1c, glycated haemoglobin; LS, least squares

participants who received higher doses of dulaglutide compared with the 1.5-mg dose shifted from the medium CVD risk Framingham group (Figure S4B) or the low CVD risk Framingham group (Figure S4C) to a higher CVD risk Framingham group by 52 weeks.

4 | DISCUSSION

The AWARD-11 study showed that once weekly dulaglutide doses of 3.0 and 4.5 mg were superior to dulaglutide 1.5 mg for glycaemic control and weight loss at 36 weeks in participants with T2D.[10] Whether these higher dulaglutide doses have a similar effect on MACE, as shown in REWIND for dulaglutide 1.5 mg, is unknown, and a CV outcomes study with these doses has not been performed. These post hoc analyses suggest that improvements in glycaemic control, body weight, serum lipids and systolic blood pressure with dulaglutide 3.0 and 4.5 mg were similar to or greater than the effects of the 1.5 mg dose, with the most prominent effects observed in subgroups of participants at higher CVD risk.

The AWARD-11 study did not include specific eligibility criteria to enrich the population with participants at higher risk of CVD. Nevertheless, nearly 60% of the population was classified as high CVD risk based on either a documented history of established CVD or in participants without established CVD, a predicted 10-year CVD risk of >20% based on the Framingham general CVD risk algorithm. Moreover, just over half of the participants in AWARD-11 would probably have qualified to participate in REWIND based on the application of the REWIND entry criteria most relevant to CVD risk. Thus, the AWARD-11 study population provided an opportunity to assess the effect of higher dulaglutide doses on major CVD risk factors in participants with T2D and increased CVD risk.

In prespecified analyses of AWARD-11, dulaglutide resulted in significant dose-related mean reductions from baseline in the exploratory lipid endpoints of total-C, VLDL-C and triglycerides, with significantly larger improvements with dulaglutide 4.5 mg versus 1.5 mg for VLDL-C and triglycerides.[10] Post hoc analyses of participants at higher baseline CVD risk, defined by REWIND entry criteria or Framingham CVD risk algorithm, suggest that the improvements in total-C, non-HDL-C, VLDL-C and triglycerides observed in the overall study population were driven largely by improvements among participants with or at increased risk for CVD. Moreover, for each lipid parameter, the magnitude of effect with the 3.0 and 4.5 mg doses of dulaglutide in participants at increased CVD risk was similar to, or numerically greater than, that with the 1.5 mg dose of dulaglutide. While dulaglutide did not improve serum lipids to the magnitude typically observed with statins, even at the highest dulaglutide dose, it should be noted that these effects were observed despite the majority (>60%) of participants in the high CVD risk Framingham group already receiving at least one lipid-lowering therapy. It is also noteworthy that the >20% reduction in serum triglycerides in the high CVD risk Framingham group observed with dulaglutide 4.5 mg approaches the magnitude of effect of fibrates on triglycerides (22%-29% reduction from baseline) in people with T2D.[13]

The improvement in systolic blood pressure with dulaglutide observed in these post hoc analyses was also driven largely by reductions in participants at increased CVD risk, whereas changes in diastolic blood pressure were small and not considered clinically relevant in any CVD risk group. The mean decrease in systolic blood pressure in the high CVD risk group of approximately 5 mmHg with dulaglutide persisted through 52 weeks of treatment and was achieved despite a high prevalence (>80%) of participants already taking antihypertensive therapy at baseline. There were no clinically relevant differences across CVD risk groups in change in heart rate, which peaked after week 12 and then waned to a mean increase of 2-3 beats/min at week 52. Thus, to the extent that improvements in serum lipids and blood pressure may contribute to the reduction in MACE risk observed in REWIND with the 1.5 mg dose, these data support the hypothesis that higher dulaglutide doses of 3.0 and 4.5 mg may have a comparable effect on MACE risk reduction.

Although not a focus of the current post hoc analysis, the explanation for why the improvements in serum lipid profile and systolic blood pressure were consistently greater among participants at increased CVD risk compared with lower risk groups is not clear. Weight loss within the range observed in this study for dulaglutide can result in improvements in serum lipid profile and blood pressure,[14] and previous studies have suggested at least a weak relationship between GLP-1 RA-induced weight loss and reduction in blood pressure.[15] However, the mean weight loss with each dulaglutide dose was comparable across all CVD risk groups, suggesting that a differential effect of dulaglutide on weight loss across CVD risk groups did not play a prominent role in the greater improvements in blood pressure and serum lipids in the higher CVD risk groups. Higher baseline values can be associated with larger treatment responses to antihypertensive and lipid-lowering therapies due to regression to the mean.[16] However, the MMRMs for change from baseline in lipids and blood pressure were adjusted for baseline values. Moreover, in most cases, the absolute difference in mean baseline for serum lipids or systolic blood pressure across groups was relatively small and probably not large enough to account for the large differences in overall treatment effect observed across the CVD risk groups.

Exploratory mediation analyses of liraglutide in the LEADER study[4] and dulaglutide in the REWIND study[5] suggested that improvement in HbA1c might partially account for the CV risk reduction with the GLP-1 RA in each study. However, it remains unclear whether this is via direct mediation or HbA1c serving as a marker for other unmeasured variables more directly responsible for MACE risk reduction, and a multifactorial mechanism is still probable. Nevertheless, the comparable dose-related dulaglutide improvements in glycaemic control measured by HbA1c reduction across CVD risk groups suggest that any risk reduction effect mediated by HbA1c would also be at least comparable with the higher dulaglutide doses of 3.0 and 4.5 mg.

These analyses have several limitations. None of the analyses was prespecified and thus, as post hoc analyses, must be considered hypothesis-generating. The original trial design did not include a placebo group because this was not necessary for testing the primary

and secondary objectives; however, the lack of placebo data is a limitation of this post hoc analysis. Most participants in AWARD-11 were categorized as being at high CVD risk. While this provided a large sample size to assess the effects of dulaglutide on patients at high CVD risk, the results from the medium and low CVD risk Framingham groups were from smaller sample sizes, which generally are associated with greater variability. Furthermore, the analyses were limited to CVD risk factors collected in AWARD-11. Other relevant risk factors, particularly those related to vascular inflammation or other direct vascular or cardiac effects, were not available.

In conclusion, this post hoc analysis suggests the magnitude of the effects of dulaglutide 3.0 and 4.5 mg on several cardiometabolic CVD risk factors were similar to, if not greater than, those of dulaglutide 1.5 mg among participants at increased CVD risk in the AWARD-11 study, including participants who would have probably qualified for the REWIND study. Thus, to the extent that improvements in glycaemic control, body weight, serum lipids and systolic blood pressure may contribute to MACE risk reduction with GLP-1 RAs, these data support the hypothesis that higher dulaglutide doses of 3.0 and 4.5 mg once weekly may have effects on CVD risk consistent with those established for the 1.5 mg dose in REWIND.

AUTHOR CONTRIBUTIONS

All authors contributed to designing the study, interpreting the data, and developing and writing the manuscript. HW also conducted statistical analyses. All authors read and approved the final version.

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FUNDING INFORMATION

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CONFLICT OF INTEREST

DAC, CN, and MAB are full-time employees of, and own stock in, Eli Lilly and Company. HW is a full-time employee of TechData Service Company.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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SUPPORTING INFORMATION

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

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