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ARTICLE

Association of the average rate of change in HbA_{1c} with severe adverse events: a longitudinal evaluation of audit data from the Bavarian Disease Management Program for patients with type 2 diabetes mellitus

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Abstract
Aims/hypothesis In patients with type 2 diabetes mellitus, the effects of HbA_{1c} variability on macrovascular events remain uncertain. The present investigation evaluates the association of HbA_{1c} variability with non-fatal cardiovascular events, emergency admissions and episodes of severe hypoglycaemia in a cohort of patients newly started on insulin therapy.
Methods HbA_{1c} variability was defined as the rate of change in values between observations. The medical records of 406,356 patients enrolled in a disease management programme for type 2 diabetes mellitus were analysed to identify a cohort of 13,777 patients with observed transition to insulin therapy. The cohort was observed for a period of at least 5 years. Cox regression models were applied to quantify the association of HbA_{1c} variability with the events of interest.
Results The models reveal a significant non-linear association between HbA_{1c} variability and the risk of experiencing myocardial infarction, stroke and hypoglycaemia. The lowest risk is seen with a variability of approximately 0.5% (5.5 mmol/mol) per quarter. Using Cox models to predict survival curves for the cohort with hypothetical HbA_{1c} variability of 0.5% (5.5 mmol/mol) and 1.5% (16.4 mmol/mol) per quarter, the proportion experiencing myocardial infarction within 2 years increases significantly from 1% to 10%. The proportion experiencing stroke increases from 1% to 29%, hypoglycaemia from 2% to 24% and the risk of emergency admission from 2% to 21%.
Conclusions/interpretation In patients newly started on insulin therapy, rapid and higher HbA_{1c} variability is associated with an increased risk of myocardial infarction, stroke, severe hypoglycaemia and emergency admission.

Keywords Disease management programme · HbA_{1c} variability · Health services research · Severe adverse events · Type 2 diabetes mellitus

Abbreviations

CVD	Cardiovascular disease
DMP	Disease Management Program
eGFR	Estimated GFR
HbA_{1c}-SD	Standard deviation of all HbA_{1c} values
RIACE	Renal Insufficiency And Cardiovascular Events

Introduction

Type 2 diabetes mellitus is a condition highly prevalent around the world. The impact of the associated micro- and macrovascular diseases such as chronic renal disease, diabetic retinopathy, coronary artery disease and peripheral artery disease means that this chronic disease both affects the quality of life and places a burden on healthcare systems and national economies [1, 2]. In the treatment of diabetes, the HbA_{1c} has proven to be a valid indicator of long-term glycaemic status

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and adequacy of a treatment. Its level is associated with the degree of micro- and macrovascular damage in the organism, and this has led to its use as one of the main laboratory variables in diabetes therapy [3, 4].

Various studies have demonstrated that HbA_{1c} variability is also an independent risk factor for micro- and macrovascular complications [5–10]. Yang et al demonstrated an association of HbA_{1c} variability with subclinical coronary atherosclerosis and also that HbA_{1c} variability is a stronger predictor of premature coronary damage than mean HbA_{1c} in patients with diabetes duration less than 10 years [11]. A recent observational study identified that HbA_{1c} variability is associated with mortality independent of the baseline HbA_{1c} level [12]. Conversely, a cross-sectional analysis within the Italian Renal Insufficiency And Cardiovascular Events (RIACE) multicentre study showed no impact of HbA_{1c} variability on macrovascular outcomes [13]. Previous studies investigated more often the associations between HbA_{1c} variability and microvascular complications than macrovascular outcomes [14]. The possible risks of HbA_{1c} variability in different subgroups are still not well understood and are intensively discussed. This discussion has even cast doubt on previous findings, suggesting possible statistical bias in the methods [15, 16]. There remains, therefore, some uncertainty as to the importance of HbA_{1c} variability as a concept distinct from either the absolute HbA_{1c} value or from a one-off rapid decrease to a target value. To date, most studies have expressed HbA_{1c} variability based on the standard deviation of all HbA_{1c} measurements [5–11, 13, 14].

The present study focuses on patients receiving first-time insulin treatment, which is very effective in lowering average glucose levels in an already high-risk population. We analysed routine data collected to monitor the Bavarian Disease Management Program (DMP) for patients with type 2 diabetes mellitus, which was introduced in 2003 to improve the quality of diabetes care. We hypothesise a positive correlation between high HbA_{1c} variability and the incidence of non-fatal cardiovascular outcomes (myocardial infarction and stroke), episodes of severe hypoglycaemia and emergency admissions. HbA_{1c} variability was assessed using a novel measure that demonstrates a different conceptual approach and thus complements previous work.

Methods

Cohort analysis Pseudonymised patient medical records were analysed by the Association of Statutory Health Insurance Physicians of Bavaria (Kassenärztliche Vereinigung Bayerns [KVB]). The records were collected for the primary purpose of quality assurance within a DMP for patients with type 2 diabetes mellitus and contain relevant medical information such as the current HbA_{1c} value, comorbidities and process variables. Coordinating general practitioners submit the records on a quarterly or half-yearly basis and receive remuneration for each record, regardless of the perceived quality of care. Data were available for the period October 2003 to December 2013.

To benefit from the more detailed baseline information collected prior to July 2008, patients were excluded if they were enrolled after this point. This yielded 406,356 patients with type 2 diabetes mellitus, of whom 148,132 patients had a record of insulin therapy. From this group, 16,806 patients had a documented transition to insulin therapy prior to July 2008, with an insulin-free baseline record encompassing at least 6 months to enable a valid baseline assessment. The baseline was determined in the 6 month period prior to the first record of insulin treatment. Patients were excluded as implausible or untypical if the baseline HbA_{1c} was less than 6.5% or if the baseline HbA_{1c} was less than 7.5% and no additional oral glucose-lowering therapy was recorded at baseline. This resulted in a coherent cohort of 13,777 patients.

The outcomes were recorded by the coordinating DMP physician in the consultation following the event. Mortality data were therefore not available. Myocardial infarction and stroke were defined as the new occurrence of these events according to medical standards. Severe hypoglycaemia was defined as hypoglycaemia that required medical attention. Emergency admission was defined as unplanned hospitalisation due to diabetic complications. The observation period was the time between the first record of insulin and either the end of follow-up or the record before the first event being analysed. For each outcome individually, patients were excluded if they had experienced the event of interest during the baseline period. Due to interval censoring, it was also necessary to exclude patients with an event recorded simultaneously with the first record of insulin. In such cases, it was unclear whether the event occurred before or after the transition to insulin.

In the context of the DMP record, missing data occur when no record is available, when an optional field is not filled in or when the information contained in the record changes. This has three main implications for the present study. First, sex was not recorded prior to July 2008. Patients without a recorded sex were therefore assigned to a third ‘missing’ category (alternative strategies of multiple imputation and the exclusion of these patients resulted in only marginal changes to the estimated effects of HbA_{1c} variability). Second, serum creatinine is an optional attribute, available at baseline for at most 90% of patients. The binary indicator ‘diabetic nephropathy’ was therefore used as the sole indicator of kidney function. Third, for patients temporarily dropping out of the DMP or having widely spaced records, information regarding HbA_{1c} and outcomes may be incomplete. The chosen method and study design were selected to account, as far as possible, for such data collection issues.

The study was approved by the Medical Ethics Committee of the University Hospital Klinikum rechts der Isar in Munich, Germany.

Approach to calculating HbA_{1c} variability The present study defined HbA_{1c} variability using the difference between successive measurements. These differences are scaled according to the time between measurements to obtain a series of values representing the rate of change in HbA_{1c} for the time between records. Therefore, the average rate of change in HbA_{1c} is a more detailed description of the present methodological approach to investigate HbA_{1c} variability. A value of 1 thus implies a rate of increase of 1 percentage point in HbA_{1c} per quarter, and a decrease of 1 percentage point (10.9 mmol/mol) over one quarter is considered equivalent to a decrease of 2 percentage points (21.9 mmol/mol) over two quarters. The DMP requires that physicians provide a patient record with HbA_{1c} every quarter or half year, although in practice regular measurements cannot be guaranteed. Differences were therefore discarded as unreliable observations of the true variability if the time between measurements was less than 1 week or greater than 6 months, or if the average change in HbA_{1c} was greater than 3 percentage points (32.8 mmol/mol) per quarter. Similar to previous studies [6, 10, 12, 13], the variability during the observation period was reduced to a single, directionless constant to facilitate interpretation. Whereas other studies used the standard deviation of all HbA_{1c} values (HbA_{1c}-SD), the present study used the mean of the absolute HbA_{1c} differences as described above. An alternative approach, modelling the individual differences in the framework of a time-varying covariates model, is presented in electronic supplementary material (ESM) 1.

Statistical analysis For each outcome separately, Cox proportional hazards models were used to assess the increase in risk due to HbA_{1c} variability. The models controlled for the following potentially confounding baseline variables: age; sex; smoking status; absolute HbA_{1c} value at baseline; diabetes history of more than 8 years (i.e. the median duration at baseline); cardiovascular disease; peripheral artery disease; the presence of diabetic complications (retinopathy, neuropathy or nephropathy); and record of previous myocardial infarction, stroke or diabetes-related emergency admission. It was not possible to control for severe hypoglycaemia prior to baseline because the small number of cases presents numerical problems. Non-linear effects were estimated by means of penalised splines and displayed graphically. To help assess the validity of the model, the proportional hazards assumption was tested using the cox.zph function in R [17].

The clinical relevance of the non-linear partial hazard ratios estimated by the Cox regression models is not readily apparent. For this reason, the models were used to predict adjusted survival curves for the cohort while fixing the hypothetical HbA_{1c} variability of each patient to 'low' (0.5% [5.5 mmol/mol]), 'increased' (1% [10.9 mmol/mol]) and 'high' (1.5% [16.4 mmol/mol]) levels, respectively. This classification resulted from the findings displayed in Fig. 1. Confidence intervals were estimated by means of 100 bootstrap samples [18, 19]. The model-based adjusted survival curves were compared with the unadjusted Kaplan–Meier estimates generated using the actual data (i.e. without setting HbA_{1c} variability). The analysis was conducted using the R environment for statistical computing, together with the survival package for estimation of the Cox regression models [20].

Results

Table 1 summarises the baseline characteristics. Patients with volatile HbA_{1c}, variability between 0.5% and 3% per quarter (5.5–32.8 mmol/mol), had higher baseline HbA_{1c} levels than patients with the lowest mean HbA_{1c} variability 0–0.49% (0–5.4 mmol/mol). They were also more likely to be male and to smoke. Additionally, the groups with higher HbA_{1c} variability had a higher percentage of previous stroke, myocardial infarction, peripheral artery disease, renal insufficiency and emergency admission. No large group differences were found regarding kidney function (measured by mean estimated GFR [eGFR]), blood pressure, or therapy with oral glucose-lowering medication in general or in the use of metformin. The final column summarises patients for whom the available HbA_{1c} measurements were insufficient to assess variability as

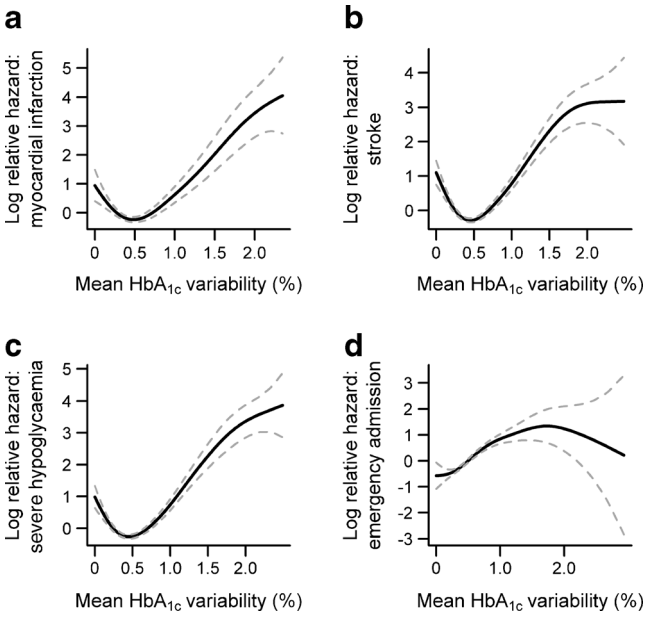

Fig. 1 Log relative hazard of mean HbA_{1c} variability per quarter for the occurrence of the respective outcomes: (**a**) myocardial infarction (**b**) stroke (**c**) severe hypoglycaemia and (**d**) emergency admission. 95% CIs are shown by the dotted lines

Table 1 Baseline variables for the cohort as a whole and then for different groups of mean HbA_{1c} variability during the follow-up

Variable	Total	Low variability[a]	Increased variability[a]	High variability[a]	*p* value	Insufficient data
n	13,777	7,779	5,134	558		306
Age, mean±SD (years)	67.4±11.1	67.8±10.5	66.6±11.7	67.4±13.6	<0.001	68.4±11.9
Female sex (%)	45.3	48.9	42.8	29.6	<0.001	22.9
Sex unknown (%)	6.8	5.1	5.7	28.9	0.003	31.4
Years since diagnosis of T2DM, mean±SD (years)	9.0±6.7	9.2±6.9	8.7±6.5	8.9±6.8	<0.001	8.2±6.4
HbA_{1c}, mean±SD (%)	8.2±1.4	8.0±1.2	8.6±1.5	9.0±1.7	<0.001	8.4±1.5
HbA_{1c}, mean±SD (mmol/mol)	66±15.3	64±13.1	70±16.4	75±18.6	<0.001	68±16.4
Previous heart attack (%)	8.6	7.8	8.2	11.7	0.12	31.4
Previous stroke (%)	7.0	6.5	7.2	10.0	0.78	8.8
Previous severe hypoglycaemia (%)	1.4	1.3	1.4	1.6	0.50	1.6
Previous diabetes related emergency admissions (%)	1.5	1.1	1.8	2.5	0.001	2.9
Peripheral artery disease (%)	11.9	11.5	11.8	14.9	0.272	17.7
Current smokers (%)	8.8	7.8	9.9	12.4	<0.001	11.4
Current and past smokers (%)	16.4	14.5	18.5	20.3	<0.001	19.9
Weight, mean±SD (kg)	84.9±18.3	83.7±17.7	86.8±18.9	84.7±19.5	<0.001	84.4±18.3
BMI, mean±SD	30.5±5.9	30.2±5.8	31.0±6.1	30.1±6.1	<0.001	29.9±5.8
Serum creatinine, mean±SD (μmol/l)	97.35±1.9	97.35±1.5	97.35±2.4	97.35±0.7	0.2	106.2±1.4
eGFR, mean±SD (mg ml^{-1} min^{-1})	77.7±27.2	77.7±26.7	78.0±27.8	76.1±28.0	0.49	75.9±28.2
eGFR<40 mg ml^{-1} min^{-1} (%)	6.7	6.2	7.1	9.4	<0.001	7.4
Blood pressure systolic, mean±SD (mmHg)	139.0±16.9	139.1±16.7	139.2±17.1	138.5±17.5	0.30	137.6±17.2
Blood pressure diastolic, mean±SD (mmHg)	80.7±9.2	80.5±9.2	81.0±9.2	81.0±9.3	<0.001	80.5±9.3
Oral glucose-lowering medication (%)	96.5	96.5	97.0	95.3	0.29	93.5
Metformin, alone or in combination (%)	68.4	68.4	69.2	65.6	<0.001	60.1
Diabetic nephropathy (%)	10.8	10.2	11.1	14.3	<0.001	12.8
Diabetic neuropathy (%)	17.8	17.4	18.6	15.4	<0.001	19.9
Diabetic retinopathy[b] (%)	7.4	7.6	7.3	6.3	<0.001	8.2

[a] Low variability 0–0.49% per quarter; increased variability 0.5–1% per quarter; high variability 1–3% per quarter

[b] Diagnosis depending on a facultative ophthalmological assessment

T2DM, type 2 diabetes mellitus

described above (e.g. measurements too widely spaced). For the distribution of follow-up and event times, see ESM 2.

Figure 1 displays the non-linear effect of mean HbA_{1c} variability as estimated by the Cox regression models. The plots reveal a clear non-linear effect of HbA_{1c} variability on the risk of experiencing myocardial infarction, stroke, hypoglycaemia and emergency admission. For the first three outcomes, the lowest risk was seen with a variability of approximately 0.5% (5.5 mmol/mol) per quarter, increasing both for patients with lower recorded variation and those with higher variation. For emergency admissions, the effect was approximately linear, with variability lower than 0.5% (5.5 mmol/mol) leading to a decreased risk. The proportional hazards assumption could be confirmed for the outcomes myocardial infarction (p=0.85) and stroke (p=0.25), but not for the outcomes of severe hypoglycaemia and emergency admission (p=0.00). This may indicate that the latter outcomes present a more complex picture, although the results obtained are consistent with those of alternative models that do pass the proportional hazards test (e.g. linear predictor for HbA_{1c} variability). ESM 1 shows an alternative model using time-varying covariables that further differentiate between positive and negative fluctuations, which together were experienced by 97% of participants.

Table 2 and Fig. 2 present the results from the adjusted survival curves generated by the Cox regression models. If all patients had a mean HbA_{1c} variability of 0.5% (5.5 mmol/mol), the models predict 5 year incidences (i.e. 100% minus the proportion without event after 5 years) of 3% for myocardial infarction and 5% each for stroke, severe hypoglycaemia and emergency admission. These predictions are comparable with the estimates obtained using the actual data, reflecting the fact that the distribution of average HbA_{1c} variability is centred around 0.5% (5.5 mmol/mol) and that fewer than 5% of all patients had a variability greater than 1% (10.9 mmol/mol). If all patients are imputed a variability of 1% (10.9 mmol/mol), the 5 year incidences are increased

Table 2 Unadjusted and adjusted likelihood (95% CI) of remaining free from myocardial infarction, stroke, severe hypoglycaemia or emergency admission at 2 and 5 years in patients stratified by the degree of HbA_{1c} variability

Outcome				Unadjusted survival estimates		Adjusted survival estimates					
				Cohort		Prediction: low variability		Prediction: increased variability		Prediction: high variability	
	Years	Total *n*	*n* with event	Proportion without event	95% CI	Proportion without event	95% CI	Proportion without event	95% CI	Proportion without event	95% CI
Myocardial infarction	0	12,371	0	1		1		1		1	
	2	10,940	130	0.99	(0.99, 0.99)	0.99	(0.99, 0.99)	0.97	(0.97, 0.98)	0.90	(0.85, 0.95)
	5	8,582	171	0.97	(0.97, 0.97)	0.97	(0.97, 0.98)	0.94	(0.93, 0.95)	0.79	(0.69, 0.88)
Stroke	0	12,546	0	1		1		1		1	
	2	10,939	365	0.97	(0.97, 0.97)	0.97	(0.97, 0.97)	0.92	(0.91, 0.93)	0.71	(0.64, 0.77)
	5	8,535	348	0.94	(0.93, 0.94)	0.95	(0.94, 0.95)	0.85	(0.84, 0.88)	0.54	(0.45, 0.63)
Severe hypoglycaemia	0	13,330	0	1		1		1		1	
	2	11,598	305	0.98	(0.97, 0.98)	0.98	(0.97, 0.98)	0.94	(0.93, 0.95)	0.76	(0.69, 0.83)
	5	8,873	412	0.94	(0.93, 0.94)	0.95	(0.94, 0.95)	0.86	(0.85, 0.88)	0.55	(0.43, 0.65)
Emergency admission	0	13,292	0	1		1		1		1	
	2	11,651	228	0.98	(0.98, 0.98)	0.98	(0.98, 0.98)	0.94	(0.93, 0.95)	0.79	(0.72, 0.84)
	5	8,982	380	0.95	(0.94, 0.95)	0.95	(0.94, 0.96)	0.85	(0.83, 0.87)	0.55	(0.45, 0.66)

The underlying Cox regression models control for the following variables: age, sex, smoking status, absolute HbA_{1c} value at baseline, diabetes history of more than 8 years (i.e. the median duration at baseline), cardiovascular disease, peripheral artery disease, the presence of diabetic complications (retinopathy, neuropathy or nephropathy) and a record of previous myocardial infarction, stroke or diabetes-related emergency admission

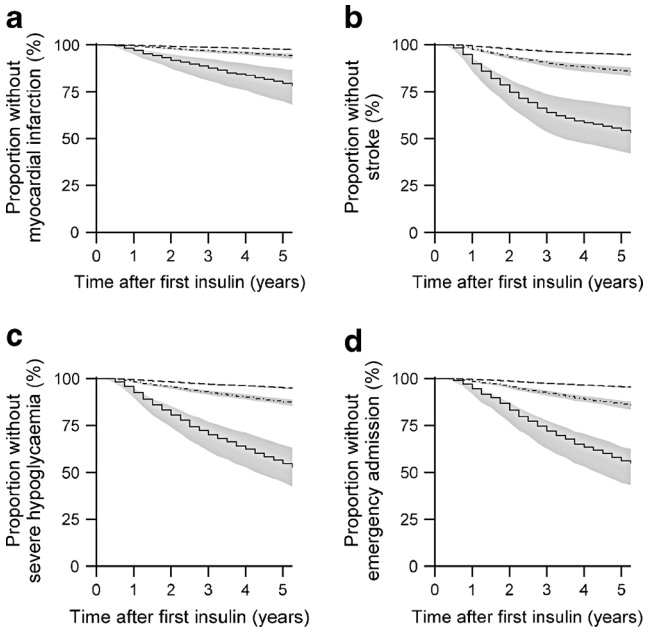

Fig. 2 Adjusted survival curves for the four outcomes as predicted by the fitted Cox regression models. The dashed lines represent the prediction after assigning each patient in the cohort an average HbA_{1c} variability of 0.5% (5.5 mmol/mol) per quarter. The dotted–dashed lines represent the prediction with an average variability of 1% (10.9 mmol/mol) per quarter and the solid lines represent the prediction with 1.5% (16.4 mmol/mol) per quarter. The shaded areas represent 95% CIs

substantially to 6% for myocardial infarction, 15% for stroke, 14% for severe hypoglycaemia and 15% for emergency admission. If all patients are assigned a variability of 1.5% (16.4 mmol/mol), the 5 year incidences are 21% for myocardial infarction, 46% for stroke, 45% for severe hypoglycaemia and 45% for emergency admission. Confidence intervals are presented in Table 2 and demonstrate that the effects are statistically significant.

Discussion

To our knowledge, the present study is the first study to evaluate the occurrence of adverse cardiovascular effects with respect to HbA_{1c} variability in the clinically important setting of insulin therapy initiation. The data describe a broad population of primary care patients, thus providing a relatively unbiased account of actual care. We proposed and applied a novel approach to investigate long-term HbA_{1c} variability. Our findings emphasise a strong correlation between the HbA_{1c} variability from initiation of insulin treatment in a previously insulin-naive patient and the adverse outcomes investigated. After adjusting for confounding factors we found that a higher average HbA_{1c} variability was significantly associated with

myocardial infarction, stroke, severe hypoglycaemic episodes and emergency admissions. Such volatility results from a fluctuation in both directions over a series of measurements. Variability is therefore an indication of unstable glucose control and can also be a marker of therapy adherence and patient compliance [21]. The exact pathophysiological mechanisms of this finding remain unclear [22–27]. Recently, several studies have shown correlations between microvascular outcomes and HbA_{1c} variability, both in type 1 diabetes mellitus [14, 28] and type 2 diabetes mellitus [5–10]. These mainly focus on microalbuminuria, and trials investigating macrovascular outcomes have not had concurrent results. The RIACE study group found no association between HbA_{1c} variability and myocardial infarction or stroke [13], although average HbA_{1c} variability in the individuals under investigation was lower (HbA_{1c}-SD values at 0.46% [5.0 mmol/mol] in patients with cardiovascular disease [CVD] and 0.47% [5.1 mmol/mol] in patients without cardiovascular disease) in comparison with other studies. For example, a Finnish cohort study of type 1 diabetes mellitus patients [28] demonstrated an association between macrovascular outcomes and HbA_{1c} variability, with HbA_{1c}-SD at 0.79% (8.6 mmol/mol) without cardiovascular events and 0.87% (9.5 mmol/mol) in patients with cardiovascular events. A Chinese study observing a long-term SD of HbA_{1c} in 8439 patients with type 2 diabetes mellitus was also able to establish that patients who developed CVD exhibited higher variability (HbA_{1c}-SD 1,4% [15.3 mmol/mol] vs 1,1% [12.0 mmol/mol]). Here, CVD was defined more widely, including, for example, myocardial infarction, heart failure and non-fatal ischaemic stroke [10]. Interestingly, the recent literature is quite inconsistent about the relationship between the effect of low HbA_{1c} and the risk of mortality or CVD [15]. Various studies demonstrated a consistent positive linear relationship between HbA_{1c} and the risk of mortality or CVD [29, 30]. Other studies revealed a non-linear (U- or J-shaped) relationship [31, 32]. The present findings confirm to a great extent the recent results from Kontopantelis et al [33]. They showed, within a retrospective cohort study of more than 246,000 patients after adjustment for several important confounders, that the relationship between HbA_{1c} levels and coronary and stroke mortality was positive curvilinear related (U-shaped). These results are in line with the present non-linear-findings, with the lowest risk for cardiovascular events and hypoglycaemia seen with an HbA_{1c} variability of approximately 0.5% (5.5 mmol/mol) per quarter.

The definition and measurement of HbA_{1c} variability present a central difficulty with such studies, as patients usually have irregular follow-up periods with measurements often unequally spaced. Our definition of HbA_{1c} variability complements the more basic approach taken by previous studies [5–11, 13, 14, 28]. These have generally defined variability as the standard deviation of all HbA_{1c} measurements during the observational period, with correction for the number of measurements available. This approach has two main problems. First, the length of time between measurements is ignored, leading to potentially misleading conclusions when HbA_{1c} measurements are widely spaced. Second, with only a small number of measurements per patient, the validity and interpretation of the standard deviation, even with correction, is unclear. Based on the squared difference of the measurements to their average value, the approach would seem to amplify large differences. The difficulty in the definition and interpretation of HbA_{1c} variability has been noted by several authors [15, 16]. Our approach provides a partial but imperfect solution to these problems; while accounting for the length of time between measurements, the variance of our statistic may be higher with widely spaced measurements. Further statistical refinement may therefore be possible. Only Skriver and colleagues used an improved definition similar to our own, averaging the absolute differences of the HbA_{1c} measurements from a defined reference point [12]. The studies differ in their choice of reference point and thereby in the interpretation of the measure. For Skriver and colleagues, variability is the residual of the observations from a line connecting the first and last observation, such that a patient with linearly increasing or decreasing HbA_{1c} is considered to have zero HbA_{1c} variability. Our definition, providing a standardised measure of the rate of change in HbA_{1c} value, would consider the same patient to have positive variability. It would seem that our measure more directly accounts for changes in HbA_{1c} level, whereas Skriver and colleagues investigate the deviation from a smooth linear trend. Further work is required to establish the most robust method of measuring HbA_{1c} variability in a clinical or study setting. Statistical simulation studies could shed further light on this question.

When comparing the results of the present study to similar studies, it is important to note that patients were observed from the initiation of insulin therapy. This patient group is potentially at higher risk of adverse events than others. Furthermore, our definition of HbA_{1c} variability differs from the standard deviation used in other studies.

This study has several important strengths. The database used enabled the identification of a homogeneous group with regularly spaced, longitudinal records of HbA_{1c} and other diabetes-related information. The size and composition of this study group represents a typical cohort of patients at high risk for HbA_{1c} variability. The underlying DMP encompasses approximately 63% [34] of all type 2 diabetes mellitus patients in Bavaria, with data submitted by over 6000 practices. Although some selection effects have been recorded [35], the large scale of the DMP means that patients are recruited from the vast majority of primary care practices in Bavaria.

The routine data from the DMP for type 2 diabetes mellitus were collected for the purposes of quality improvement and not primarily for medical research. For this reason, several limitations should be considered. In contrast to controlled

clinical studies, the DMP data are not subject to systematic external control or validation. Moreover, relevant information such as the insulin dosage or treatment regimen was not collected. In particular, the DMP data structure means that oral glucose-lowering medication can only be differentiated between metformin and 'other oral glucose-lowering medication' without further information on substance of dosage. A further limitation is that no record of patient dropout was available. In particular, myocardial events leading to death are not distinguishable from other forms of dropout. Mortality data were not available and therefore only non-lethal, documented outcomes could be observed, possibly leading to a bias that is difficult to quantify because of lack of data. It is noteworthy that the incidence of first myocardial infarction over the follow-up period is lower than that of stroke. As repeated events were not considered, this may reflect the higher incidence of myocardial infarction at baseline. Alternatively, myocardial infarction may more often lead to immediate dropout (e.g. death) and thus be missing from the underlying data set. Another limitation has to be considered regarding the patients' sex. For approximately 900 patients with dropout before July 2008, the sex was unknown. Sensitivity analyses showed that various methods of dealing with these patients (e.g. remove from analysis, assign a 'neutral' sex or imputation using the available data) lead only to marginal changes in the estimated effect of HbA_{1c} variability.

Finally, the DMP patient records are collected at intervals of either 3 or 6 months. Although the average lifespan of erythrocytes is 120 days, HbA_{1c} is better correlated with the mean average blood glucose level within the past 8–12 weeks [36]. Thus, an evaluation of HbA_{1c} variability should ideally measure HbA_{1c} at intervals of 2 or 3 months in all patients. The frequency of HbA_{1c} measurement compares favourably with other studies, but a controlled trial would be required to provide optimal data quality.

In summary, the results of the present study are, to a great extent, in line with findings of previous studies and recommendations like ACCORD [37], the ADA/EASD guidelines [38], which advise focusing more on a patient's overall condition and comorbidities when determining HbA_{1c} target values. In particular, our results suggest that patients experiencing a rapid and higher HbA_{1c} variability are at increased risk for myocardial infarction, stroke, severe hypoglycaemia and emergency admissions.

These results support previous findings indicating that hard and fast targeting to normalise HbA_{1c} values can lead to poorer outcomes. Further investigation is necessary to evaluate the general extent to which long-term variability in glucose control causes adverse effects in patients with type 2 diabetes mellitus. Further research is required to demonstrate whether HbA_{1c} variability represents a reliable (possible causal) predictor of adverse events in everyday clinical practice, especially when considering changes in glucose-lowering treatment.

Compliance with ethical standards

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