HbA_{1c} Reduction in Dulaglutide-Treated Patients Irrespective of Duration of Diabetes, Microvascular Disease, and BMI: A Post Hoc Analysis From the REWIND Trial

Anita Y.M. Kwan,[1] Hertzel C. Gerstein,[2] Jan Basile,[3] Denis Xavier,[4] Juan M. Maldonado,[1] Sohini Raha,[1] and Manige Konig[1]

Diabetes Care 2022;45:547–554 | https://doi.org/10.2337/dc21-1160

OBJECTIVE

To evaluate participant characteristics and long-term changes in glycated hemoglobin (HbA_{1c}) levels in patients treated with dulaglutide 1.5 mg in a post hoc analysis of the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial.

RESEARCH DESIGN AND METHODS

Change from baseline in HbA_{1c} was assessed during and up to 72 months of treatment before and after adjustment for duration of diabetes, prior microvascular disease (nephropathy or retinopathy), and BMI. Slope analyses were used to assess the change in HbA_{1c} during 0–12 months and 12–72 months of therapy.

RESULTS

HbA_{1c} was significantly reduced in patients treated with dulaglutide compared with placebo during 72 months of treatment (least-squares mean difference = −0.61%, $P < 0.001$), regardless of diabetes duration, prior microvascular disease, and BMI (all interaction $P > 0.07$). Significant reductions were apparent at all time points and were independent of these baseline characteristics. Slope analyses revealed that the dulaglutide group experienced a higher rate of HbA_{1c} reduction compared with the placebo group from 0 to 12 months before and after adjustment. The dulaglutide group also experienced a higher rate of HbA_{1c} increase from 12 to 72 months compared with the placebo group that became nonsignificant after adjustment for diabetes duration, prior microvascular disease, and BMI combined. Despite the greater rate of HbA_{1c} increase in the dulaglutide group during this period, mean HbA_{1c} values remained below baseline in the dulaglutide group and below mean HbA_{1c} values in the placebo group.

CONCLUSIONS

Dulaglutide 1.5-mg treatment was statistically associated with a long-lasting decrease in HbA_{1c} over 72 months, irrespective of baseline duration of diabetes, microvascular disease, and BMI.

Glucose lowering reduces symptoms of hyperglycemia and many of the long-term complications of diabetes (1). Patient characteristics may affect the glycemic responses

[1]Eli Lilly and Company, Indianapolis, IN
[2]Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
[3]Medical University of South Carolina, Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC
[4]St. Johns Medical College and Research Institute, Bangalore, India

Correspondence: Manige Konig, konig_manige@lilly.com

Received 1 June 2021 and accepted 19 December 2021

Clinical trial reg. no. NCT01394952, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.17380850.

to various therapies (2). Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of glucose-lowering drugs used to treat type 2 diabetes and include dulaglutide. Post hoc analysis of the Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD) trials suggests that the 6-month glycemic effect of dulaglutide is independent of BMI and duration of diabetes (3–5). Whether these characteristics or the presence of microvascular disease affects glucose lowering during short- or long-term therapy remains unknown (6).

The Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) cardiovascular (CV) outcomes trial demonstrated that the addition of dulaglutide 1.5 mg to the standard care for type 2 diabetes and either CV risk factors or previous CV disease (CVD) reduced the hazard of a composite outcome of CV death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes (6). During this trial, patients assigned to dulaglutide had a least-squares mean (LSM) glycated hemoglobin (HbA_{1c}) that was 0.61% lower than patients assigned to placebo during a median follow-up period of 5.4 years (6). In addition to the CV efficacy of dulaglutide demonstrated in REWIND, HbA_{1c} outcomes over long-term use is an important clinical consideration to help tailor therapy and further improve and manage diabetes complications. The current post hoc analysis assesses whether changes in HbA_{1c} levels in the dulaglutide 1.5 mg group varied with diabetes duration, microvascular disease (retinopathy and/or nephropathy), or BMI, either separately or combined, and whether the rate of change in HbA_{1c} during the first 12 months and subsequent 60 months of therapy differed in patients assigned to dulaglutide 1.5 mg versus placebo added to standard care for diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Patients

A full description of study methods, efficacy, and safety results from the REWIND CV outcomes trial has been previously published (6,7), and additional details of the REWIND trial can be found at https://clinicaltrials.gov as NCT01394952. Briefly, this was a multicenter, global, randomized, double-blind, placebo-controlled clinical trial. Adults aged ≥50 years with either established or newly diagnosed type 2 diabetes and additional CV risk factors or established CVD, aged ≥55 years with subclinical CVD, or aged ≥60 years with two or more CV risk factors were included. Patients (N = 9,901) were randomized (1:1) to receive either a once-weekly subcutaneous injection of dulaglutide 1.5 mg or placebo, in addition to the standard of care for type 2 diabetes and CVD of the specific country, during a median follow-up of 5.4 years. The primary outcome was the time to the first occurrence of the composite end point of nonfatal myocardial infarction, nonfatal stroke, or death from CV causes (including unknown causes), which was assessed in the intention-to-treat (ITT) population.

The current post hoc analysis assessed change from baseline in HbA_{1c} accounting for three baseline characteristics: duration of diabetes, history of microvascular disease, and BMI. Duration of diabetes was calculated based on the self-reported date of diagnosis. Prior microvascular disease, defined as a history of diabetic retinopathy or diabetic nephropathy, was based on the investigator's assessment of this history as recorded on the case report form. Weights and heights, recorded at the baseline visit, were used for calculation of BMI.

Statistical Analysis

Change in HbA_{1c} From Baseline Over Time and Overall

Analyses were conducted in all patients who received one or more dose of the study medication and who had a baseline HbA_{1c} measurement plus one or more postbaseline HbA_{1c} measurements. For the change in HbA_{1c} from baseline, a mixed-effects model for repeated measures (MMRM) was used to compare patients treated with dulaglutide 1.5 mg to the placebo group (each group also received standard of care for diabetes), adjusting for diabetes duration, microvascular disease, and BMI at baseline as factors individually and together. All models also included baseline HbA_{1c}, treatment, visit, and interaction between treatment and visit as fixed effects where patients enter the model as a random effect. The results are reported as the LSM value for change in HbA_{1c} from baseline over time up to 72 months for patients treated with dulaglutide and placebo. HbA_{1c} beyond 72 months was not assessed due to a decline in the number of patients beyond that time point. A comparison between the dulaglutide and placebo treatment groups was conducted based on the LSM differences at all time points and for overall change, and corresponding P values were calculated for all time points and for the overall change (8). An additional MMRM assessed the interaction of treatment with diabetes duration, prior microvascular disease, and BMI on the HbA_{1c} change from baseline. Interaction P values ≤0.05 were considered to be nominally significant.

Analyses were performed for three separate subgroups to assess the consistency of the change in HbA_{1c} across the subgroups with and without adjusting for diabetes duration, microvascular disease, and BMI at baseline as factors individually and together. The three subgroups were created by dividing patients based on their baseline HbA_{1c} <7.2% or ≥7.2%, baseline insulin use (yes/no), and country (U.S. and Canada; Latin America; and Europe and Asia Pacific). In all of the above MMRM models, the subgroup variables were added along with their interaction with the treatment group, and interaction P values were reported.

The use of concomitant medications at baseline and postbaseline and a comparison of changes from baseline to postbaseline in concomitant medication use between treatment groups are summarized to assess the concomitant medications that may have an impact on change in HbA_{1c} over time.

The proportion of patients achieving HbA_{1c} <7% at each scheduled time point served to approximate the average maintenance of HbA_{1c} target in both treatment groups.

Analysis of Slope of HbA_{1c} Change

Slope analyses were used to delineate differences in the rate of HbA_{1c} changes over time. For these analyses, the average rate of change in HbA_{1c} was assessed during both the first 12 months of treatment (using baseline and month 12 as time points) and from 12 months to 72 months (using months 12 and 72 as time points). Results are expressed as monthly and yearly changes in HbA_{1c} and were obtained using random coefficient

models (9). Assessments of HbA_{1c} slope (change in HbA_{1c} per month or year) were conducted before and after adjusting for baseline characteristics: diabetes duration, microvascular disease, BMI, and the combination of the three. The models also included treatment as a categorical variable and visit as a continuous variable. By using patient and time as random effects, intercepts and slopes over time were permitted to differ from patient to patient. Fitted individual HbA_{1c} slopes for the dulaglutide and placebo groups were plotted by smoothed histograms using density plots for both treatment periods. The mean monthly slope for the initial 12 months of treatment and the mean yearly slope for the 12- to 72-month treatment period were reported and compared between the dulaglutide and placebo groups using a *t* test. For both the MMRM and the slope analysis, patients with nonmissing values at the corresponding visit were included.

RESULTS

The REWIND trial enrolled patients with HbA_{1c} ≤9.5% at screening and collected HbA_{1c} measurements of randomized patients at baseline, 3 months, 12 months, and annually thereafter. From the total REWIND trial ITT population ($N = 9,901$), 9,876 patients had a nonmissing HbA_{1c} baseline measurement and at least one postbaseline measurement and were included in this post hoc analysis. The number of patients included for analysis at each annual follow-up visit is reported in Fig. 1. Mean baseline HbA_{1c} was similar between the dulaglutide and placebo groups (7.34% vs. 7.35%) (Table 1). The baseline characteristics of the full ITT population have been published elsewhere (6,7).

Change in HbA_{1c} From Baseline Over Time and Overall

At all time points, HbA_{1c} was significantly reduced from baseline in dulaglutide-treated versus placebo-treated patients, regardless of baseline diabetes duration, microvascular disease (nephropathy and/or retinopathy), or BMI ($P < 0.001$, all time points) (Fig. 1*A–C*, solid lines). Compared with patients in the placebo group, those in the dulaglutide group had a 0.61% (95% CI −0.65 to −0.58; $P < 0.001$) lower overall LSM change in HbA_{1c} after adjusting for diabetes duration (Fig. 1*A*, solid line). A similar overall LSM difference was observed after adjusting for microvascular disease (Fig. 1*B*), BMI (Fig. 1*C*), and the combination of the three baseline characteristics (Fig. 1*D*). At 12 months, the HbA_{1c} LSM of the dulaglutide group was lower (6.70%) than the placebo group (7.40%: LSM difference −0.70%; 95% CI −0.74 to −0.67; $P < 0.001$). At 72 months, the HbA_{1c} LSM of the dulaglutide group remained slightly lower (7.12%) than the placebo group (7.59%; LSM difference −0.47%; 95% CI −0.55 to −0.40; $P < 0.001$). Similar values were observed before and after adjusting for the baseline characteristics. Treatment-by-diabetes–duration interaction, treatment-by-microvascular–disease interaction, and treatment-by-BMI interaction were not significant for change from baseline ($P = 0.811$, $P = 0.074$, and $P = 0.200$, respectively). The interaction between the treatment and the subgroup based on baseline HbA_{1c} above or below the median (7.2%), with and without adjusting for each of diabetes duration, microvascular disease, BMI, and the combination of the three, was significant ($P < 0.001$). The same pattern was observed for the subgroups of country (U.S. and Canada; Latin America; and Europe and Asia Pacific) (interaction $P < 0.001$).

Concomitant antihyperglycemic medication usage at baseline and postbaseline were analyzed to examine differences between patients treated with dulaglutide versus placebo (Supplementary Table 1). Addition of antihyperglycemic medications according to standard of care in both treatment groups was allowed starting at 3 months. At baseline, medication use was similar between both groups, with the exception of thiazolidinediones, which was higher in the dulaglutide group. Postbaseline, antihyperglycemic medication use increased in both treatment groups but was significantly lower across all antihyperglycemic agent classes in the dulaglutide group compared with the placebo group. The interaction between the treatment and baseline insulin use on HbA_{1c} was not significant before ($P = 0.601$) and after adjusting for each of diabetes duration ($P = 0.701$), microvascular disease ($P = 0.697$), BMI ($P = 0.688$), and the combination of the three ($P = 0.577$).

The percentage of patients with HbA_{1c} <7% was calculated for each time point (Supplementary Fig. 1). At each time point, a higher percentage of patients in the dulaglutide group had a HbA_{1c} value <7% than those in the placebo group.

Analysis of Slope of HbA_{1c} Change

During the first 12 months of treatment, the modal distribution of individual HbA_{1c} slopes suggests that a greater proportion of dulaglutide patients experienced a higher rate of HbA_{1c} reduction than placebo patients (Fig. 2, left panels). From 12 to 72 months, a greater proportion of dulaglutide patients experienced a higher rate of HbA_{1c} increase per year compared with the placebo group (Fig. 2, right panels). The difference during the first 12 months persisted after adjustment for diabetes duration, microvascular disease, and BMI. Conversely, during the next 60 months, the difference in the rate of HbA_{1c} change became nonsignificant after adjusting for these three baseline characteristics together.

Mean slopes were calculated to understand the average change in HbA_{1c} per month or year (Fig. 3). This is different from the slope peaks presented in Fig. 2, which represent the rate of HbA_{1c} change per month or year experienced by the highest proportion of patients. These were analyzed using the same treatment periods – 0 to 12 months (Fig. 3*A*) and 12 to 72 months (Fig. 3*B*). The mean rate of HbA_{1c} reduction per month was significantly greater in patients treated with dulaglutide compared with placebo in the analysis for the first 12 months of treatment (Fig. 3*A*), before and after adjusting for baseline duration of diabetes, microvascular disease, BMI, and the combination of these three baseline characteristics. From 12 to 72 months, there was a mean increase in the rate of HbA_{1c} change per year in both groups, and a significantly greater rate of HbA_{1c} increase was observed in the dulaglutide group, before but not after adjusting for all three baseline characteristics together ($P = 0.317$) (Fig. 3*B*). Despite the greater rate of HbA_{1c} increase in the dulaglutide group during this period, mean HbA_{1c} values remained below baseline in the dulaglutide group and below mean HbA_{1c} values in the placebo group (Fig. 1).

CONCLUSIONS

These analyses show that dulaglutide-treated patients had durably reduced

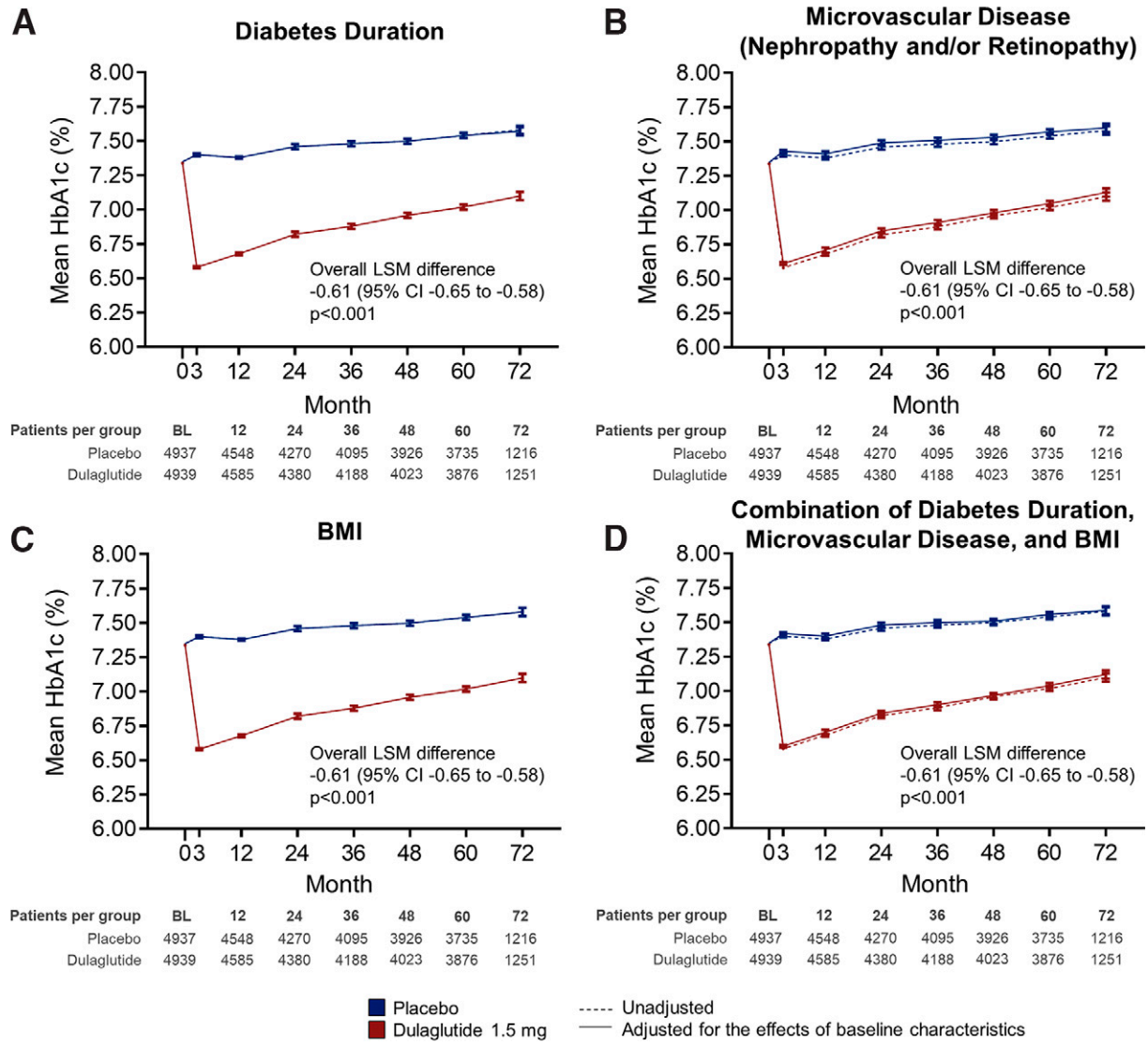

Figure 1—Change from baseline (BL) in HbA_{1c} over 72 months shows that HbA_{1c} values were significantly lower in the dulaglutide group before and after adjusting for baseline duration of diabetes (*A*), microvascular disease (nephropathy and/or retinopathy) (*B*), BMI (*C*), and the combined effect of these three baseline characteristics (*D*). Patients per group represents the number of patients in each treatment group eligible for follow-up at each annual visit after excluding deceased patients. Dashed lines are not visible in some graphs due to solid lines being superimposed on them. Treatment-by-diabetes-duration interaction, treatment-by-microvascular disease interaction, and treatment-by-BMI interaction were not significant for change from baseline in HbA_{1c} ($P = 0.811$, $P = 0.074$, and $P = 0.200$, respectively).

HbA_{1c} levels during therapy for up to 6 years and that this finding was similar in patients with different diabetes durations, different BMIs, and in the presence or absence of microvascular disease. They also show that most of the glucose reduction occurred during the first 12 months of therapy, after which the achieved degree of glycemia was generally maintained with a gradual rise over the subsequent 5 years. The rise during the 12- to 72-month period was greater for the dulaglutide group than for the placebo group, although the difference was not statistically significant after adjusting for baseline duration of diabetes, microvascular disease, and BMI together, and mean HbA_{1c} values remained below baseline in the dulaglutide group and below mean HbA_{1c} values in the placebo group. A greater number of patients achieved HbA_{1c} <7% at each study time point in the dulaglutide group than in the placebo group, which implies that the maintenance of HbA_{1c} target over time was more effective in the dulaglutide group compared with placebo on average.

The slope analysis included in this study further delineates HbA_{1c} changes over prespecified treatment periods and provides an alternative way to analyze these changes. During the first 12 months of treatment and after adjusting for all three studied baseline characteristics, a mean slope of −0.0197% per month was observed in the dulaglutide group. During the following 60 months of treatment, the mean slope of the dulaglutide group was 0.0596% per year after adjusting for the three baseline characteristics. These observed patterns of change can provide insight to clinicians and patients into what the long-term HbA_{1c} outcome could be.

These results are consistent with the AWARD trials, which showed that

Table 1—Baseline characteristics and patient demographics

	Dulaglutide 1.5 mg *n* = 4,939	Placebo *n* = 4,937
Age, years	66.2 (6.5)	66.2 (6.5)
Female sex, *n* (%)	2,303 (46.6)	2278 (46.1)
White race, *n* (%)	3,745 (75.8)	3,732 (75.6)
Duration of diabetes, years	10.5 (7.3)	10.6 (7.2)
HbA_{1c}, %	7.34 (1.1)	7.35 (1.1)
BMI, kg/m^2	32.3 (5.7)	32.3 (5.8)
CVD disease,* *n* (%)	1,554 (31.5)	1,549 (31.4)
CV event,† *n* (%)	1,025 (20.8)	1,006 (20.4)
Hypertension, *n* (%)	4,595 (93.0)	4,604 (93.3)
Previous heart failure, *n* (%)	419 (8.5)	431 (8.7)
Antihyperglycemic medications		
Metformin, *n* (%)	4,013 (81.3)	4,003 (81.1)
Sulfonylurea, *n* (%)	2,266 (45.9)	2,278 (46.1)
Insulin, *n* (%)	1,186 (24.0)	1,173 (23.8)
DPP-4 inhibitor, *n* (%)	266 (5.4)	298 (6.0)
Thiazolidinedione, *n* (%)	99 (2.0)	66 (1.3)
Other glucose-lowering drugs, *n* (%)	14 (0.3)	18 (0.4)

Data are presented as mean (SD) or as otherwise indicated. DPP-4, dipeptidyl peptidase-4. A list of baseline characteristics and patient demographics of the full intention-to-treat population has been previously published (6). *Myocardial infarction, ischemic stroke, unstable angina with electrocardiogram changes, myocardial ischemia on imaging or stress test, or coronary, carotid, or peripheral revascularization. †Myocardial infarction or ischemic stroke.

neither baseline BMI nor duration of diabetes was associated with patients' responses to dulaglutide (3–5). Previous AWARD studies showed that treatment with dulaglutide results in HbA_{1c} reduction early in treatment in populations of study patients at lower risk for CVD (10–14). The current analysis involved a population at higher CVD risk and provides preliminary evidence that dulaglutide may be efficacious for HbA_{1c} reduction across a broad range of patients. The small increase in HbA_{1c} observed over 12–72 months could be explained by disease progression over a 5-year period. The increase in HbA_{1c} coincided with a gradual reduction in the percentage of patients with an HbA_{1c} <7%. Future studies should examine long-term HbA_{1c} outcomes in real-world use.

Patients treated with dulaglutide had a significant decrease in HbA_{1c} regardless of duration of diabetes, the presence of microvascular disease, and BMI. Previous assessments of HbA_{1c} lowering with GLP-1 receptor agonists in people with comorbidities suggested varying effects of diabetes duration (15,16), with no effect of BMI (17,18). The effect of microvascular disease on this outcome has not been previously analyzed.

It is becoming more evident that treatment approaches and goals should be personalized for each individual with type 2 diabetes (1,16). The decisions centered around personalized treatment must consider certain baseline characteristics and risk factors of patients. The American Association of Clinical Endocrinologists (AACE) algorithm and American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) joint statement accounts for such factors (19,20). In some countries, GLP-1 receptor agonists are only considered for patients with a BMI >30 kg/m^2 (21). In this post hoc analysis, HbA_{1c} reduction occurred independently of BMI as well as duration of diabetes and the presence of microvascular disease. This supports previous findings that dulaglutide may benefit a wide range of patients with different stages of disease progression. The current analysis found that the HbA_{1c} benefit associated with dulaglutide occurred early in treatment and that the achieved degree of improvement in glycemia was generally maintained with a gradual rise over 72 months, a finding that is significant given that the ADA recommends early glycemic control to prevent long-term microvascular complications (1). Notably, REWIND trial results suggested that dulaglutide reduced incident renal outcomes (22).

This study has several strengths and limitations. The REWIND trial had the longest duration of treatment and follow-up for a GLP-1 receptor agonist in a CV outcomes trial to date (23,24). The length of this study allowed us to evaluate baseline characteristics, such as duration of diabetes, microvascular disease, and BMI, and changes in HbA_{1c} for up to 72 months. In addition, the REWIND trial has the highest representation of people with type 2 diabetes and CV risk factors (primary prevention), as opposed to people with a history of established CVD (secondary prevention), of any GLP-1 receptor agonist CV outcomes trial to date (6). Finally, patients' baseline HbA_{1c} was typical of those in the general population of people with diabetes. This post hoc analysis allowed us to evaluate patients treated with dulaglutide in this population, especially focusing on the sustained reduction of HbA_{1c} with a gradual rise for up to 72 months.

The main limitation of this study is that it is a post hoc analysis, and results should be interpreted carefully. This analysis is also limited by the fact that the REWIND trial was not designed to achieve or maintain certain HbA_{1c} targets. In addition, it is limited by the fact that HbA_{1c} levels were not concealed and investigators used a variety of different glucose-lowering agents (other than GLP-1 receptor agonists) to control HbA_{1c} levels according to their best judgment and not according to a protocol-defined target. In the REWIND study, treatment adherence to dulaglutide exceeded that of real-world observations, although real-world studies on adherence to dulaglutide had shorter follow-ups (25,26). Drop-in antihyperglycemic therapies clearly could have had an effect on the change in HbA_{1c} from baseline, but the reverse may also be true, as change in HbA_{1c} could have an effect on the introduction of drop-in therapies at different time points in both treatment groups; therefore, an analysis on the impact of drop-in therapies on the change in HbA_{1c} is not presented as there is no clear assignment of response and predictor variables in this case. Standard care varied from patient to patient, although similar antihyperglycemic

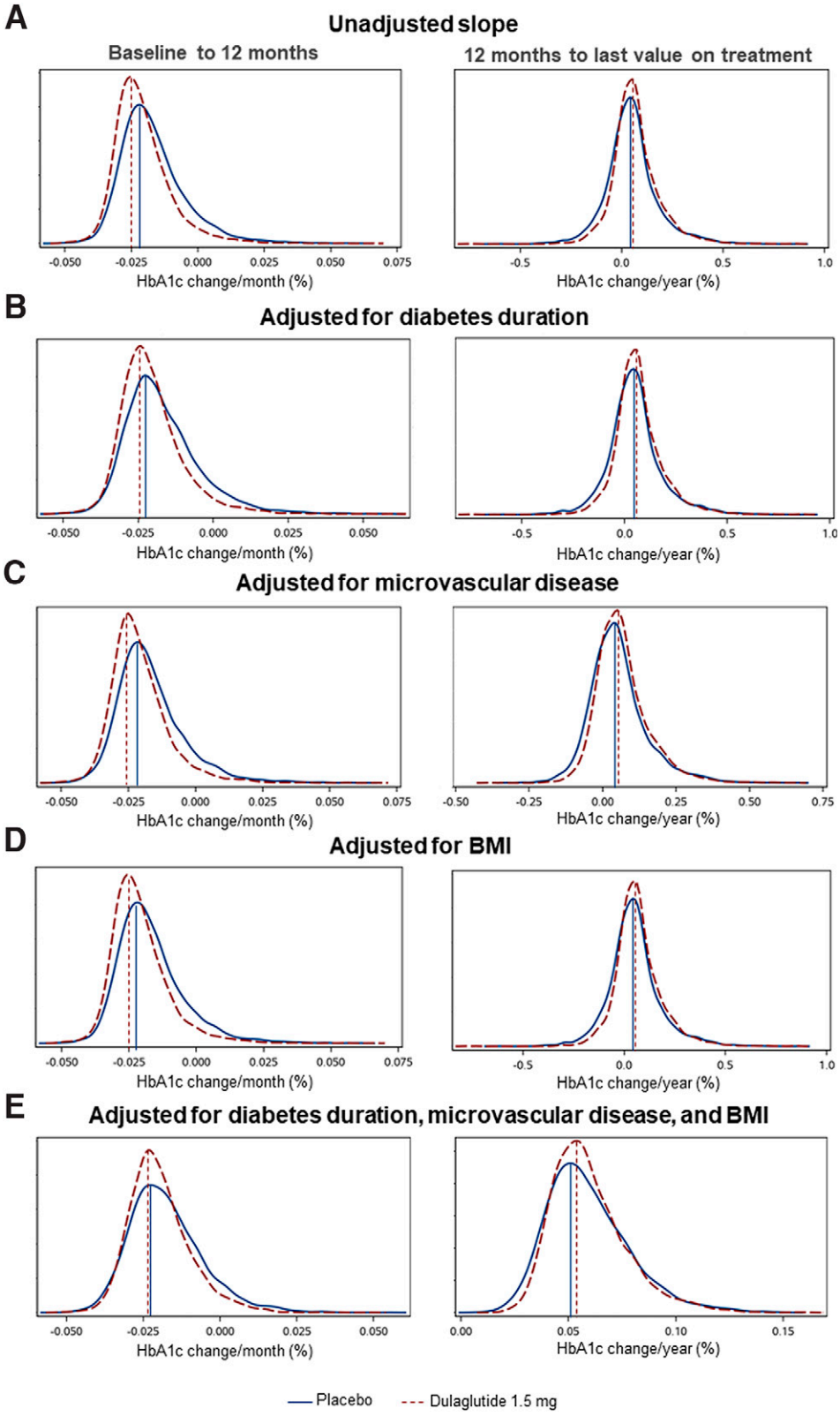

Figure 2—Distribution of individual patient slopes (HbA_{1c} change per month or year [%]) shows a greater left shift for the dulaglutide group from baseline to 12 months (left panels) and a greater right shift from 12 to 72 months (right panels) compared with placebo. The negative rates observed from baseline to 12 months (left panels) indicate a slope reduction, and the greater left shift of the dulaglutide group indicates a greater rate of HbA_{1c} reduction per month relative to placebo. The positive rates observed from 12 to 72 months (right panels) indicate a slope increase, and the greater right shift of the dulaglutide group indicates a greater rate of HbA_{1c} increase per year relative to placebo. The peaks of the curves (marked with vertical lines) indicate the HbA_{1c} change per month or year experienced by the highest proportion of patients. Changes in HbA_{1c} per month or year were obtained using unadjusted data (*A*); after adjustment for diabetes duration (*B*), microvascular disease (*C*), or BMI (*D*); and after adjustment for the combined effect of the three baseline characteristics (*E*).

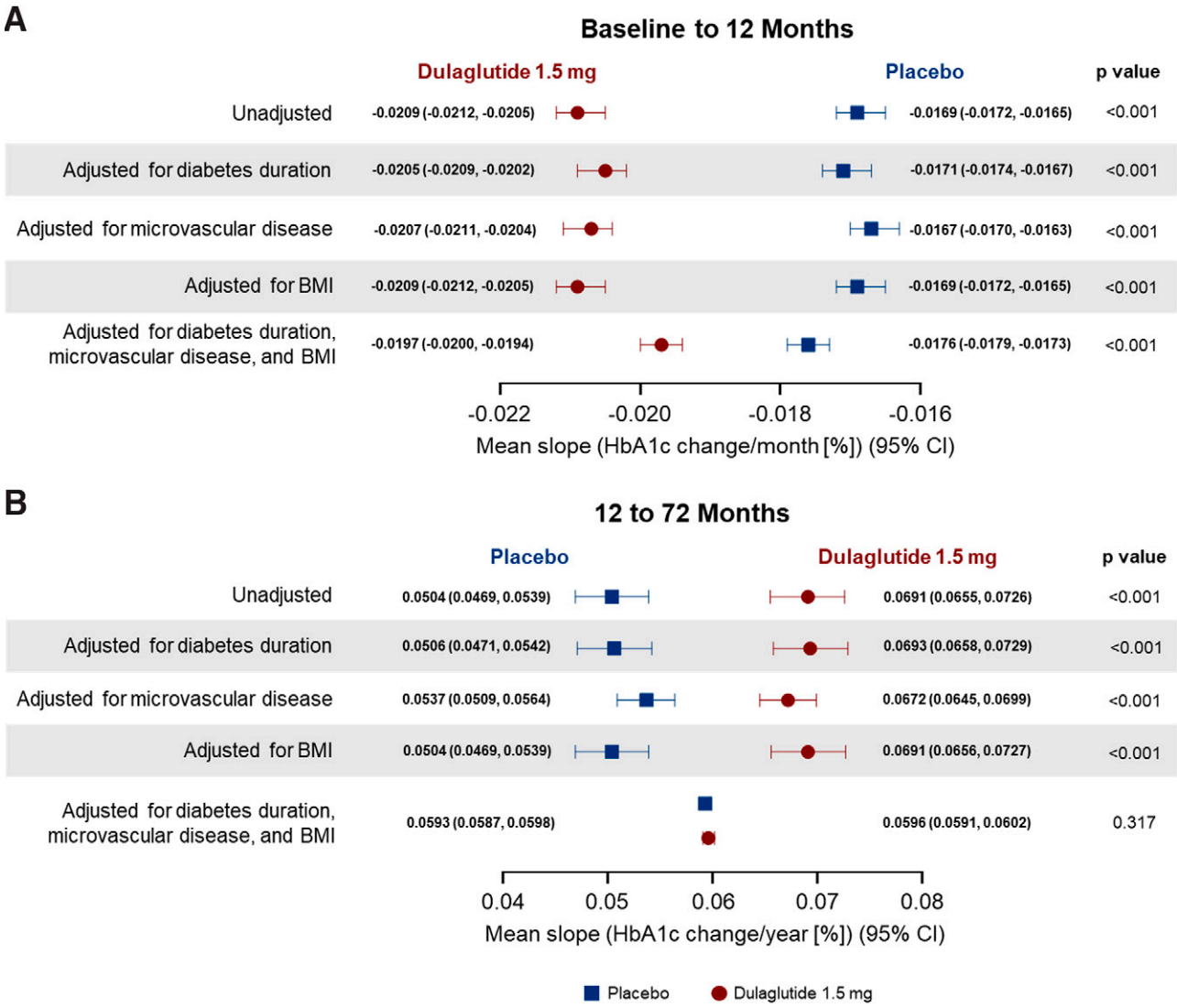

Figure 3—*A*: Mean slopes (HbA_{1c} change per month or year [%]) show a greater rate of reduction in HbA_{1c} per month in patients treated with dulaglutide from baseline to 12 months, with or without adjustment for baseline characteristics. *B*: Conversely, a greater rate of increase in HbA_{1c} per year was seen in patients treated with dulaglutide from 12 to 72 months, with the exception of the data adjusted for the combination of diabetes duration, microvascular disease, and BMI. Mean slopes were calculated from individual patient slopes represented in Fig. 2 and indicate the mean rate of change in HbA_{1c} experienced by patients per month or year during the specified treatment period.

medications were used in the two treatment groups, with greater sulfonylurea and insulin use in the placebo group by the end of the study. It is unknown whether findings are applicable to older patients with a high CVD risk and/or poorer glycemic control.

In conclusion, middle-aged and older patients with type 2 diabetes and a modestly increased risk of CVD treated with dulaglutide 1.5 mg had a robust, long-term reduction of HbA_{1c}, regardless of important baseline characteristics. HbA_{1c} reduction was most evident in the initial 12 months of treatment and increased at a similar rate to placebo from 12 to 72 months after adjusting for baseline diabetes, microvascular disease (nephropathy and/or retinopathy), and BMI together.

Acknowledgments. Ana Hickey, PhD, Eli Lilly and Company, provided medical writing and editorial services.

Funding. D.X. has received research grants from the UK Medical Research Council, and the Wellcome Trust.

Duality of Interest. Funding of this study is from Eli Lilly and Company. A.Y.M.K., J.M.M., and M.K. are employees and stockholders of Eli Lilly and Company. S.R. is an employee of Eli Lilly and Company. H.C.G. holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care and 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. J.B. has received research grants from Eli Lilly and Company (REWIND), ReCor (Radiance I and II), and Ablative Solutions (Target BP). D.X. discloses research grants from Cadila, Boehringer Ingelheim, AstraZeneca, Sanofi, Eli Lilly and Company, Pfizer, and Bristol-Myers Squibb, and speaker's fees from Sanofi and Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.Y.M.K. and M.K. contributed to the conception of the work. A.Y.M.K., H.C.G., and M.K. designed the analysis plan. S.R. was responsible for the statistical analysis. A.Y.M.K., J.B., J.M.M., and S.R. analyzed the data. A.Y.M.K., H.C.G., J.B., D.X., J.M.M., S.R., and M.K. interpreted the results. A.Y.M.K.

and S.R. helped to draft the manuscript. A.Y.M.K., H.C.G., J.B., D.X., J.M.M., S.R., and M.K. participated in the critical review of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. A.Y.M.K. and M.K. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract and poster form at the American College of Cardiology (ACC).20/World Congress of Cardiology (WCC) Virtual Annual Scientific Sessions held 28–30 March 2020 and the 56th Annual Meeting of the European Association for the Study of Diabetes held 21–25 September 2020.

References

1. American Diabetes Association. Glycemic targets: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S73–S84
2. 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;43:487–493
3. 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;20:409–418
4. Gentilella R, Sesti G, Vazquez L, et al. Dulaglutide is an effective treatment for lowering HbA1c in patients with type 2 diabetes regardless of body mass index. Diabetes Obes Metab 2019;21:2660–2666
5. Wysham C, Guerci B, D'Alessio D, Jia N, Botros FT. Baseline factors associated with glycaemic response to treatment with once-weekly dulaglutide in patients with type 2 diabetes. Diabetes Obes Metab 2016;18:1138–1142
6. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130
7. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Trial Investigators. 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;20:42–49
8. Senn S. Change from baseline and analysis of covariance revisited. Stat Med 2006;25:4334–4344
9. Wanner C, Heerspink HJL, Zinman B, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and kidney function decline in patients with type 2 diabetes: a slope analysis from the EMPA-REG OUTCOME trial. J Am Soc Nephrol 2018;29:2755–2769
10. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care 2014;37:2149–2158
11. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care 2014;37:2159–2167
12. Skrivanek Z, Gaydos BL, Chien JY, et al. Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5). Diabetes Obes Metab 2014;16:748–756
13. Pozzilli P, Norwood P, Jódar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes Obes Metab 2017;19:1024–1031
14. Dungan KM, Weitgasser R, Perez Manghi F, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes Obes Metab 2016;18:475–482
15. Rosenstock J, Shenouda SK, Bergenstal RM, et al. Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes. Diabetes Care 2012;35:955–958
16. Davies MJ, Leiter LA, Guerci B, et al. Impact of baseline glycated haemoglobin, diabetes duration and body mass index on clinical outcomes in the LixiLan-O trial testing a titratable fixed-ratio combination of insulin glargine/lixisenatide (iGlarLixi) vs insulin glargine and lixisenatide monocomponents. Diabetes Obes Metab 2017;19:1798–1804
17. Montanya E, Fonseca V, Colagiuri S, Blonde L, Donsmark M, Nauck MA. Improvement in glycated haemoglobin evaluated by baseline body mass index: a meta-analysis of the liraglutide phase III clinical trial programme. Diabetes Obes Metab 2016;18:707–710
18. Wolffenbuttel BHR, Van Gaal L, Durán-Garcia S, Han J. Relationship of body mass index with efficacy of exenatide twice daily added to insulin glargine in patients with type 2 diabetes. Diabetes Obes Metab 2016;18:829–833
19. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2019 executive summary. Endocr Pract 2019;25:69–100
20. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
21. Meetoo D, Alsomali S. NG28: promoting patient-centred care for adults with type 2 diabetes. Nurse Prescr. 2016;14:236–245
22. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet 2019;394:131–138
23. 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;7:776–785
24. 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;9:653–662
25. Robinson S, Boye KS, Mody R, et al. Real-world effectiveness of dulaglutide in patients with type 2 diabetes mellitus: a literature review. Diabetes Ther 2020;11:1437–1466
26. Mody R, Yu M, Nepal B, Konig M, Grabner M. Adherence and persistence among patients with type 2 diabetes initiating dulaglutide compared with semaglutide and exenatide BCise: 6-month follow-up from US real-world data. Diabetes Obes Metab 2021;23:106–115