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ORIGINAL RESEARCH

The Association Between HbA1c Levels and the Risk of Myocardial Infarction and Stroke in People with Type 2 Diabetes: A Post Hoc Analysis of the REPRESENT Study

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ABSTRACT

Introduction: The aim of this work was to analyze the association between baseline glycated hemoglobin (HbA1c) levels and other factors on the risk of first myocardial infarction (MI) and on the risk of first stroke in people with type 2 diabetes (T2D) in Spain.

Methods: This post hoc analysis of the REPRESENT study used the IQVIA electronic medical records database. Cumulative incidences were estimated using the Kaplan–Meier method, and Cox regression models were used to identify associated risk factors, including gender, age, HbA1c, or prior cardiovascular disease (other than MI/stroke).

Results: Median follow-up was 7 years. In people without prior MI/stroke, the incidence (95% confidence interval [CI]) of first MI/stroke was 0.31 (0.28–0.34) and 0.18 (0.15–0.20) events per 100 patient-years, respectively. Baseline HbA1c levels < 6.5% were independently associated with lower risk of first MI (hazard ratio [HR] 0.76 [95% CI 0.61–0.94]) and of first stroke (HR 0.74 [95% CI 0.56–0.98]). Male sex, age ≥ 50 years, and previous cardiovascular disease were independently associated with a higher risk of MI/stroke.

Conclusions: This analysis found an association between baseline HbA1c levels < 6.5% and lower risk of a first MI or stroke in a T2D cohort in Spain, suggesting a role of stringent glycemic control in the prevention of cardiovascular complications.

Prior Presentation: This work was presented at the 33rd National Congress of the Spanish Society for Diabetes (SED) on 27–29 April 2022, in Las Palmas de Gran Canaria, Spain; and at the 63rd Spanish Society for Endocrinology and Nutrition (SEEN) Congress on 26–28 October 2022, in Las Palmas de Gran Canaria, Spain.

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PLAIN LANGUAGE SUMMARY

People with type 2 diabetes (T2D) are known to have a greater risk of cardiovascular disease, including heart attacks (also known as myocardial infarctions [MIs]) and strokes, than people without T2D. The REPRESENT study looked at the rates of first MI/stroke over a 7-year period in a group of Spanish people with T2D and analyzed the relationship between the risk of first MI/stroke and low blood sugar levels at the start of the study, as well as other factors such as age, sex, and previous cardiovascular disease. Blood sugar levels were measured using glycated hemoglobin (HbA1c), and stringent glycemic control, was defined by an HbA1c of < 6.5%. Hb1c levels < 6.5% at the start of the study were associated with a decrease in the risk of a first MI and a decrease in the risk of first stroke. Men, those aged 50 years or older, and those with previous cardiovascular disease had an increased risk of first MI or stroke compared with women, those aged < 50 years and those without previous cardiovascular disease. The results of this analysis of people with T2D in Spain suggest that HbA1c of < 6.5% have a role to play in preventing heart-related complications in people with T2D.

Keywords: Glycated hemoglobin; Myocardial infarction; Stroke; Type 2 diabetes

Key Summary Points
Why carry out this study?
People with type 2 diabetes (T2D) have an increased risk of cardiovascular disease, including myocardial infarction (MI) and stroke.
Although there is evidence showing a relationship between glycated hemoglobin (HbA1c) < 7% and a lower risk of complications, very few studies have analyzed the benefits of more stringent HbA1c levels (i.e., HbA1c < 6.5%).
What was learned from the study?
Stringent baseline HbA1c levels, HbA1c < 6.5%, were independently associated with a lower risk of first MI and of first stroke, while male sex, age ≥ 50 years, and previous cardiovascular disease were independently associated with a higher risk of MI/stroke.
The results of this post hoc analysis are consistent with prior studies and provide further information on the importance of stringent glycemic control and cardiovascular risk factor management in specific groups of people with T2D.

INTRODUCTION

Cardiovascular disease (CVD) affects approximately 32% of people with type 2 diabetes (T2D) and is their leading cause of mortality [1, 2]. According to the International Diabetes Federation, people with diabetes are two- to threefold more likely to develop CVD than people without diabetes [3]. Diabetes is recognized as a major cause of myocardial infarction (MI) and stroke, and people with T2D with a history of MI have > 40% increased risk of recurrence [4].

Given the high incidence and economic burden of CVD in T2D, the control of cardiovascular (CV) risk factors should be an integral part of the treatment of T2D [5, 6]. In the past decade, the focus has increasingly shifted toward lifestyle interventions and the pharmacologic management of CV risks for people with T2D [7, 8]. Numerous CV outcomes trials (CVOTs) have evaluated the CV safety and efficacy profile of new glucose-lowering treatments, especially in the glucagon-like peptide-1 receptor agonist (GLP-1 RA) or sodium-glucose cotransporter-2 inhibitor (SGLT2i) classes, demonstrating not only the safety but also a significant cardioprotective effect of some of these drugs [9].

Although the results of several long-term studies have pointed to a direct relationship between lower glycated hemoglobin (HbA1c) levels and decreased CV events [10–12], there is

still uncertainty regarding the long-term prognostic value of HbA1c levels and optimal targets in people with T2D. Studies of large cohorts of people with T2D and long follow-ups have shown the benefit of early insulin treatment to reduce HbA1c levels and, in some cases, a significant reduction of CV risk [7, 11, 12]. However, some studies showed that the effects of glycemic control could be distinct in patients with or without previous cardiovascular disease [10]. Independent of CV risk or prior CVD, studies have shown that people with T2D can benefit from strict glycemic control, especially early after T2D diagnosis [13, 14]. Current guidelines recommend a general objective of HbA1c < 7%, but people with long life expectancy may benefit from more intensive glycemic targets, assuming these can be achieved safely without increasing the risk of hypoglycemia [15, 16]. However, there are limited data on the benefit or prognostic value of HbA1c targets lower than 7% (e.g., 6.5%).

REPRESENT was a retrospective observational study examining the generalizability of three GLP-1 RA CVOTs to the real world [17]. REPRESENT used a major electronic medical records database to describe the sociodemographic, clinical, and treatment characteristics of a Spanish cohort of people with T2D, and to analyze the incidence of first MI/stroke over a 7-year period. The objective of the current post hoc analysis of the REPRESENT study was to analyze the association between stringent baseline HbA1c levels, and other factors such as age, sex, or previous CVD, and the risk of first MI or stroke in a cohort of people with T2D in Spain.

METHODS

Study Design

This was a post hoc analysis of the REPRESENT study—the primary results of which have been previously published [17]. The REPRESENT study was a retrospective observational study based on the IQVIA electronic medical records database with data from over 1,175,000 individuals across Spain (December 2019). Data used in this study were secondary and anonymized. Adults over 18 years of age with a T2D diagnosis before 2013 or those with newly diagnosed T2D between January 2013 and December 2015 (inclusion period) were included in the analysis.

The index date was defined as the date of the first record of T2D within the inclusion period or January 1, 2013 for those with a diagnosis before 2013. All subjects included had at least one HbA1c value recorded at the index date or within 2 years prior to the index date (for HbA1c values, 1 month beyond index date was allowed). Follow-up continued until the last available record in the database or December 2019. In this analysis, all first MI (International Classification of Diseases, Ninth Revision [ICD-9] codes 410.xx) and stroke (ICD-9 codes 433.xx, 434.xx) events in the total population and in the subpopulations of patients with/without prior CVD at baseline were included [18]. The definition of CVD was guided by the American Diabetes Association (ADA) definition of established atherosclerotic CVD (defined as coronary heart disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin; see Supplementary Table S1) [19]. Patients were classified as with or without previous MI or stroke at baseline. Patients without prior MI or stroke were subclassified as patients with prior CVD (other than MI or stroke) or without prior CVD at baseline (Supplemental Fig. S1). The factors associated with the occurrence of the first MI or stroke were evaluated in patients without prior MI or stroke at baseline.

Data Analysis

All first events of MI or stroke occurring after the index date were included in the analysis. Incidence rates of MI and stroke were estimated as the number of patients with at least one event of the type under analysis per 100 patient-years. Patient-years were defined as time from index date until either the first occurrence of the event of interest or the last follow-up with no event. Kaplan–Meier estimates were used to generate cumulative incidence from index date to first MI/stroke occurrence, and explorative Cox proportional hazard models were used to identify

potential prognostic variables for the incidence of first MI or stroke and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The variables included in the analysis were sex, age, smoking habit, HbA1c, date of T2D diagnosis (diagnosis before the index date: yes/no), hyperlipidemia, hypertension, estimated glomerular filtration rate (eGFR), obesity, retinopathy, and prior CVD other than MI or stroke (based on the ICD-9 codes).

Models were used that treated baseline HbA1c as a binary variable (≤ 6.5 or > 6.5), as a categorical variable (< 5.7, 5.7 to < 6.5, 6.5 to < 7.0, or ≥ 7.0), or as a continuous variable. The Cochran–Armitage trend test was used to analyze differences in the incidence of first MI/stroke between HbA1c categories.

Statement of Ethics Compliance

The REPRESENT study and this post hoc analysis were approved by the accredited Clinical Research Ethics Committees of the Hospital Clínic de Barcelona before study initiation (Reg. HCB/2020/0663). The study was also conducted according to Good Clinical Practice guidelines (International Conference of Harmonization) and the Declaration of Helsinki. As this study was based on an existing database from the REPRESENT study, no informed consent was required to participate in the study. The database granted permission for this post hoc study.

RESULTS

Population

The REPRESENT cohort comprised 24,268 people with T2D [17]. The median follow-up was 7.0 years. The mean (SD) age was 66.8 (12.5) years and the mean baseline HbA1c was 7.2 (1.5)% (Table 1), with 64.5% of patients having a HbA1c level ≥ 6.5% at the index date (baseline). Obesity (body mass index [BMI] > 30) was recorded in 51.0% of patients. Most people were treated with oral glucose-lowering drugs such as metformin (66.0%), and only 14.1% were treated with insulin (Table 1). In the REPRESENT cohort,

Table 1 Baseline (index date) characteristics of the REPRESENT cohort

Variable	Total (*N* = 24,268)
Age, years, mean (SD)	66.8 (12.5)
18–49 years, *N* (%)	2188 (9.0)
50–64 years, *N* (%)	7705 (31.7)
65–74 years, *N* (%)	7340 (30.2)
≥ 75 years, *N* (%)	7035 (29.0)
Sex, male, *N* (%)	13,480 (55.5)
Newly diagnosed, *N* (%)	7093 (29.2)
HbA1c, %, mean (SD)	7.2 (1.5)
BMI[a], kg/m^2, mean (SD)	30.8 (5.5)
Class I obese: BMI ≥ 30 to < 35, *N* (%)	4784 (31.8)
Class II obese: BMI ≥ 35 to < 40, *N* (%)	1979 (13.2)
Class III obese: BMI ≥ 40, *N* (%)	900 (6.0)
Presence of comorbidities, *N* (%)	18,152 (74.8)
Hypertension	13,957 (57.5)
Hyperlipidemia	4619 (19.0)
History of CVD	3400 (14.0)
eGFR[b], ml/min/1.73 m^2, mean (SD)	82.6 (19.7)
eGFR < 60 ml/min/1.73 m^2, *N* (%)	2798 (14.1)
Glucose-lowering treatments (alone or in combination), *N* (%)	
Metformin	16,012 (66.0)
Dipeptidyl peptidase inhibitors	4562 (18.8)
Sulfonylureas	4150 (17.1)
Insulin	3430 (14.1)
GLP-1 RAs	151 (0.6)
SGLT2is	72 (0.3)

BMI body mass index, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *GLP-1 RAs* glucagon-like peptide-1 receptor agonists, *HbA1c* glycated hemoglobin, *SD* standard deviation, *SGLT2is* sodium-glucose cotransporter-2 inhibitors

[a]There are missing data for BMI (total with data available, *N* = 15,022). Data on BMI in the 24 months prior to the index date

[b]There are missing data for eGFR (total with data available, *N* = 19,836)

a total of 710 (2.9%) patients had a prior MI, 214 (0.9%) had prior stroke, and 917 (3.8%) had a prior MI and/or stroke (Supplemental Fig. S1). Therefore, of all patients at baseline, 23,558 patients had no prior MI, and 24,054 patients had no prior stroke (Table 2). The proportion of people with T2D without prior MI or stroke with a HbA1c ≥ 6.5% was 64.4% and 64.5%, respectively (Table 2). The baseline demographic and clinical characteristics of the people with or without prior MI or stroke are shown in Supplemental Table S2.

Incidence of MI and Stroke

In patients without prior MI, the incidence (95% CI) of first MI was 0.31 (0.28–0.34) events per 100 patient-years, while in patients without prior stroke, incidence of first stroke was 0.18 (0.15–0.20) events per 100 patient-years. In patients with prior CVD, the incidence was 0.75 (0.62–0.90) for first MI and 0.29 (0.22–0.38) for first stroke (Supplemental Table S3). Kaplan–Meier cumulative incidence analysis for time from index date to first occurrence of MI and stroke are shown in Supplemental Figures S2 and S3, respectively.

Risk Factors

In the Cox proportional hazards models, a baseline HbA1c level < 6.5% was independently associated with lower risk of first MI (HR 0.76 [95% CI 0.61–0.94]) and of first stroke (HR 0.74 [95% CI 0.56–0.98]) (Figs. 1 and 2). Figure 3 shows the percentage of MI or stroke events in people with diabetes with HbA1c < 6.5% versus ≥ 6.5%. Other risk factors included male sex, prior CVD, and age ≥ 50 years, which were also independently associated with an increased risk of a first MI and a first stroke. An eGFR < 60 ml/min/1.73 m^2 was associated with increased risk of a first MI, but not of first stroke (Figs. 1 and 2).

If considered a continuous variable, each 1% increase in HbA1c was associated with a 1.13 and 1.20 increase in the hazard of MI and stroke, respectively. When HbA1c was considered a categorical variable (< 5.7, 5.7 to < 6.5, 6.5 to < 7.0, or ≥ 7.0), significant differences in the probability of having a MI or a stroke between categories were found ($p = 0.0005$ and $p = 0.0314$ for MI and stroke, respectively) (see Supplemental Table S4).

DISCUSSION

In this post hoc analysis of risk factors affecting the incidence of MI or stroke in a large cohort of people with T2D in Spain, baseline HbA1c levels < 6.5% were independently associated with lower risk of first MI and of first stroke. This result suggests that interventions to favor stringent HbA1c control (< 6.5%) could reduce the risk of major CV complications in people with T2D. Non-modifiable factors, such as male sex, prior CVD, and age ≥ 50 years were

Table 2 Baseline HbA1c categories stratified by absence of prior MI or stroke

Categories by HbA1c (%)	Patients without prior MI (*N* = 23,558), *n* (%)	Patients without prior stroke (*N* = 24,054), *n* (%)
< 5.7	1372 (5.8)	1387 (5.8)
5.7 to < 6.5	7010 (29.8)	7146 (29.7)
6.5 to < 7.0	4610 (19.6)	4717 (19.6)
≥ 7	10,566 (44.9)	10,804 (44.9)
< 6.5	8382 (35.6)	8533 (35.5)
≥ 6.5	15,176 (64.4)	15,521 (64.5)

HbA1c glycated hemoglobin, *MI* myocardial infarction

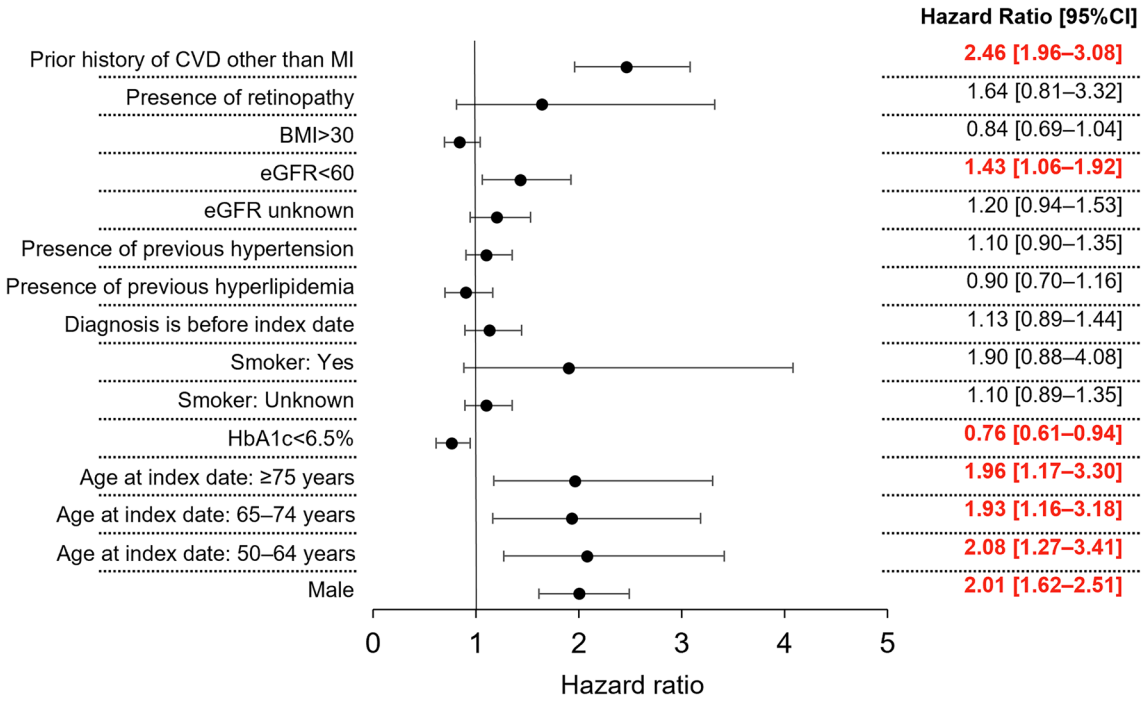

Fig. 1 Risk factors of first MI in people with T2D without previous MI. For HbA1c < 6.5%, the reference group was HbA1c ≥ 6.5%, and for the age groups the reference group was age 18–49 years. *Values in bold red* correspond to categories with significant *p* values ($p < 0.05$) in the corresponding Cox regression model. Prior history of CVD other than MI, $p < 0.0001$; eGFR < 60, $p = 0.0193$; HbA1c < 6.5%, $p = 0.0107$; age at index date ≥ 75 years, $p = 0.0111$; age at index date 65–74 years, $p = 0.0108$; age at index date 50–64 years, $p = 0.0035$. *BMI* body mass index, *CI* confidence interval, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *MI* myocardial infarction, *T2D* type 2 diabetes

independently associated with increased risk of a first MI and of a first stroke, while an eGFR < 60 ml/min/1.73 m^2 was also associated with increased risk of a first MI, but not of first stroke.

A relationship between lower HbA1c levels and reduced risk of macrovascular complications has been observed before in several long-term studies of people with T2D. A meta-analysis of several of these studies showed a 15% reduction in MI risk (HR 0.85 [95% CI 0.76–0.94]) for a 0.88% lower HbA1c [20]. A study of participants in the UK Prospective Diabetes Study (UKPDS) also revealed an up to 33% reduction in MI ($p = 0.005$) after a 10-year follow-up in patients with overweight receiving intensive therapy for glycemic control [21]. Further, a recent re-examination of the UKPDS data has shown that a sustained HbA1c level < 6.5% over a period of 5 years was associated with a significant reduction in MI risk [12]. Another study based on the Swedish National Diabetes Register of people with T2D (mean follow-up, 5.7 years) showed that HbA1c levels below 53 mmol/mol (7%) were associated with an acute MI of HR 0.84 (95% CI 0.75–0.93), and a stroke of HR 0.95 (95% CI 0.84–1.07) [5]. This study showed HbA1c levels were among the strongest predictors for acute MI risk. In Spain, a study of 11,003 people with uncontrolled T2D (HbA1c ≥ 6.5%) observed a linear and increasingly positive relationship between HbA1c levels and hospitalization due to coronary heart disease [10]. In this study, the relative risk for coronary heart disease and stroke hospitalization (comparing patients with and without uncontrolled diabetes) was 1.38 (95% CI 1.20–1.59) and 1.05 (95% CI 0.91–1.21), respectively.

The results of this post hoc analysis would suggest that stringent control of HbA1c levels

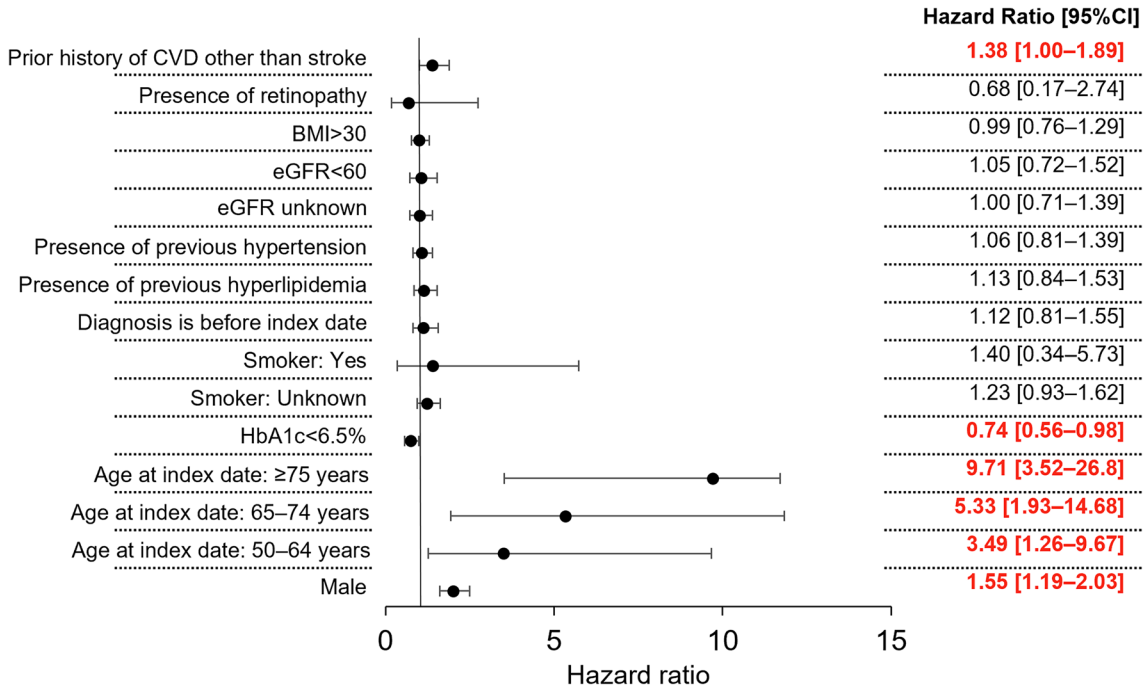

Fig. 2 Risk factors of first stroke in people with T2D without previous stroke. For HbA1c < 6.5%, the reference group was HbA1c ≥ 6.5%, and for the age groups the reference group was age 18–49 years. *Values in bold red* correspond to categories with significant *p* values ($p < 0.05$) in the corresponding Cox regression model. Prior history of CVD other than MI, $p = 0.0478$; HbA1c < 6.5%, $p = 0.0343$; age at index date ≥ 75 years, $p < 0.0001$; age at index date 65–74 years, $p = 0.0012$; age at index date 50–64 years, $p = 0.0162$. *BMI* body mass index, *CI* confidence interval, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *MI* myocardial infarction, *T2D* type 2 diabetes

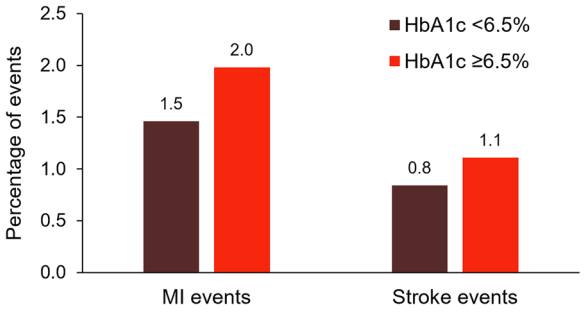

Fig. 3 Association between HbA1c levels (< 6.5% or ≥ 6.5%) and risk of MI or stroke in people with T2D. *HbA1c* glycated hemoglobin, *MI* myocardial infarction, *T2D* type 2 diabetes

could significantly help in reducing the risk of development of macrovascular complications later in life. Early intervention for stringent HbA1c control has been suggested before to reduce diabetes-related CV complications. For example, the UKPDS showed that one percentage unit lower HbA1c from the diagnosis of diabetes significantly lowered the risk of MI events 15 and 20 years later, compared with reducing HbA1c by the same amount from 10 years after diagnosis [12]. Also, the Diabetes & Aging Study found that, among patients with newly diagnosed diabetes and 10 years of survival, HbA1c levels ≥ 6.5% (≥ 48 mmol/mol) for the first year after diagnosis were associated with worse outcomes [11]. These results highlight the importance of early treatment intensification aimed at reaching the HbA1c target, as currently recommended by the ADA–European Association for the Study of Diabetes consensus, and of implementing strategies aimed at reducing the risk of CVD as early as possible after T2D diagnosis [15]. Although historically the treatment for T2D followed a step-by-step

approach—where a new medication was added to the existing regimen to reach the glycemic target—current evidence justifies a more proactive approach, especially in those patients with established CVD, increased CVD risk, or long life expectancy [15, 22]. Early intensification can result in diabetes remission in some cases [23, 24]. Current guidelines suggest a HbA1c target for most adults, excluding pregnant women, of 53 mmol/mol (7%) or less [15]. A target of HbA1c < 7% can be reasonable if it can be accomplished in a safe manner without significant hypoglycemia or other treatment side effects, especially when using pharmacologic treatments, which are not associated with hypoglycemia risk [15].

In this post hoc analysis, the incidence of first MI or stroke was approximately two- to three-times higher in patients with prior CVD compared with patients without prior CVD. The molecular mechanisms involved in the damage caused by persistent hyperglycemia point to prolonged increases in reactive oxygen species production and altered secretion of inflammatory cytokines, among other processes [25–27]. Insulin resistance, hyperinsulinemia, and vascular calcification may lead to atherosclerosis and the formation of unstable plaques that ultimately can cause coronary events and stroke [27]. Given the added risk in people with T2D with prior CVD, current guidelines promote the early use of drugs with cardiorenal benefit in these patients, such as GLP-1 RAs or SGLT2is [15]. Although these drugs were originally introduced as glucose-lowering agents, they are now also recommended for organ protection based on the results from the CVOTs [9]. In this regard, it should be noted that although these drugs could have potentially affected the results of our study, the effects are likely to be very minor, as studies have shown a limited use of these drugs at the time of study data collection in Spain [28, 29]. In the population studied here, only 0.6% and 0.3% had prescriptions for GLP-1 RAs and SGLT2is, respectively, at index date (Table 1).

In the interpretation of the results, it should be noted that although the Cox regression analysis did not find a relationship between the occurrence of macrovascular events and other major CV risk factors such as hypertension or hyperlipidemia, the baseline control of these CV risk factors was not included in the model.

There are additional limitations that must be considered when interpreting the results of this study. Due to the retrospective design of our study, only associations but not cause and effect relationships could be explored. The IQVIA medical records database covered a population of 1.2 million patients at the time of the study, but this was based on voluntary participation of the treating physicians and may not be fully representative of the population with diabetes. However, the characteristics of patients in our study are similar to those reported in other studies with Spanish cohorts [30]. As with any database study, there was heterogeneity of data quality and the frequency of data capture and coverage for some key study-related parameters. Missing data were present for certain variables (e.g., BMI). Also, prescriptions and diagnosis were only collected in the database since 2008. As a consequence, a diagnosis date was not available in the database for patients diagnosed before 2008. Therefore, the effect of diabetes duration on CV outcomes in our study was evaluated as a dichotomous variable: newly diagnosed diabetes during the inclusion period vs. known T2D diagnosis before the index date. Consequently, time since diagnosis could not be calculated as this approach resulted in an underestimation of the time from diagnosis in this subpopulation. Further, it was not possible to identify repeated events under the same ICD-9 code. Analyses were conducted in patients with CVD "other than MI or stroke," as applicable, which may have resulted in the underestimation of the incidence of MI or stroke in this subpopulation. Another database limitation was that death data were not available, as these patients were categorized as "lost to follow-up due to any reason," and therefore evaluating the rate of cardiovascular or non-cardiovascular mortality in this population was not possible. It should also be considered that, at the index date when baseline data were collected, the cohort consisted of patients with heterogeneous stages of the disease and that HbA1c, or the presence of certain comorbidities, could change over the follow-up period. The results apply to the entire population with T2D, in which most patients

were not newly diagnosed. Although it would be interesting to know the effect of stringent HbA1c control specifically in a population of patients with a recent diagnosis, only 29.2% of our sample was newly diagnosed. Being a small sample, the number of events would probably be insufficient to be able to perform this analysis. However, the purpose of this study was to reflect the regular patient population in routine practice at any point in time, providing the average risk of a real-life population of people with T2D.

CONCLUSIONS

The results of this post hoc analysis are consistent with prior long-term follow-up studies and provide further information on the importance of glycemic control to prevent CV events in people with T2D, as has been recommended by current guidelines. In this regard, the results of this retrospective observational study, with the limitations inherent to this type of design, support the notion of the cardiovascular benefits of HbA1c levels < 7.0% and suggest an association between HbA1c levels < 6.5% and a lower incidence of MI and stroke. Additional prospective and interventional studies would be necessary to demonstrate the potential benefits of achieving and maintaining stringent glycemic control (i.e., HbA1c < 6.5%).

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Data Availability. The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions.

Declarations

Conflict of Interest. Irene Cristina Romera, Jennifer Redondo-Antón, Miriam Rubio-de Santos, Silvia Díaz-Cerezo, and Esther Artime are employees and minor shareholders of Lilly and Company. Albert Rafels-Ybern is an employee of IQVIA information. Emilio Ortega declares personal fees (consulting and lectures) and/or non-financial support from Akcea, Amgen, AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Lilly/Boehringer-Lilly, MSD, NovoNordisk, Pfizer, and Sanofi. Ignacio Conget reports honoraria for speaking from Medtronic, Eli Lilly, Novo Nordisk, Sanofi-Aventis, Astra Zeneca, Boehringer

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Ethical Approval. The REPRESENT study and this post hoc analysis were approved by the accredited Clinical Research Ethics Committees of the Hospital Clínic de Barcelona before study initiation (Reg. HCB/2020/0663). The study was also conducted according to Good Clinical Practice guidelines (International Conference of Harmonization) and the Declaration of Helsinki. As this study was based on an existing database from the REPRESENT study, no informed consent was required to participate in the study. The database granted permission for this post hoc study.

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