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Original article

Limited benefit of haemoglobin glycation index as risk factor for cardiovascular disease in type 2 diabetes patients

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ABSTRACT

Background. – The haemoglobin glycation index (HGI) has been proposed as a marker of interindividual differences in haemoglobin glycosylation. Previous studies have shown a relationship between high HGI and risk of cardiovascular disease (CVD) in patients with diabetes. However, no studies have investigated the role of previous CVD in this association.
Methods. – The study cohort comprised patients with type 2 diabetes mellitus (T2DM; $n = 1910$) included in the Second Manifestations of Arterial Disease (SMART) study. The relationship between either HGI or HbA_{1c} and a composite of cardiovascular events as the primary outcome, and mortality, cardiovascular mortality, myocardial infarction and stroke as secondary outcomes, was investigated using Cox proportional-hazards models. Similar analyses were performed after stratification according to previous CVD.
Results. – A 1-unit higher HGI was associated with a 29% greater risk of a composite of cardiovascular events (HR: 1.29, 95% CI: 1.06–1.57) in patients without previous CVD, whereas no such relationship was seen in patients with previous CVD (HR: 0.96, 95% CI: 0.86–1.08). The direction and magnitude of the hazard ratios (HRs) of HGI and HbA_{1c} in relation to outcomes were similar. Additional adjustment for HbA_{1c} in the association between HGI and outcomes lowered the HRs.
Conclusion. – Similar to HbA_{1c}, higher HGI is related to higher risk of cardiovascular events in patients with T2DM without CVD. As HbA_{1c} has proved to be a comparable risk factor, and obtaining and interpreting the HGI is complicated, any additional benefit of applying the HGI in clinical settings is likely to be limited.

Introduction

Type 2 diabetes mellitus (T2DM) is a major global health problem with approximately 422 million patients diagnosed worldwide [1]. Patients with T2DM have a twofold greater risk of cardiovascular disease (CVD) [2] and an increased risk of microvascular complications [3]. Since glycosylated haemoglobin (HbA_{1c}) was discovered in the late 1960s, it has become the standard test for monitoring glycaemic control, a cornerstone in the treatment of T2DM [4]. In 2002, the haemoglobin glycation index (HGI) was, for the first time, proposed as a possible marker of interindividual differences in haemoglobin glycosylation [5] and has since been investigated in a number of studies [6–10]. The HGI is the difference between observed HbA_{1c} and predicted HbA_{1c}, as calculated by the population linear regression equation of HbA_{1c} as a function of blood glucose.

In fact, a wide discordance between observed and predicted HbA_{1c} has been found associated with a threefold higher risk of retinopathy and a sixfold greater risk of nephropathy in patients with type 1 diabetes mellitus (T1DM) included in the Diabetes Control and Complications Trial (DCCT) [7]. A substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) investigated the effect modification of HGI on the relationship between strict glycaemic control ($HbA_{1c} < 6.0\%$) [11] and cardiovascular outcomes and mortality. Strict glycaemic control proved to be associated with a 14% greater risk of mortality in patients

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with high HGI (higher HbA_{1c} than predicted based on fasting plasma glucose) when compared to patients with low and moderate HGI scores [8]. However, there has also been some opposition to adopting the HGI as a marker of interindividual differences in haemoglobin glycosylation, based on the argument that the HGI is either a surrogate for HbA_{1c} or a reflection of other factors, such as insulin use, duration of diabetes and glycaemic variability [12,13].

Thus, the purpose of the present study was to examine the association between HGI and cardiovascular events and mortality in patients with T2DM with and without a history of CVD, and to determine whether this relationship differed from that of HbA_{1c}. It also investigated whether previous CVD at baseline was an effect modifier in the relationship between HGI and cardiovascular events.

Materials and methods

Study population

The present cohort consisted of 1910 patients with T2DM included in the Second Manifestations of Arterial Disease (SMART) study, an ongoing single-centre prospective cohort study carried out at the University Medical Centre Utrecht (UMCU) in the Netherlands. T2DM was defined as either a referral or self-reported diagnosis of T2DM, or a fasting plasma glucose (FPG) $\geq$ 7 mmol/L at study inclusion, with initiation of glucose-lowering treatment within 1 year, or baseline use of antihyperglycaemic agents or insulin. Participants with known T1DM were excluded. Patients were enrolled from September 1996 to February 2015. SMART study inclusion criteria were manifested vascular disease or risk factors associated with CVD, and age between 18 and 80 years. All patients included in SMART underwent vascular screening at baseline, including a health questionnaire, a standardized physical examination and the collection of fasting blood samples, as described previously [14].

Follow-up of patients

Participants in the SMART study were asked to fill out a questionnaire twice a year. If a possible event was reported, then hospital discharge letters and results of the relevant laboratory and radiological examinations were also collected. Using this additional information, all events were audited by three members of the SMART study endpoint committee, comprising physicians from various departments. The primary outcome of interest for the present study was a major vascular event [a composite of myocardial infarction, stroke (infarction or haemorrhagic), retinal infarction, terminal heart failure (death as cause of heart failure), sudden death and vascular mortality], whereas secondary outcomes included total mortality, cardiovascular mortality, myocardial infarction and stroke (Table S1; see supplementary materials associated with this article online).

Measurement of variables

HbA_{1c} was measured at baseline in all patients enrolled in the SMART study. HbA_{1c} was measured using an automated high-performance liquid chromatography (HPLC) analyzer (ADAMS A1c HA-8180; Menarini Diagnostics, Florence, Italy). FPG was measured at baseline in all patients, using a glucose hexokinase method and an AU-5811 routine chemistry analyzer (Beckman Coulter, Brea, CA, USA). Glomerular filtration rate was estimated (eGFR) in mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) equation: GFR (mL/min/1.73 m^2) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times$ (0.742 if female) $\times$ (1.212 if African American). Proteinuria was defined as an albumin/creatinine ratio (ACR) 3–30 mg/mmol (microalbuminuria) or > 30 mg/mmol (macroalbuminuria). Information on duration of diabetes, alcohol consumption, level of education and smoking was obtained through a patient questionnaire.

Calculation of haemoglobin glycation index (HGI)

Baseline and time-matched FPG and HbA_{1c} data from our cohort were used to estimate the linear relationship between FPG and HbA_{1c} in our study population (Fig. S1; see supplementary materials associated with this article online). The linear approach was chosen in concordance with previous studies [6–9], although the linear correlation between FPG and HbA_{1c} was not strong (R^2 = 0.39). The predicted HbA_{1c} was calculated for each participant by inserting FPG in the population linear regression equation (predicted HbA_{1c} = 0.28 * FPG (mmol/L) + 4.68). Baseline HGI was calculated as the difference between the observed HbA_{1c} at baseline and the predicted HbA_{1c} (observed HbA_{1c} − predicted HbA_{1c}).

Data analyses

Participants' baseline characteristics are presented as means ± standard deviation (SD) in cases of normal distribution or as medians with interquartile range (IQR) in cases of variables with skewed distribution. Categorical variables are presented as frequency. For continuous variables, independent-samples *t*-tests were used for normally distributed variables, with Kruskal–Wallis tests for non-normally distributed variables, and χ^2 tests for categorical variables. Baseline characteristics were also compared according to tertiles of HGI (low, moderate and high subgroups) and of HbA_{1c} (low, moderate and high subgroups).

Missing data for HbA_{1c} (n = 133, 7.0%), FPG (n = 33, 0.2%) and confounders [history of CVD] (n = 81, 4.2%), body mass index (BMI; n = 4, 0.2%), systolic blood pressure (n = 4, 0.2%), cholesterol (n = 10, 0.5%), high-density lipoprotein (HDL) cholesterol (n = 14, 0.7%), eGFR (n = 9, 0.5%) and level of education (n = 877, 45.9%) were singly imputed by weighted probability-matching, based on multivariable linear regression using all covariate and outcome data.

Analyses were performed to assess the association between HGI and the primary and secondary study outcomes (Table S1). Similar analyses were also performed with HbA_{1c} as the determinant. If a patient had multiple events, only the first event was used in the analyses. Cox proportional-hazards models were used to determine hazard ratios (HRs) and 95% confidence intervals (CIs), with satisfaction of the proportional-hazards assumption based on visual inspection of Schoenfeld residuals plots.

To assess the relationship between HGI and cardiovascular events and mortality, four models were constructed. Model I was adjusted for gender and age, whereas model II was further adjusted for BMI, diabetes duration, non-HDL cholesterol level, eGFR, use of insulin and systolic blood pressure. Confounders were included based on previous investigations and on univariate linear regression between HGI and different covariates (data not shown). In addition, exploratory models were constructed, adding HbA_{1c} and level of education, respectively, to model II to build models III and IV, respectively. Similar models (except model III) were constructed with HbA_{1c} as the determinant.

To test for effect modification, the cross-product of gender, age, insulin use, duration of diabetes, eGFR, level of education and previous CVD, respectively, and HGI was also added to the Cox proportional-hazards models with the composite of cardiovascular events as the outcome.

Sensitivity analyses were performed, excluding patients with missing HbA_{1c}, FPG or history of CVD data to ensure that the

Table 1
Baseline characteristics of study participants.

	All patients (n = 1910)	Previous CVD (n = 1260)	No previous CVD (n = 569)	P^*
Haemoglobin glycation index (HGI)	−0.00 ± 1.00	−0.08 ± 0.93	0.2 ± 1.1	< 0.001
Gender, male [n (%)]	1329 (70%)	948 (75%)	338 (59%)	< 0.001
Age (years)	60 ± 10	63 ± 9	55 ± 11	< 0.001
Current alcohol use [n (%)]	860 (46%)	585 (47%)	238 (43%)	0.03
Current smoking [n (%)]	464 (25%)	321 (26%)	126 (22%)	< 0.001
Level of education [n (%)]				0.04
Low	365 (35%)	259 (35%)	85 (34%)	
Moderate	410 (40%)	302 (41%)	90 (36%)	
High	258 (25%)	175 (24%)	73 (29%)	
Duration of diabetes (years)	4 (1–10)	4 (1–10)	3 (0–7)	< 0.001
Weight (kg)	87 ± 17	86 ± 15	91 ± 20	< 0.001
Body mass index (kg/m^2)	29 ± 5	28 ± 4	30 ± 6	< 0.001
Waist circumference (cm)	101 ± 13	101 ± 12	102 ± 15	0.07
Systolic blood pressure (mmHg)	145 ± 21	145 ± 21	146 ± 21	0.21
Diastolic blood pressure (mmHg)	83 ± 12	81 ± 11	86 ± 12	< 0.001
Insulin [n (%)]	455 (24%)	302 (24%)	134 (24%)	0.85
Metformin only [n (%)]	371 (19%)	247 (19%)	106 (18%)	0.63
Glucose-lowering agents [n (%)]	1262 (66%)	822 (65%)	388 (68%)	0.22
Laboratory measurements				
Glucose (mmol/L)	8.7 ± 2.9	8.5 ± 2.7	9.2 ± 3.2	< 0.001
HbA_{1c} (%)	7.1 ± 1.3	6.9 ± 1.1	7.5 ± 1.5	< 0.001
Insulin (mU/L)	13.0 (8.0–20.0)	13.0 (8.0–20.0)	13.0 (9.0–22.0)	0.36
eGFR (mL/min/1.73 m^2)	78.5 ± 22.1	75.9 ± 21.0	85.1 ± 22.6	< 0.001
Proteinuria [n (%)]				0.66
Microalbuminuria[a]	368 (21%)	249 (22%)	107 (21%)	
Macroalbuminuria[b]	61 (4%)	41 (4%)	14 (3%)	
Total cholesterol (mmol/L)	4.8 ± 1.4	4.6 ± 1.2	5.3 ± 1.6	< 0.001
Non-HDL-C (mmol/L)	3.7 ± 1.4	3.5 ± 1.2	4.1 ± 1.7	< 0.001
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.4	0.001
LDL-C (mmol/L)	2.8 ± 1.1	2.6 ± 1.0	3.0 ± 1.1	< 0.001
Triglycerides (mmol/L)	1.7 (1.2–2.5)	1.6 (1.2–2.4)	1.8 (1.2–2.7)	< 0.001
Hb (mmol/L)	8.7 ± 0.9	8.7 ± 0.9	8.9 ± 0.8	< 0.001

Data are means ± SD or medians (IQR) unless otherwise specified. HDL-C/LDL-C: high-density/low-density lipoprotein cholesterol; Hb: haemoglobin.
[*] Patients with vs. without previous cardiovascular disease (CVD).
[a] Albumin/creatinine ratio (ACR) 3–30 mg/mmol.
[b] ACR > 30 mg/mmol; eGFR: estimated glomerular filtration rate.

association was not influenced by imputation methods. All analyses were performed using IBM SPSS Statistics 21.0 software (IBM Corp., Armonk, NY, USA) and RStudio 3.3.2 software (R packages Hmisc and survival; R Foundation, Vienna, Austria).

Results

Patients' baseline characteristics are presented in Table 1. Those with T2DM had an average follow-up duration of 9.6 years (IQR: 5.6–13.4), during which time, 380 (19.9%) patients experienced a cardiovascular event [myocardial infarction, stroke (infarction or haemorrhagic), retinal infarction, terminal heart failure, sudden death or vascular mortality] and 436 (22.8%) patients died, with 243 (12.7%) dying of a vascular cause. In addition, 127 (6.6%) patients had myocardial infarction and 97 (5.1%) had stroke, while 140 (7.3%) patients were lost to follow-up. Patients' mean age was 60 ± 10 years, 70% were male and 69% had a history of CVD.

Baseline characteristics of the study population according to tertiles of HGI and of HbA_{1c} are shown in Tables S2 and S3 (see supplementary materials associated with this article online), respectively.

Association of HGI and HbA_{1c} with cardiovascular events and mortality in T2DM patients with and without CVD at baseline

As previous CVD was proved to be the only effect modifier (P = 0.02 for interaction with CVD at baseline) between HGI and a composite of cardiovascular events, all analyses were stratified according to the presence or absence of previous CVD. In patients with previous CVD, an inverse relationship between HGI and myocardial infarction was seen after adjusting for confounders (model II HR: 0.78, 95% CI: 0.63–0.96). No statistically significant relationship was seen between HGI and a composite of cardiovascular events, total mortality, cardiovascular mortality or stroke (Table 2), nor between HbA_{1c} and any of the outcomes, in patients with previous CVD (Table 3). In patients without previous CVD, a significant relationship was found between HGI and a composite of cardiovascular events after adjusting for confounders (model II HR: 1.29, 95% CI: 1.06–1.57). No significant association was observed between HGI and total mortality, cardiovascular mortality, myocardial infarction or stroke (Table 2).

Likewise, a significant relationship between HbA_{1c} and a composite of cardiovascular events was observed in patients without previous CVD after adjusting for confounders (model II HR: 1.23, 95% CI: 1.04–1.45), although here, the P = 0.14 for interaction was not significant. Also, there was no significant relationship between HbA_{1c} and total mortality, cardiovascular mortality, myocardial infarction or stroke (Table 3).

Sensitivity analyses of only patients with complete data for HbA_{1c}, FPG and history of CVD did not alter our results. Although the inverse effect of HGI and myocardial infarction was not significant, this was probably due to a lack of power after excluding 123 of 1313 patients with T2DM (Table S4; see supplementary materials associated with this article online).

Additional adjustments for HbA_{1c} and level of education

To evaluate whether the relationship between HGI and cardiovascular events and mortality was influenced by HbA_{1c}, further adjustments were made for HbA_{1c}. HR magnitude

Table 2
Relationship between haemoglobin glycation index (HGI) and cardiovascular events and mortality in type 2 diabetes patients with and without cardiovascular disease (CVD).

	All patients ($n = 1910$)	Previous CVD ($n = 1313$)	No previous CVD ($n = 597$)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Composite of cardiovascular events			
Events, *n* (%)	380 (19.9)	315 (24.0)	65 (10.9)
Model I	1.04 (0.94–1.14)	1.01 (0.90–1.13)	1.30 (1.08–1.56)*
Model II	1.00 (0.90–1.11)	0.96 (0.86–1.08)	1.29 (1.06–1.57)*
Model III	0.93 (0.80–1.08)	0.89 (0.75–1.05)	1.17 (0.86–1.59)
Model IV	0.99 (0.89–1.10)	0.95 (0.85–1.07)	1.30 (1.07–1.57)*
Total mortality			
Events, *n* (%)	436 (22.8)	345 (26.3)	91 (15.2)
Model I	1.12 (1.03–1.22)*	1.14 (1.03–1.26)*	1.19 (1.01–1.40)*
Model II	1.07 (0.97–1.17)	1.07 (0.96–1.18)	1.14 (0.96–1.36)
Model III	0.99 (0.86–1.13)	0.96 (0.82–1.13)	1.09 (0.83–1.42)
Model IV	1.07 (0.97–1.17)	1.07 (0.97–1.19)	1.14 (0.96–1.36)
Cardiovascular mortality			
Events, *n* (%)	243 (12.7)	205 (15.6)	38 (6.4)
Model I	1.05 (0.94–1.19)	1.03 (0.90–1.19)	1.34 (1.07–1.69)*
Model II	1.00 (0.88–1.13)	0.97 (0.84–1.11)	1.27 (0.99–1.63)
Model III	0.92 (0.76–1.10)	0.82 (0.67–1.01)	1.38 (0.91–2.08)
Model IV	0.99 (0.87–1.12)	0.95 (0.82–1.10)	1.30 (1.02–1.65)*
Myocardial infarction			
Events, *n* (%)	127 (6.6)	106 (8.1)	21 (3.5)
Model I	0.87 (0.72–1.04)	0.81 (0.66–1.01)	1.26 (0.91–1.74)
Model II	0.82 (0.68–0.99)*	0.78 (0.63–0.96)*	1.33 (0.92–1.91)
Model III	0.78 (0.60–1.01)	0.74 (0.56–0.99)*	1.10 (0.64–1.89)
Model IV	0.82 (0.68–0.99)*	0.78 (0.63–0.96)*	1.35 (0.94–1.94)
Stroke			
Events, *n* (%)	97 (5.1)	79 (6.0)	18 (3.0)
Model I	1.11 (0.92–1.33)	1.11 (0.90–1.38)	1.25 (0.88–1.78)
Model II	1.09 (0.90–1.33)	1.06 (0.85–1.33)	1.42 (0.97–2.08)
Model III	1.04 (0.78–1.40)	1.05 (0.75–1.48)	1.22 (0.65–2.29)
Model IV	1.06 (0.87–1.29)	1.01 (0.81–1.27)	1.37 (0.95–1.99)

Model I: adjusted for gender, age; model II: adjusted for gender, age, body mass index, insulin use, duration of diabetes, non-high-density lipoprotein (HDL) cholesterol, estimated glomerular filtration rate (eGFR), systolic blood pressure; model III: HbA_{1c} added to model II; model IV: level of education added to model II.
* $P < 0.05$.

Table 3
Relationship between HbA_{1c} and cardiovascular events and mortality in type 2 diabetes patients with and without cardiovascular disease (CVD).

	All patients ($n = 1910$)	Previous CVD ($n = 1313$)	No previous CVD ($n = 597$)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Composite of cardiovascular events			
Events, *n* (%)	380 (19.9)	315 (24.0)	65 (10.9)
Model I	1.07 (0.99–1.16)	1.07 (0.98–1.17)	1.23 (1.06–1.42)*
Model II	1.04 (0.95–1.13)	1.02 (0.92–1.12)	1.23 (1.04–1.45)*
Model IV	1.03 (0.94–1.12)	1.01 (0.92–1.12)	1.24 (1.05–1.45)*
Total mortality			
Events, *n* (%)	436 (22.8)	345 (26.3)	91 (15.2)
Model I	1.12 (1.05–1.20)*	1.15 (1.06–1.25)*	1.15 (1.01–1.30)*
Model II	1.08 (1.00–1.16)	1.09 (1.00–1.20)	1.11 (0.97–1.28)
Model IV	1.08 (1.00–1.16)	1.10 (1.01–1.20)*	1.11 (0.96–1.28)
Cardiovascular mortality			
Events, *n* (%)	243 (12.7)	205 (15.6)	38 (6.4)
Model I	1.09 (0.99–1.20)	1.12 (1.01–1.25)*	1.16 (0.96–1.41)
Model II	1.05 (0.94–1.16)	1.06 (0.94–1.19)	1.13 (0.90–1.42)
Model IV	1.04 (0.93–1.15)	1.05 (0.93–1.19)	1.15 (0.92–1.43)
Myocardial infarction			
Events, *n* (%)	127 (6.6)	106 (8.1)	21 (3.5)
Model I	0.96 (0.84–1.11)	0.94 (0.79–1.11)	1.24 (0.95–1.60)
Model II	0.92 (0.79–1.07)	0.88 (0.73–1.05)	1.29 (0.97–1.72)
Model IV	0.92 (0.79–1.07)	0.88 (0.74–1.06)	1.30 (0.98–1.72)
Stroke			
Events, *n* (%)	97 (5.1)	79 (6.0)	18 (3.0)
Model I	1.10 (0.95–1.27)	1.11 (0.93–1.32)	1.22 (0.94–1.58)
Model II	1.08 (0.92–1.27)	1.04 (0.86–1.27)	1.30 (0.98–1.71)
Model IV	1.05 (0.89–1.24)	1.01 (0.83–1.23)	1.27 (0.97–1.66)

Model I: adjusted for gender, age; model II: adjusted for gender, age, body mass index, insulin use, duration of diabetes, non-high-density lipoprotein (HDL) cholesterol, estimated glomerular filtration rate (eGFR), systolic blood pressure; model IV: level of education added to model II.
* $P < 0.05$.

decreased from, for example, 1.29 (95% CI: 1.06–1.57) to 1.17 (95% CI: 0.86–1.59) for a composite of cardiovascular events as the outcome in patients with no previous CVD, and additional adjustment for level of education changed neither the direction nor magnitude of the HRs. When performing the same analyses with HbA_{1c} as the determinant instead of HGI, the HRs closely resembled those of the latter (Tables 2 and 3). The linear relationship between HGI and HbA_{1c} showed a correlation of $R^2 = 0.61$, indicating a close relationship between the two (Fig. S2; see supplementary materials associated with this article online).

The group with no previous CVD differed from the group with previous CVD in relation to HGI and outcomes. Yet, the same linear regression formula was used to calculate HGI in both groups, as this was a population regression equation based on the whole cohort. This was also consistent with previous studies of HGI.

Discussion

The present study has demonstrated that a higher HGI score is associated with a higher risk of cardiovascular events in patients with T2DM but without previous CVD. The same result was seen with HbA_{1c} and risk of cardiovascular events in patients with T2DM but without previous CVD. However, an inverse relationship was found between higher HGI and myocardial infarction in those with previous CVD. Nevertheless, as the direction and magnitude of HRs for HGI and outcomes resembled those for HbA_{1c} and outcomes, and as adjusting for HbA_{1c} reduced the magnitude of the HRs, it appears that the HGI closely resembles HbA_{1c} as a risk factor for cardiovascular morbidity and mortality.

Although the correlation between blood glucose and HbA_{1c} measurements is generally good [15], this is not always the case. In fact, the relationship between blood glucose levels and HbA_{1c} may be influenced by factors affecting haemoglobin glycosylation, such as age [16], race [17,18], genetic variations [19], and differences in erythrocyte life span and environment [7], as well as iron deficiency and anaemia [20]. One way to approach this discordance is the HGI [5], which is the difference between the observed and predicted HbA_{1c} as calculated from the population regression equation of HbA_{1c} for FPG. Thus, high and low HGI scores also represent HbA_{1c} levels that are higher and lower, respectively, than predicted compared with other patients with similar FPG levels. In addition, a single FPG measurement may not always correlate with HbA_{1c} levels due to day-to-day changes in both FPG and postprandial glucose excursions.

Nevertheless, to the best of our knowledge, this is the first-ever prospective study to investigate the relationship between both HGI and HbA_{1c} as separate determinants and cardiovascular events in patients with T2DM with and without (stable) CVD at baseline. Several previous studies have investigated the link between HGI and the micro- and macrovascular complications of diabetes. A substudy of the ACCORD trial found increased mortality and greater risk of hypoglycaemia with intensive treatment of patients in the highest tertile of HGI compared with the lowest and moderate tertiles [8]. This could be due to the fact that patients with a high HGI often have more pronounced glucose excursions, with more frequent low blood glucose levels than reflected by their HbA_{1c} and thus are more exposed to the detrimental factors related to episodic hypoglycaemia [21]. However, in view of our present results, it is important to note that in the original ACCORD trial, patients in the intensive-treatment arm with higher HbA_{1c} levels also had a greater risk of mortality compared to those with lower HbA_{1c} values [22]. Such similar results for both HGI and HbA_{1c} as risk factors for mortality in the ACCORD could be an indication that HGI is a proxy for HbA_{1c}.

In a substudy of the DCCT, a high HGI was associated with a threefold increase in risk of retinopathy and a sixfold increase in risk of nephropathy in patients with T1DM [7]. Yet, when a critical opponent of the study analyzed the DCCT data including HbA_{1c} as a covariate, the results were non-significant [12]. Moreover, a recent evaluation of the AleCardio trial found an increased risk of both cardiovascular and total mortality in patients with high HGI scores [23], with a 1% increase in HGI associated with a 16% greater risk of cardiovascular mortality. However, this association was no longer evident after additional adjustment for HbA_{1c}, whereas HRs for the relationship between HGI and outcomes were comparable to those seen between HbA_{1c} and outcomes. A report from the ADVANCE trial compared HGI and HbA_{1c} as predictors of CVD in two groups of intensive and standard glucose control, respectively [24], and found that higher HGI was associated with an increased risk of macro- and microvascular diabetes complications and mortality. Yet, despite using the same confounders, HbA_{1c} was the stronger predictor.

These data have now been expanded by showing that this not only applies to a trial population, but also to a stable real-life population of patients with T2DM with and without CVD. These data, when considered together, indicate that the HGI is nothing more than a surrogate for HbA_{1c}.

A recent study from South Korea found a significant relationship between the highest HGI tertile and cardiovascular events in patients with either prediabetes or T2DM [9], while another South Korean study in patients with T2DM found no significant relationship between HGI and any diabetic complication [10]. Another recent study of non-diabetic Caucasian Italians found that high HGI was associated with a significant increase in carotid intima–media thickness, an indicator of subclinical atherosclerosis, in those predisposed to T2DM [6]. However, none of these studies took the potential effect modification of CVD at baseline into account, and only one study carried out additional analyses with HbA_{1c} as a confounder [9]. Moreover, previous studies of HGI as a risk factor for CVD also differed in their patient populations and type of blood glucose measurement, making the results difficult to interpret.

It was previously shown that hyperglycaemia (high HbA_{1c}) increases the risk of mortality and CVD in patients with T2DM as it is associated with abnormalities of coagulation, dyslipidaemia and other known risk factors associated with an increased risk of CVD [25] mainly due to the formation of glycosylation end-products [26]. If HGI is nothing more than a surrogate for HbA_{1c}, the results obtained in studies showing a relationship between high HGI and increased risk of CVD and mortality might simply be reflecting the fact that patients with a high HGI also have a high HbA_{1c}. The clinical use of HGI is further hampered by the need to construct a linear relationship between blood glucose and HbA_{1c} because the population linear regression equation used to calculate the predicted HbA_{1c} differs between populations across different studies.

Furthermore, several factors need to be taken into consideration when interpreting the HGI. Glycaemic variability, understood as fluctuations in blood glucose, has been proposed as a risk factor of diabetes complications [27–30]. A high HGI might, in theory, be a reflection of high glycaemic variability, rendering the association between a high HGI and increased risk of CVD simply a reflection of this phenomenon. Insulin use also affects FPG and postprandial glucose levels, but not HbA_{1c} to the same extent [13], and could lead to higher HGI. Moreover, the use of glucose-lowering agents can alter the relationship between FPG and HbA_{1c}, with a smaller rise of HbA_{1c} for every unit increase of FPG [31]. Thus, higher HGI may, in theory, also reflect higher daytime and postprandial glucose levels compared with FPG, or the use of insulin or glucose-lowering agents.

Another problem to consider when using the HGI is the measurement of blood glucose. Although one study showed a

correlation between HGI calculated from FPG and the HGI calculated from all glucose data [5], T2DM patients may be subject to 'doctor-pleasing', causing them to achieve a lower FPG at the time of the clinical visit, but with a higher-than-expected HbA_{1c}, thereby resulting in a higher HGI. However, when level of education was added to the model as a marker of socioeconomic status related to compliance, no change in risk was seen.

For our analyses, the cohort was divided into patients with and without previous CVD. Yet, the patients without previous CVD were still high-risk patients, as all patients were enrolled during hospitalization and all had at least one CVD risk factor.

The effect modification of previous CVD may have been due to a number of factors. One possible explanation is that in patients with previous CVD, high HGI (and, thus, high HbA_{1c}) is not the main factor behind endothelial damage leading to a cardiovascular event. It may well be that other known risk factors for CVD (such as hypertension and dyslipidaemia) play a larger role in the pathogenesis of CVD in patients with established CVD. This might indicate a need for individualized treatment of T2DM patients, especially those in high-risk groups.

The inverse relationship between HGI and myocardial infarction in patients with previous CVD might possibly have been due to the fact that low HGI (and, thus, low HbA_{1c}) could be an indicator of frequent hypoglycaemia and, therefore, an increased risk of morbidity and mortality [21,32,33], thereby rendering patients with previous CVD more at risk of myocardial infarction with lower HGI (and, thus, lower HbA_{1c}). In any case, the association between HbA_{1c} and risk of myocardial infarction was in the same direction as that between HGI and myocardial infarction, albeit not statistically significant.

The present study has several strengths, including its prospective design and large number of events because of the substantial follow-up duration and large cohort size. In addition, the data completeness lowered the risk of information bias. However, some study limitations still need to be considered. The predicted HbA_{1c} used to calculate the HGI was based on only one FPG measurement, which is a limitation in terms of precise HGI calculation, as the participants' mean blood glucose could be either higher or lower than suggested. Ideally, more measurements of blood glucose, including postprandial levels, should be used to calculate the HGI. Furthermore, the linear regression equation used to calculate the predicted HbA_{1c} cannot be extrapolated to other populations: a new equation has to be devised for each population. Moreover, as the SMART study was conducted in a single central academic university hospital, the diversity of the cohort was limited to almost only Caucasians. Finally, there were few events relevant to the secondary outcomes of stroke and myocardial infarction, thereby raising caution as regards the validity of those outcome results.

Conclusion

In patients with T2DM but without CVD, higher HGI was related to higher risk of cardiovascular events whereas in patients with previous CVD, higher HGI was related to lower risk of myocardial infarction. However, as HbA_{1c} confers a similar risk, and given the strong correlation between HGI and HbA_{1c} in patients, any additional benefit of using HGI as a risk factor for cardiovascular events is most likely limited.

Ethical statement

The study was approved by the Medical Ethics Committee of UMCU, and written informed consent was obtained from all participants (approval number 13-597/D NL45885.041.13).

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary materials (Figs. S1, S2 and Tables S1–S4) associated with this article can be found at http://www.scincedirect.com at https://doi.org/10.1016/j.diabet.2018.04.006.

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