Received: 30 October 2017 | Revised: 7 February 2018 | Accepted: 18 February 2018

DOI: 10.1002/edm2.16

ORIGINAL ARTICLE

WILEY Endocrinology, Diabetes & Metabolism Open Access

Slope of change in HbA_{1c} from baseline with empagliflozin compared with sitagliptin or glimepiride in patients with type 2 diabetes

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Funding information
Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Summary

Aims: To analyse the effect of baseline glycated haemoglobin (HbA_{1c}) on the reduction in HbA_{1c} with empagliflozin compared with sitagliptin or glimepiride in patients with type 2 diabetes.

Materials and methods: Using regression analyses of individual patient data from two Phase III studies, we compared the change in HbA_{1c} according to a unit change in baseline HbA_{1c} (the slope) with empagliflozin 10 mg or 25 mg vs sitagliptin (monotherapy) after 24 weeks, and with empagliflozin 25 mg vs glimepiride (as add-on to metformin) after 52 weeks.

Results: Steeper slopes of HbA1c decline were observed with empagliflozin 10 or 25 mg vs sitagliptin monotherapy at week 24. Regression analysis showed slopes of −0.59 (95% CI −0.70, −0.47), −0.49 (95% CI −0.62, −0.37) and −0.29 (95% CI −0.42, −0.15) for empagliflozin 10 mg, empagliflozin 25 mg and sitagliptin, respectively ($P < .001$ and $P < .05$ for empagliflozin 10 mg and empagliflozin 25 mg, respectively, vs sitagliptin). Similarly, a steeper slope of HbA_{1c} decline was observed with empagliflozin 25 mg vs glimepiride as add-on to metformin at week 52. Regression analysis showed slopes of − 0.52 (95% CI −0.59, −0.44) and −0.32 (95% CI −0.39, −0.25) for empagliflozin 25 mg and glimepiride, respectively ($P < .001$ for empagliflozin 25 mg vs glimepiride).

Conclusions: Incremental reductions in HbA_{1c} with increasing baseline HbA_{1c} are greater with empagliflozin compared with sitagliptin or glimepiride in patients with type 2 diabetes.

KEYWORDS
blood glucose, glycosylated haemoglobin A, sodium-glucose transporter 2

1 | INTRODUCTION

It is well documented that the higher the baseline HbA_{1c}, the greater the decline in HbA_{1c} when oral antidiabetes agents are given to patients with type 2 diabetes.[1-4] In patients with type 2 diabetes treated with an oral antidiabetes agent for ≥12 weeks, a 0.2%-0.5% greater decrement in HbA_{1c} has been reported for every 1% higher baseline HbA_{1c}.[1] In a meta-regression analysis of randomized controlled trials, treatment with dipeptidyl peptidase-4 (DPP4) inhibitors for ≥12 weeks led to a ≥ 0.26% greater reduction in HbA_{1c} for every percentage point of baseline HbA_{1c} >7%.[2] The universality of these findings suggests a nonspecific mechanism. This mechanism

has yet to be determined, but could be related to on-treatment improvements in beta-cell or alpha-cell functions.[5,6]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors inhibit sodium-glucose cotransport in the proximal tubule. This reduces the blood glucose level at which the capacity for glucose transport by SGLTs is saturated, and therefore, the blood glucose level at which glucose is spilled into the urine—also referred to as the renal threshold for glucose.[7] By lowering the renal threshold for glucose, glucose that would otherwise be reabsorbed in the kidney is excreted into the urine. The constitutive renal threshold for plasma glucose in patients with type 2 diabetes is typically in the range of ~10-11 mmol/L (180-200 mg/dL) without SGLT2 inhibitor treatment.[8] The amount of filtered glucose in the kidney is dependent on glomerular filtration rate (GFR) and blood glucose. Therefore, the amount of reabsorbed glucose increases linearly with blood glucose (for a given GFR) until the renal threshold for glucose is reached; with higher glucose levels, the reabsorbed glucose stays constant except for a minor splay between the two parts of the absorption curve.[9,10] Glucose lowering with SGLT2 inhibitors is expected to increase linearly with increasing blood glucose up to approximately 10-11 mmol/L (representing the renal threshold for glucose in the untreated situation). This effect of SGLT2 inhibitors could differ from, and could possibly be in addition to, a nonspecific increase in glucose lowering with increasing blood glucose common to any glucose-lowering intervention. No study has compared the slope of the decrement in HbA_{1c} in relation to baseline HbA_{1c} with an SGLT2 inhibitor vs other oral antidiabetes agents.

Empagliflozin is a potent and selective inhibitor of SGLT2.[11] In Phase III trials in patients with type 2 diabetes, empagliflozin 10 mg/d and 25 mg/d as monotherapy or as add-on therapy significantly reduced HbA_{1c} compared with placebo after 24 weeks of treatment.[12-15] The reduction in HbA_{1c} with empagliflozin monotherapy was significantly greater in patients with baseline HbA_{1c} ≥8.5% compared with patients with baseline HbA_{1c} <8.5%.[12]

We hypothesized that with increasing baseline HbA_{1c} up to ~ 11% (ie, with a large proportion of blood glucose below the untreated renal threshold for glucose), empagliflozin would produce a greater HbA_{1c} reduction in patients with type 2 diabetes compared with antidiabetes agents with other mechanisms of action. To test this hypothesis, we compared the slopes of regression in HbA_{1c} with empagliflozin vs with sitagliptin or glimepiride using data from two randomized controlled trials in patients with type 2 diabetes. A major advantage of this analysis compared with previous analyses with other oral antidiabetes agents is the use of individual patient data as opposed to mean data.

2 | METHODS

2.1 | Patients and study designs

Study 1 (EMPA-REG MONO™) was a Phase III, double-blind, active- and placebo-controlled trial. Drug-naïve patients with type 2 diabetes (no oral or injected antidiabetes medication for ≥12 weeks prior to randomization), aged ≥18 years, with body mass index (BMI) ≤45 kg/m^2 and HbA_{1c} ≥7% to ≤10%, were randomized to receive empagliflozin 10 mg/d, empagliflozin 25 mg/d, sitagliptin 100 mg/d or placebo for 24 weeks. The primary end-point was change from baseline in HbA_{1c} at week 24.[12]

Study 2 (EMPA-REG H2H-SU™) was a Phase III, double-blind, active-controlled trial. Metformin (immediate release, IR)-treated patients with type 2 diabetes, aged ≥18 years, with BMI ≤45 kg/m^2 and HbA_{1c} ≥7% to ≤10% were randomized to receive empagliflozin 25 mg/d or glimepiride 1-4 mg/d as add-on to metformin for 104 weeks. Patients were required to be on an unchanged dose of metformin IR (≥1500 mg/d, maximum tolerated dose or maximum dose according to the local label) for ≥12 weeks prior to randomization. Glimepiride was initiated at a dose of 1 mg/d, with a recommendation for uptitration if fasting plasma glucose was >6.1 mmol/L to 2 mg/d at week 4, 3 mg/d at week 8 and 4 mg/d at week 12. The mean ± SD maximum titrated glimepiride dose was 2.71 ± 1.24 mg/d. The primary end-point was change from baseline in HbA_{1c} at week 52 and week 104.[16]

2.2 | Statistical analyses

To compare the decline in HbA_{1c} with empagliflozin 10 mg and 25 mg vs sitagliptin after 24 weeks (Study 1) and with empagliflozin 25 mg vs glimepiride after 52 weeks and 104 weeks (Study 2), the least squares (LS) mean change from baseline in HbA_{1c} in each study was analysed using a mixed model for repeated measurements (MMRMs). The model included the fixed categorical effects of treatment, visit and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline, baseline-by-treatment, baseline-by-visit interaction and baseline-by-treatment-by-visit interaction. An unstructured covariance model was used to model the within-patient measurements. This model allowed estimation of the treatment-specific slope (ie, the magnitude of change in HbA_{1c} for a unit change in baseline HbA_{1c}) and its 95% confidence interval (CI) for the regression of change from baseline in HbA_{1c} on the baseline HbA_{1c}. *P*-values for the test of a difference of the slopes between treatment groups were calculated. Regression lines from scatter plots were estimated from a simple linear model within each treatment group, for which the change from baseline at the week of interest was calculated as the intercept + baseline HbA_{1c}*slope. Thus, the difference between the slopes and the regression lines in the scatter plots was analysed using different models; slope values from both approaches are reported. Analyses were conducted in all patients who received ≥1 dose of study medication and who had a baseline HbA_{1c} measurement. HbA_{1c} values are presented as %. The following formula can be used to convert values to mmol/mol: [HbA_{1c} (%) - 2.15] × 10.929.

3 | RESULTS

3.1 | Study 1

Baseline patient characteristics were similar between the empagliflozin and sitagliptin groups (Table 1). LS mean reductions

TABLE 1 Baseline characteristics

	Study 1			Study 2	
	Empagliflozin 10 mg (n = 224)	Empagliflozin 25 mg (n = 224)	Sitagliptin (n = 223)	Empagliflozin 25 mg (n = 765)	Glimepiride (n = 780)
Male, n (%)	142 (63)	145 (65)	141 (63)	432 (56)	421 (54)
Race, n (%)					
Asian	143 (64)	144 (64)	143 (64)	254 (33)	253 (32)
White	77 (34)	73 (33)	76 (34)	498 (65)	519 (67)
Other	4 (2)	7 (3)	4 (2)	13 (2)	8 (1)
Age, years	56.2 ± 11.6	53.8 ± 11.6	55.1 ± 9.9	56.2 ± 10.3	55.7 ± 10.4
Time (y) since diagnosis of type 2 diabetes, n (%)					
≤1	87 (39)	91 (41)	93 (42)	79 (10)	93 (1.2)
>1 to 5	92 (41)	83 (37)	86 (39)	341 (45)	336 (43)
>5	45 (20)	50 (22)	44 (20)	345 (45)	351 (45)
Body weight, kg	78.4 ± 18.7	77.8 ± 18.0	79.3 ± 20.4	82.5 ± 19.2	83.0 ± 19.2
eGFR, mL/min/1.73 m^2,	87.7 ± 19.2	87.6 ± 18.3	87.6 ± 17.3	88.2 ± 18.9	88.2 ± 17.8
HbA_{1c}, %	7.87 ± 0.88	7.86 ± 0.85	7.85 ± 0.79	7.92 ± 0.81	7.92 ± 0.86
SBP, mm Hg	133.0 ± 16.6	129.9 ± 17.5	132.5 ± 15.8	133.4 ± 15.9	133.5 ± 16.0
DBP, mm Hg	79.2 ± 9.6	78.3 ± 9.4	80.1 ± 10.0	79.5 ± 9.6	79.4 ± 9.2

Values are mean ± SD, unless otherwise stated, in all patients who received ≥1 dose of study medication and who had a baseline HbA_{1c} measurement.
DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate by Modification of Diet and Renal Disease (MDRD) equation; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure.

in HbA_{1c} at week 24 by baseline HbA_{1c} are shown in Figure 1. A steeper slope of HbA_{1c} reduction was observed with empagliflozin 10 mg or 25 mg compared with sitagliptin. The regression analysis showed slopes of −0.59 (95% CI: −0.70, −0.47), −0.49 (95% CI −0.62, −0.37) and −0.29 (95% CI −0.42, −0.14) for empagliflozin 10 mg, empagliflozin 25 mg and sitagliptin, respectively. The slope was significantly different for both empagliflozin 10 mg ($P < .001$) and empagliflozin 25 mg ($P = .023$) compared with sitagliptin. There was no significant difference between the slopes for empagliflozin 10 mg vs empagliflozin 25 mg. Scatter plots of change from baseline in HbA_{1c} at week 24 by baseline HbA_{1c} are shown in Figure S1. The conclusions from slopes derived from regression lines of the scatter plots were similar to those from the LS means slope analyses (Figure S1).

3.2 | Study 2

Baseline patient characteristics were similar between the empagliflozin and glimepiride groups (Table 1). LS mean reductions in HbA_{1c} at week 52 and week 104 by baseline HbA_{1c} are shown in Figure 2. Steeper slopes of HbA_{1c} reduction were observed with empagliflozin 25 mg than with glimepiride. The regression analysis showed slopes of −0.52 (95% CI −0.59, −0.44) and −0.32 (95% CI −0.39, −0.25) for empagliflozin 25 mg and glimepiride, respectively, at week 52 and −0.48 (95% CI −0.56, −0.40) and −0.37 (95% CI −0.45, −0.28) for empagliflozin 25 mg and glimepiride, respectively, at week 104. The slopes were steeper for empagliflozin 25 mg compared with glimepiride, reaching significance at week 52 ($P < .001$), and were of borderline significance at week 104 ($P = .07$). The slopes relating to the reduction in HbA_{1c} as a function of time for empagliflozin-treated patients in this study were very similar to the slope for empagliflozin 25 mg in Study 1. Scatter plots of change from baseline in HbA_{1c} at weeks 52 and 104 by baseline HbA_{1c} are shown in Figure S2. The conclusions from slopes derived from regression lines of the scatter plots were similar to those from the LS means slope analyses (Figure S2).

4 | DISCUSSION

We analysed the effect of baseline HbA_{1c} on the slope of HbA_{1c} reduction with empagliflozin compared with two other commonly used antidiabetes agents (sitagliptin and glimepiride) using individual patient data from two randomized controlled trials.[12,16] Our findings demonstrate that the decrement in HbA_{1c} by baseline HbA_{1c}, as reflected by the slope of HbA_{1c} reduction, was greater with empagliflozin compared to both sitagliptin and glimepiride in patients with type 2 diabetes. The similar slopes of regression in HbA_{1c} with empagliflozin 25 mg in Studies 1 and 2 emphasize the reproducibility of the empagliflozin results. Based on the results of Study 1, it can be predicted that for a starting HbA_{1c} of 10.0%, 9.0% and 8.0%,

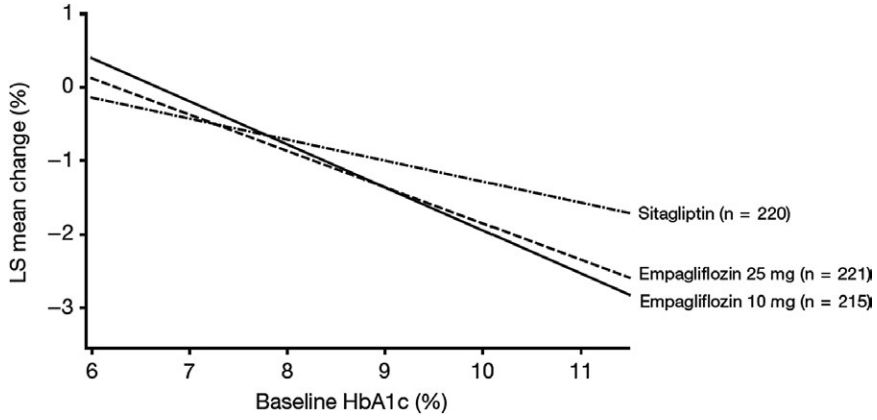

FIGURE 1 LS mean change in HbA_{1c} by baseline HbA_{1c} with empagliflozin 10 mg and 25 mg and sitagliptin monotherapy after 24 wk analysed using a mixed model for repeated measurements. HbA_{1c}—glycated haemoglobin

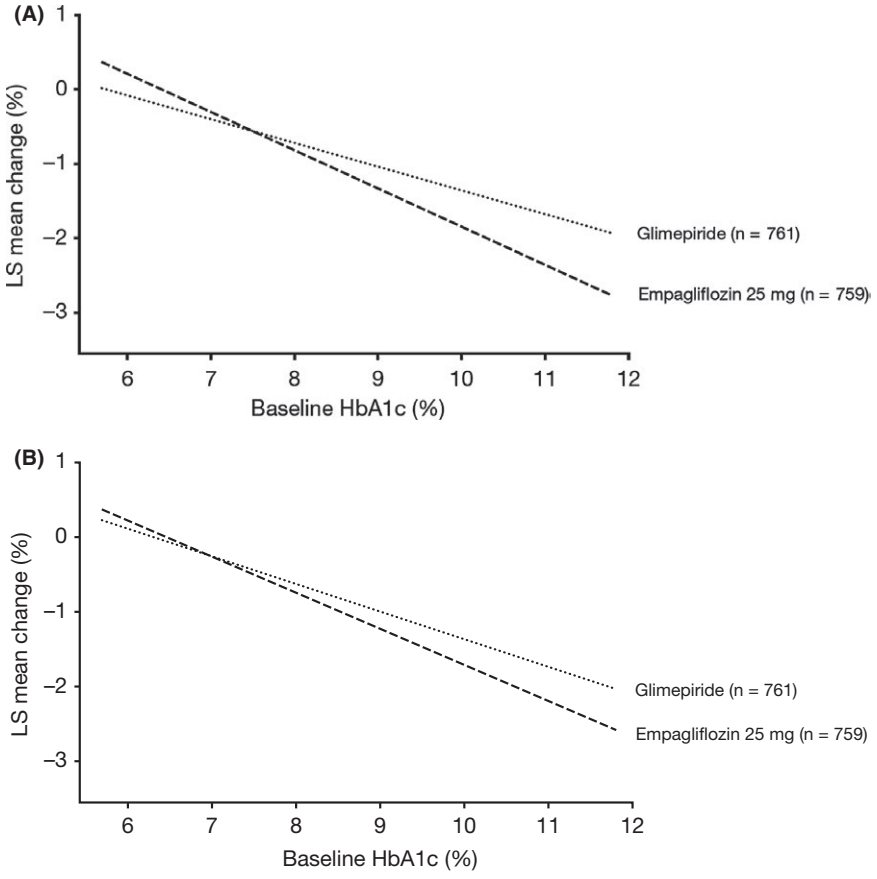

FIGURE 2 LS mean change in HbA_{1c} by baseline HbA_{1c} with empagliflozin 25 mg and glimepiride 1-4 mg as add-on to metformin (A) after 52 wk and (B) after 104 wk analysed using a mixed model for repeated measurements. HbA_{1c}—glycated haemoglobin

the decline in HbA_{1c} after 24 weeks is −1.85%, −1.36% and −0.87%, respectively, with empagliflozin 25 mg and −1.28%, −1.00% and −0.71%, respectively, with sitagliptin. Based on the results of Study 2, it can be predicted that for a starting HbA_{1c} of 10.0%, 9.0%, and 8.0%, the decline in HbA_{1c} after 52 weeks is −1.85%, −1.33% and −0.82%, respectively, with empagliflozin 25 mg and −1.35%, −1.03% and −0.71%, respectively, with glimepiride. In Study 2, the difference between the slopes for empagliflozin and glimepiride narrowed slightly and nonsignificantly at 104 weeks vs 52 weeks. Although this could reflect a waning of the effect of empagliflozin, we believe that this most likely represents a chance observation. Most importantly, this difference did not approach statistical significance. It also is possible that the small nonsignificant difference in the slope could be explained by the fact that urinary glucose excretion would be expected to decrease as the HbA_{1c} declined in the empagliflozin group. However, the reduction in HbA_{1c} was near maximal at 12 weeks and did not change thereafter.

The observation of greater reductions in HbA_{1c} with increasing baseline HbA_{1c} is consistent with the mechanism of action of SGLT2 inhibitors, which act by reducing the renal threshold for glucose spillage into the urine to values less than the normal fasting plasma glucose concentration.[9] SGLT2 inhibitors target glucose that would otherwise be reabsorbed by the kidney. Thus, it is expected that the higher the glucose concentration up till the

(untreated) renal threshold for glucose, the greater the incremental excretion of glucose into the urine with SGLT2 inhibition, and, ultimately, the greater the expected decline in HbA_{1c}. It should be noted that the reduction in HbA_{1c} observed with SGLT2 inhibitors is approximately 50% of that expected based on urinary glucose excretion, likely because of an increase in endogenous glucose production[17] and increased glucose reabsorption by SGLT1, which is capable of reabsorbing up to 30%-40% of the filtered glucose load.[7] If the increase in endogenous glucose production were to be prevented or if glucose reabsorption by SGLT1 were blocked, the decline in HbA_{1c} for any given starting HbA_{1c} would potentially be even greater with empagliflozin compared to sitagliptin or glimepiride. Further, the slope of HbA_{1c} reduction in other commonly used antidiabetes agents will be influenced by their mechanism of action, that is, increased insulin secretion, glucagon suppression, inhibition of endogenous glucose production or insulin sensitization, which impose physiological limits to their efficacy. SGLT2 inhibitors reduce the renal threshold for glucose to well below the fasting plasma glucose concentration observed in individuals with normal glucose tolerance.[9] This may contribute to a disproportionately greater HbA_{1c} reduction with SGLT2 inhibitors than with other antidiabetes agents with increasing plasma glucose levels as long as GFR is not significantly reduced. Glycosuria with empagliflozin decreases with decreasing estimated GFR,[18] and in patients with type 2 diabetes who have a reduced GFR, the glucose-lowering effect of empagliflozin is reduced.[19]

These are some limitations to the present analyses. First, these were post-hoc analyses. Second, these exploratory analyses did not include the placebo arm of Study 1; this is different from the approach of the primary analysis of the study that included placebo as the main comparator.

In conclusion, reductions in HbA_{1c} with increasing baseline HbA_{1c} are greater with empagliflozin compared with sitagliptin or glimepiride in patients with type 2 diabetes.

ACKNOWLEDGEMENTS

Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Elizabeth Ng of FleishmanHillard Fishburn, London, the United Kingdom, during the preparation of this article. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version. Some of the data included in this manuscript were presented in abstract form at the 75th Scientific Sessions of the American Diabetes Association, Boston, Massachusetts, 5-9 June 2015.

CONFLICT OF INTERESTS

The studies included in these analyses were funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. RAD discloses membership of Advisory Boards (Astra Zeneca, Novo Nordisk, Janssen, Boehringer-Ingelheim, Intarcia, Elcelyx), research support (Boehringer-Ingelheim, Takeda, Astra Zeneca, Janssen) and speaker's bureau (Novo-Nordisk, Astra Zeneca). EF discloses membership of Scientific Advisory Boards (Boehringer Ingelheim/Eli Lilly and Company, Merck Sharp & Dohme, Sanofi), ad hoc consulting (Janssen, AstraZeneca), occasional speaking engagements (AstraZeneca, Takeda, Novo Nordisk, Sanofi, Mitsubishi, Eli Lilly and Company, Boehringer Ingelheim, Merck Sharp & Dohme) and research grant support (Eli Lilly and Company and Boehringer Ingelheim). GS discloses membership of Advisory Boards (Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Takeda and Johnson & Johnson) and is a speaker for Eli Lilly, Boehringer Ingelheim, Takeda, AstraZeneca, Bristol-Myers Squibb, Sanofi, Merck and Novo Nordisk. SH, UE, CL and SSL are employees of Boehringer Ingelheim. TH was an employee of Boehringer Ingelheim at the time these analyses were conducted. SSL owns shares in Novo Nordisk A/S and shares in dynamically traded investment funds which may own stocks from pharmaceutical companies.

AUTHOR CONTRIBUTIONS

RAD, EF, GS, SH, UE, CL, TH and SSL contributed to the interpretation of data and to the drafting of the manuscript and have approved the final version. All authors had full access to the study data and were responsible for the final decision to submit the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: DeFronzo RA, Ferrannini E, Schernthaner G, et al. Slope of change in HbA_{1c} from baseline with empagliflozin compared with sitagliptin or glimepiride in patients with type 2 diabetes. *Endocrinol Diab Metab*. 2018;1:e16. https://doi.org/10.1002/edm2.16