Variability in Glycated Hemoglobin and Risk of Poor Outcomes Among People With Type 2 Diabetes in a Large Primary Care Cohort Study

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OBJECTIVE

Diabetes guidelines focus on target glycated hemoglobin (HbA_{1c}) levels. Long-term variability in HbA_{1c} may be predictive of hospitalization or mortality, but its importance at different average levels or trajectories is unclear.

RESEARCH DESIGN AND METHODS

Using English primary care data, 58,832 patients with type 2 diabetes had HbA_{1c} average (mean of annual means), variability (coefficient of variation), and trajectory (annual regression slope) estimated during 2006–2009. Hazard ratios (HRs) for mortality and emergency hospitalization during 2010–2015, with adjustment for age, sex, smoking, BMI, duration of diabetes, and deprivation, were estimated using Cox regression. The simultaneous impact of HbA_{1c} average, variability, and trajectory was estimated using percentiles.

RESULTS

In mutually adjusted models, HbA_{1c} variability showed a consistent dose-response relationship with all-cause mortality, while average level was only important among individuals in the highest or lowest 10% of the distribution, and trajectory had no independent effect. Individuals with the most unstable HbA_{1c} (top 10%) were almost twice as likely to die (HR 1.93 [95% CI 1.72–2.16]) than were those with the most stable (bottom 10%)—an association attenuated but not explained by hypoglycemia. For emergency hospitalizations, similar trends were seen except for coronary artery disease (CAD) and ischemic stroke (IS), where increasing average rather than variability was predictive.

CONCLUSIONS

HbA_{1c} variability was strongly associated with overall mortality and emergency hospitalization and not explained by average HbA_{1c} or hypoglycemic episodes. Only for CAD and IS hospitalizations was no association found, with average HbA_{1c} strongly predictive. Targets should focus on both stability and absolute level of HbA_{1c}.

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There is substantial evidence that increases in chronic levels of average hyperglycemia (as generally measured by glycated hemoglobin [HbA_{1c}]) are associated with higher risk of various diabetes (DM) complications including microvascular and macrovascular events (1,2), particularly when levels are substantially elevated (for example, >8% HbA_{1c} [64 mmol/mol]) (3). Randomized controlled trials (RCTs) showed that lower HbA_{1c} is associated with significant reductions in risk of microvascular complications (3,4), though less convincingly or consistently in risk of all-cause mortality or cardiovascular disease (CVD) (5–8). Average HbA_{1c} does not explain all the variation in risk observed though; including variability in HbA_{1c} improved prediction of microvascular events in secondary analyses of the Diabetes Control and Complications Trial (9). Recent studies using latent growth modeling have also demonstrated that patients with type 2 DM (T2DM) with "low and stable" patterns of HbA_{1c} over time have lower risks than those with upward, downward, or more variable patterns (10,11). It has thus been hypothesized that longer-term variability in serial HbA_{1c} measurements may also be important (12,13).

Existing studies of HbA_{1c} variability have provided somewhat conflicting evidence. A systematic review of observational studies published in 2015 found some evidence of higher risk associated with HbA_{1c} variability for both type 1 DM and T2DM (12). Among the 43,000 T2DM patients across 13 studies, higher variability resulted in increased risks of CVD and all-cause mortality, as well as certain microvascular outcomes (particularly retinopathy and neuropathy) (12). However, most of the included studies had limitations such as little adjustment for key confounders (12). Almost all included studies were based solely on secondary care patients, while globally most patients with diabetes are managed in the community or primary care. Also, there were high levels of heterogeneity between studies that could not be explained, possibly related to different definitions and measurements of variability, follow-up durations, DM durations, or losses to follow-up. Not all recent studies have shown substantially increased risks associated with variability (after adjustment for mean HbA_{1c}) (12,14); a recent overview concluded that variability in HbA_{1c} was "not yet established" as an independent risk factor for DM complications (13).

While randomized data might be ideal, individual RCTs lack statistical power for teasing out the relative impact of variability, after accounting for interrelated HbA_{1c} parameters such as trajectory (direction and gradient of any trend in HbA_{1c} over time; whether up or down) and average HbA_{1c}. Larger registry or database analyses are therefore critical, but relatively few have been published (15,16), and all had limitations. In particular, few previously published registry or observational studies adjusted for hypoglycemic episodes. These are known to increase mortality risk (17,18) and are not strongly correlated with average HbA_{1c} (19,20). Given the continued uncertainty, we assessed the importance of HbA_{1c} variability in predicting key outcomes (all-cause mortality, cause-specific mortality, emergency hospitalization, and cause-specific hospitalization) in a large representative retrospective cohort of primary care patients in England. Unlike previous studies, our large analysis included both men and women, middle-aged and older age-groups (ages 40–89 years), and better characterization of variability and average HbA_{1c} as well as adjustment for key confounders (12,15,16).

RESEARCH DESIGN AND METHODS

Data Source

The Clinical Practice Research Datalink (CPRD) is a large primary care database representative of the U.K. population (21,22). This study is based on 361 general practices in England only with anonymous linkage to Hospital Episode Statistics and Office for National Statistics death registration data (23). Hospital Episode Statistics records clinical and administrative information on all National Health Service–funded inpatient episodes and allows for identification of method of admission (e.g., emergency), in addition to the primary reason for the admission (24). Linkage is also available to the Index of Multiple Deprivation (IMD), the official measure for small area deprivation in the U.K., a composite ecological measure based on postcodes (25). IMD combines data from seven domains (income, employment, education skills and training, health and disability, crime, barriers to housing and services, and living environment), ranking local areas from the most deprived (1) to the least deprived (32,884) (25).

Study Design

We carried out a further analysis of individuals with DM from a previously published retrospective matched cohort study (7,22). DM type was classified using a combination of DM Read Codes and prescribing of anti-DM medication (22). Read Codes are a primary care clinical terminology used extensively in the U.K. (26). They have a hierarchical structure similar to ICD codes, and cross-mapping is possible between systems (27). In this analysis, we included only patients who were identified as having T2DM by 1 January 2008 ($n = 82,492$) and continuously registered with their practice to at least 1 January 2010 (Supplementary Fig. 1). From this group, we then restricted to 58,832 (71.3%) patients with at least one HbA_{1c} measurement in each calendar year during the 4-year baseline period (2006–2009). All patients were then followed for outcomes from 1 January 2010 until the earliest date of the following: death, de-registration from practice, practice leaving CPRD, or 31 December 2015. Mean follow-up time for all patients was ~4.1 years.

Outcomes

We measured the following primary outcomes during follow-up: all-cause mortality and first emergency hospitalization (defined as an admission that was unpredictable and at short notice because of clinical need). In further analyses, we divided mortality into cardiovascular (CVD) (any ICD-10 code beginning with "I") and noncardiovascular using underlying cause of death. We subsequently subdivided CVD into those deaths related to CAD (I20–I25.9) and IS (I63–I64) versus all other CVD codes. These causes were chosen based on a prior study demonstrating strong associations with average HbA_{1c} (28).

We also stratified emergency hospitalizations into infection-related, CVD, and CAD + IS admissions. We included infection using previously defined codes (8,25) due to strong associations with hyperglycemia and since infections may also promote HbA_{1c} variability (7,22).

HbA_{1c} Summaries

Using all recorded HbA_{1c} measurements from 2006 to 2009, we estimated, for each patient, the following: Average HbA_{1c} using the mean of annual means in each year, variability in HbA_{1c} using the coefficient of variation (CoV), and trajectory in HbA_{1c} estimated from the individual patient annual slope from a linear regression model.

Patients had a minimum of four recorded HbA_{1c} measurements to be included (one per year in the main analysis or four at any time in a less restrictive sensitivity analysis). We summarized the impact of average, variability, and trajectory of HbA_{1c} by creating six categories for each measure (using the 10th, 25th, 50th, and 75–90th percentiles as cut points [see Supplementary Fig. 2]). These categories are not of equal size because we wanted to be able to investigate extremes. However, using the same percentiles for each measure ensures a fair comparison of the importance of each of these three HbA_{1c} summary measures. We chose reference categories according to the category with the a priori lowest risk—for level, this was the 10–25th percentiles (HbA_{1c} >6.09–6.58% [43–48 mmol/mol]) due to the J-shaped distribution observed; for variability, the most stable 10% (CoV 0–3.14); and for trajectory, the category with the smallest annual slope (>−0.20 to 0.01% per year).

Confounders

In our primary analyses, we adjusted for age, sex, practice, smoking status, BMI, duration of DM, and deprivation (IMD). In secondary analyses, we further adjusted for baseline (1 January 2010) comorbidities, hypoglycemic episodes, anti-DM medications, and medications to reduce cardiovascular risk (statins, antihypertensives).

For comorbidities, we searched the primary care record for any Read Code denoting a history of atrial fibrillation, metastatic cancer, chronic obstructive pulmonary disease, dementia, epilepsy, heart failure, psychosis, schizophrenia or bipolar disorder, stroke, or transient ischemic attack (29). Hypoglycemic episodes were similarly identified using Read Codes and, additionally, ICD-10 codes on the linked hospital record. We categorized use of anti-DM medications in the baseline period (2006–2009) into five mutually exclusive hierarchical categories: any use of insulin, sulfonylureas (without insulin), biguanides (without insulin or sulfonylureas), other anti-DM medications (with or without biguanides), and none.

Statistical Analysis

Cox regression was used to estimate hazard ratios (HRs) for all-cause mortality and time to first emergency hospitalization during follow-up, with adjustment for age, age^2, sex, practice, smoking status, BMI, durations of DM, and deprivation (IMD). We then compared the impact of average, variability, and trajectory of HbA_{1c} by separately fitting the comparable categories described above to the models. Subsequently, we fitted mutually adjusted models, which included two and then all three of these HbA_{1c} summaries. In sensitivity analyses, we further adjusted for additional confounders including a history of significant hypoglycemic episodes, comorbidities using a score (29) validated for use with U.K. primary care data, and medication both for DM and for reducing cardiovascular risk (antihypertensives, statins), as described above.

Our main analyses were carried out with baseline (2006–2009) HbA_{1c} measures. We then carried out a number of sensitivity analyses. In the first, we excluded all patients who died within the first 2 years after baseline to assess the impact of "reverse causality," as it seemed plausible that control might become more variable in the last few years before death. In a second, less restrictive analysis, we included 74,339 (>90%) of patients who had at least four measurements of HbA_{1c} at any time during the baseline period (2006–2009), relaxing the requirement to have at least one measurement per year. Finally, we fitted a model with time-dependent HbA_{1c} summaries, where we updated each of the three main parameters (average, variability, and trajectory) on an annual basis (2011–2015) by including the most recent year of data into the 4-year run-in period and dropping the earliest year.

We assessed whether the pattern of relationships among average, variability, and trajectory of HbA_{1c} was similar for different cause-specific outcome measures (CVD, CAD, IS, and infection mortality or admissions). All analyses were performed in SAS, version 9.4.

RESULTS

The mean age of the 58,832 eligible patients was 67.7 years (SD 10.9) in 2008, with 55.3% men (Supplementary Table 1). Over the 4-year run-in period, eligible patients averaged 7.9 total measurements of HbA_{1c}, with a mean level of 7.4% (SD 0.7) and a slight downward trajectory (−0.01% per year). Average level and CoV were positively correlated ($r = 0.40$), while trajectory was only weakly negatively correlated with variability ($r = -0.12$) and not at all with average ($r = -0.002$) (Supplementary Fig. 2). Higher average levels, increasing variability, and positive or negative trajectories were all associated with younger age and obesity, while longer duration of DM was only related to increasing average level (Table 1 and Supplementary Fig. 3). Type of DM treatment had a significant impact on all HbA_{1c} measures, with those on insulin having higher average levels, more variability, and positive or negative trajectories (Supplementary Fig. 4).

HbA_{1c} and Mortality

In separately adjusted Cox models, both higher and very low levels of average HbA_{1c} (<6.09% [43 mmol/mol] or >7.16% [55 mmol/mol]), increasing variability, and positive or negative trajectories of HbA_{1c} were all associated with higher all-cause mortality (Table 2). In mutually adjusted models (adjustment for variability, average, and trajectory of HbA_{1c} simultaneously), the impact of average HbA_{1c} was now only seen in the top 10% of the HbA_{1c} distribution (HR 1.35 [95% CI 1.24–1.47] for HbA_{1c} >8.88% [74 mmol/mol] vs. reference category of >6.09–6.58% [43–48 mmol/mol]), while only a small impact of negative trajectory remained. Adjustment for CoV explained virtually all the effect of trajectory (Supplementary Table 2). By contrast, a graded increase in mortality risk was seen with increasing variability, ranging from HR 1.32 (95% CI 1.21–1.44) in the 25–50th percentile group for CoV to HR 1.93 (95% CI 1.72–2.16) in the top 10th percentile category. Further adjustment for history of hypoglycemic events attenuated the impact of variability, but variability still maintained a stronger and more consistent association with mortality than average HbA_{1c} (Table 2). Sensitivity analyses adjusting for comorbidities

Table 1—Summary of HbA_{1c} average, trajectory, and variability (CoV) by baseline patient characteristics

	N	Age, years	Sex (% male)	BMI, kg/m^2	Duration, years	No. of HbA_{1c} measurements	On any insulin (%)	On biguanides only (%)	History of hypoglycemia (%)
All patients	58,832	67.7 (10.9)	55.3	30.6 (6.2)	7.8 (6.2)	7.9 (2.6)	20.2	23.2	3.3
Average HbA_{1c} (%)*									
3.63–6.09	5,891	69.9 (10.8)	53.9	29.1 (6.0)	6.0 (5.5)	6.6 (2.1)	2.7	23.4	1.6
>6.09–6.58	8,812	70.3 (10.4)	51.9	29.8 (6.1)	6.3 (5.2)	7.0 (2.2)	4.3	32.8	1.9
>6.58–7.16	14,746	69.1 (10.2)	54.4	30.2 (5.9)	7.1 (5.7)	7.7 (2.3)	7.4	37.1	2.5
>7.16–7.91	14,646	67.5 (10.5)	57.0	30.8 (6.1)	8.1 (6.2)	8.4 (2.5)	19.4	21.0	3.7
>7.91–8.88	8,894	65.5 (11.0)	57.6	31.7 (6.4)	9.5 (7.0)	8.8 (2.8)	43.2	7.3	5.3
>8.88	5,843	62.2 (11.4)	56.5	32.6 (6.8)	10.0 (6.6)	8.6 (2.8)	61.0	2.7	5.3
HbA_{1c} (%) trajectory, per year†									
≤−0.48	5,897	65.4 (11.1)	56.0	31.8 (6.8)	7.9 (6.5)	8.3 (2.6)	32.6	16.4	4.9
>−0.48 to −0.20	8,827	68.0 (10.8)	55.7	30.7 (6.3)	8.5 (6.7)	8.2 (2.6)	24.3	21.8	3.7
>−0.20 to 0.01	14,699	69.3 (10.4)	53.7	29.9 (6.1)	7.8 (6.2)	7.8 (2.6)	16.1	26.1	2.8
>0.01–0.19	14,697	68.7 (10.5)	55.5	30.0 (5.9)	7.3 (5.7)	7.6 (2.5)	13.7	26.1	2.6
>0.19–0.43	8,832	66.9 (10.9)	55.9	31.1 (6.1)	7.6 (6.0)	7.9 (2.6)	19.0	24.4	3.4
>0.43	5,880	64.6 (11.8)	56.9	32.2 (6.5)	7.9 (6.1)	8.0 (2.6)	29.8	15.6	4.1
HbA_{1c} CoV‡									
0–3.14	5,879	71.3 (9.8)	50.1	28.8 (5.5)	6.6 (5.3)	6.7 (2.1)	4.8	28.6	1.1
>3.14–4.71	8,827	70.1 (10.1)	52.5	29.5 (5.8)	7.4 (6.1)	7.4 (2.4)	10.0	30.4	1.7
>4.71–7.33	14,710	68.6 (10.4)	54.7	30.2 (6.0)	8.0 (6.2)	8.0 (2.5)	17.2	27.1	3.0
>7.33–11.40	14,709	66.6 (10.9)	57.0	31.1 (6.2)	8.4 (6.4)	8.3 (2.6)	25.3	20.3	3.8
>11.40–16.64	8,824	65.4 (11.2)	58.8	31.9 (6.5)	8.2 (6.4)	8.4 (2.7)	30.2	15.5	5.0
>16.64	5,883	64.8 (11.6)	56.9	32.3 (7.0)	7.0 (5.9)	8.2 (2.6)	30.5	15.8	5.2

Data are means (SD) unless otherwise indicated. *Average of the previous four annual means (2006, 2007, 2008, and 2009). Categories correspond to the following cut points: 16–43, >43–48, >48–55, >55–63, >63–74, and >74 mmol/mol. †Mean annual slope from the linear regression of all measurements in the previous 4 years. ‡CoV derived from the mean and SD of all measurements in the previous 4 years. Note that all cutoffs correspond to the following percentiles: 10th, 25th, 50th, 75th, and 90th.

Table 2—Adjusted HRs (95% CI) for mortality by HbA_{1c} average, trajectory, and variability (CoV)

	Average only	Trajectory only	Variability only	All HbA_{1c} measures	All HbA_{1c} measures plus hypoglycemia
Average HbA_{1c} (%)*					
3.63–6.09	1.10 (1.02–1.19)			1.14 (1.05–1.24)	1.12 (1.04–1.22)
>6.09–6.58	1			1	1
>6.58–7.16	0.99 (0.93–1.06)			0.93 (0.87–0.99)	0.94 (0.88–1.01)
>7.16–7.91	1.10 (1.03–1.18)			0.95 (0.88–1.02)	0.97 (0.90–1.04)
>7.91–8.88	1.35 (1.26–1.45)			1.06 (0.98–1.14)	1.07 (1.00–1.16)
>8.88	1.82 (1.69–1.96)			1.35 (1.24–1.47)	1.35 (1.24–1.48)
HbA_{1c} (%) trajectory, per year†					
≤−0.48		1.63 (1.51–1.75)		1.08 (1.00–1.18)	1.11 (1.02–1.21)
>−0.48 to −0.20		1.20 (1.13–1.29)		0.99 (0.93–1.05)	1.00 (0.94–1.07)
>−0.20 to 0.01		1		1	1
>0.01–0.19		0.97 (0.92–1.03)		0.99 (0.94–1.05)	0.98 (0.92–1.04)
>0.19–0.43		1.14 (1.06–1.23)		0.98 (0.91–1.06)	0.98 (0.91–1.06)
>0.43		1.52 (1.40–1.64)		1.03 (0.95–1.12)	1.04 (0.95–1.14)
HbA_{1c} CoV‡					
0–3.14			1	1	1
>3.14–4.71			1.01 (0.93–1.10)	1.03 (0.95–1.12)	1.03 (0.94–1.11)
>4.71–7.33			1.27 (1.17–1.38)	1.32 (1.21–1.44)	1.25 (1.15–1.37)
>7.33–11.40			1.49 (1.38–1.62)	1.51 (1.38–1.66)	1.39 (1.26–1.52)
>11.40–16.64			1.78 (1.62–1.95)	1.71 (1.53–1.91)	1.50 (1.34–1.68)
>16.64			2.12 (1.93–2.23)	1.93 (1.72–2.16)	1.67 (1.49–1.87)
History of hypoglycemia§					
No					1
Yes					1.36 (1.24–1.49)

All models mutually adjust for HbA_{1c} measures (unless indicated) plus age, age^2, sex, duration of DM, index of multiple deprivation, smoking, and BMI. *Average of the previous four annual means (2006, 2007, 2008, and 2009). †Mean annual slope from the linear regression of all measurements in the previous 4 years. ‡CoV derived from the mean and SD of all measurements in the previous 4 years. Note that all cutoffs correspond to the following percentiles: 10th, 25th, 50th, 75th, and 90th. §History of any hypoglycemic event recorded prior to 2010.

did not affect the estimates of mortality risk associated with any of the HbA_{1c} measures, while adjustment for DM treatment category explained the greater risk associated with highest average level but not any of the associations with variability (Supplementary Table 3). Results were similar for older and younger groups (Supplementary Fig. 5). Exclusion of patients with <2 years' survival after baseline did not substantially change any coefficient (Supplementary Table 4). Including more patients by relaxing the inclusion criteria to four HbA_{1c} measurements at any time did not significantly alter any patterns of risk (Supplementary Table 5).

The impact of variability on mortality risk was seen at both the highest and lowest levels of average HbA_{1c} (Fig. 1 and Supplementary Table 6). Among 14,703 patients (25%) with the lowest average HbA_{1c} levels (<6.6% [48 mmol/mol]), HR for mortality was 1.40 (95% CI 1.06–1.85) for those with the highest levels of CoV (>16.64%). For 14,737 patients with the highest average HbA_{1c} levels (>7.9% [63 mmol/mol), the respective HR for the highest CoV was 2.14 (95% CI 1.32–3.47). The impact of increasing average HbA_{1c} for those patients with the highest and lowest CoV was again restricted to those in the top category; for the 25% of patients with the lowest CoV, average HbA_{1c} of 8.88% (74 mmol/mol) or higher had a raised risk (HR 1.49 [95% CI 1.06–2.11]) of mortality, similar to the HR of 1.31 (95% CI 1.11–1.54) for those with the same average HbA_{1c} and the highest levels of CoV.

In time-updated Cox models, CoV became a stronger predictor of mortality risk (HR 2.97 [95% CI 2.60–3.38] for those with the highest CoV of ≥16.64%), while the average HbA_{1c} was no longer statistically significant, even at the highest level of >8.88% (>74 mmol/mol) (HR 1.05 [95% CI 0.95–1.16]) (Supplementary Table 7).

However, the pattern of variability being more strongly associated than average level was somewhat altered when the cause of death was CAD and IS (Supplementary Table 8). Here, a rise in mortality was seen with any average HbA_{1c} >7.91% (63 mmol/mol), and there was almost a doubling in risk of death for those with the highest HbA_{1c} levels (HbA_{1c} >8.88% [74 mmol/mol], HR 1.88 [95% CI 1.60–2.21]). Associations with variability were still present but slightly weaker for CAD and IS deaths (HR 1.54 [95% CI 1.23–1.93]) for the most variable patients (CoV >16.64%).

HbA_{1c} and Hospitalizations

Both average and CoV HbA_{1c} showed statistically positive associations with time to first emergency hospitalization, while trajectory was not related (Table 3). Overall, and for infection and all CVD hospitalizations, the magnitude of the association was more comparable between average level and variability, especially at extreme levels. For CAD and IS hospitalizations the pattern was different; a stronger graded association with average HbA_{1c} was now seen. Risk was increased for any HbA_{1c} >7.16% (55 mmol/mol), and for the top 10% (>8.88% [>74 mmol/mol]) there was over a doubling in risk of hospitalization (HR 2.13 [95% CI 1.91–2.37]). Further, associations with rising CoV were no longer statistically significant (Table 3). Trajectory was not independently associated with hospitalization.

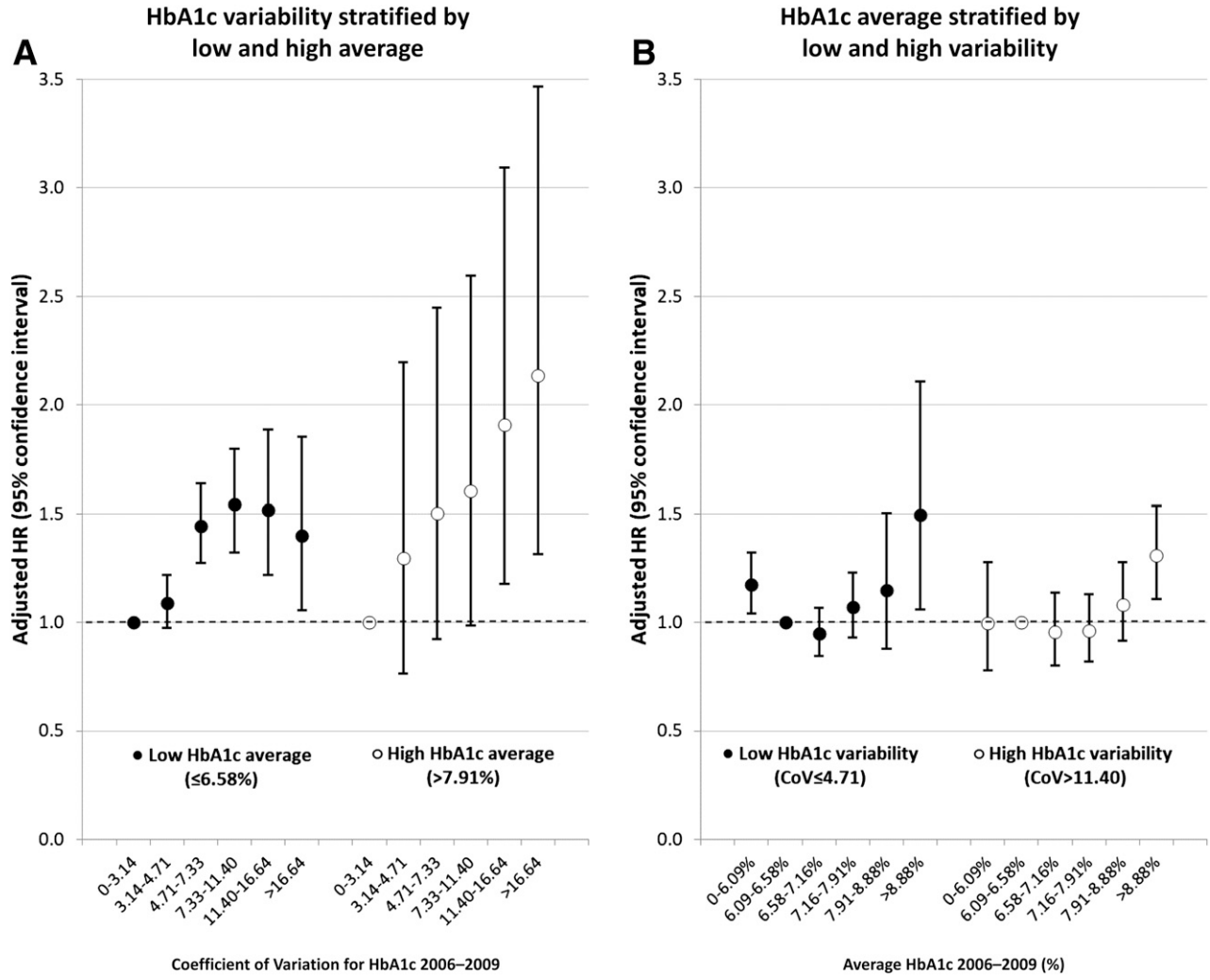

Figure 1—Stratified analyses demonstrating the effect of HbA_{1c} variability at high and low values of average HbA_{1c} and of average HbA_{1c} at high and low levels of variability. *A* and *B*: Effects of HbA_{1c} variability on the risk of all-cause mortality stratified by high and low average HbA_{1c} (*A*) and the effects of HbA_{1c} average on the risk of all-cause mortality stratified by high and low variability (*B*). "High" and "low" are defined as the top 25% and bottom 25% of the distributions of HbA_{1c} average and variability. HbA_{1c} of 6.58% converts to 48.4 mmol/mol and 7.91% to 63.0 mmol/mol.

CONCLUSIONS

Key Messages

Increasing variability and raised average level of HbA_{1c} were both associated with higher risks of mortality. Trajectory of trend in HbA_{1c} was not associated after adjustment for variability. There appeared to be a J-shaped relationship between average HbA_{1c} and mortality, with increased risks at very low levels of average HbA_{1c} (<6.09% [43 mmol/mol]) and the highest level (>8.88% [74 mmol/mol], the top 10% of our distribution). A steeper and more monotonic relationship was observed between variability and mortality, with even small rises in CoV increasing risk. Associations with variability were also consistent, being present at both higher and lower levels of average HbA_{1c} and among both younger and older people with T2DM. This was particularly evident after we carried out time-updated analyses, or adjusted for treatment category, when the highest levels of variability almost trebled the risk of mortality, and average HbA_{1c} was no longer associated with mortality at all. The magnitude of associations with variability was attenuated slightly after adjustment for severe hypoglycemic episodes; adjustments for a comorbidity score or use of key medications had little effect on any measure.

However, with CAD and IS as the outcome, these associations were altered. For mortality, associations with average HbA_{1c} became stronger than CoV, and for first emergency hospitalization, associations with average HbA_{1c} were further strengthened, and the relationship with CoV was no longer statistically significant.

Comparisons With Recent Literature

Recent systematic reviews have identified a range of potential risks associated with HbA_{1c} variability but have had great difficulty in reaching clear conclusions about the magnitude of these risks and how they interplay with average HbA_{1c} (12–14). This uncertainty may be due to the lack of standard approach to summarizing HbA_{1c} variability or agreement about how much might be clinically significant. Many studies use a relative measure (e.g., using categories of the distribution of HbA_{1c} variability such as quartiles), but this is hard to compare across studies and even within the same

Table 3—Mutually adjusted HRs (95% CI) for first emergency hospital admission during 2010–2015 by HbA_{1c} average, trajectory, and variability

	First emergency hospital admission 2010–2015			
	Any	Infection only	Cardiovascular only	CAD/IS only
Average HbA_{1c} (%)*				
3.63–6.09	1.10 (1.04–1.15)	1.11 (1.02–1.21)	1.02 (0.95–1.10)	0.99 (0.89–1.10)
>6.09–6.58	1	1	1	1
>6.58–7.16	0.98 (0.94–1.02)	1.02 (0.95–1.10)	0.95 (0.90–1.01)	1.06 (0.97–1.16)
>7.16–7.91	0.98 (0.94–1.02)	1.03 (0.94–1.12)	1.06 (0.99–1.12)	1.26 (1.16–1.38)
>7.91–8.88	1.12 (1.07–1.18)	1.24 (1.14–1.36)	1.20 (1.12–1.28)	1.46 (1.32–1.61)
>8.88	1.42 (1.35–1.50)	1.63 (1.48–1.80)	1.63 (1.51–1.75)	2.13 (1.91–2.37)
HbA_{1c} (%) trajectory, per year†				
≤−0.48	1.00 (0.95–1.06)	0.97 (0.88–1.07)	0.98 (0.91–1.07)	0.96 (0.85–1.08)
>−0.48 to −0.20	1.01 (0.97–1.06)	1.01 (0.93–1.10)	1.04 (0.98–1.11)	1.08 (0.99–1.18)
>−0.20 to 0.01	1	1	1	1
>0.01–0.19	0.96 (0.93–1.00)	0.99 (0.93–1.06)	0.98 (0.93–1.04)	1.02 (0.95–1.10)
>0.19–0.43	0.99 (0.95–1.03)	1.00 (0.92–1.08)	0.99 (0.93–1.05)	1.04 (0.96–1.13)
>0.43	1.03 (0.97–1.08)	1.04 (0.95–1.14)	1.00 (0.92–1.08)	1.09 (0.97–1.21)
HbA_{1c} CoV‡				
0–3.14	1	1	1	1
>3.14–4.71	1.10 (1.04–1.15)	1.06 (0.96–1.18)	1.04 (0.96–1.13)	1.03 (0.96–1.13)
>4.71–7.33	1.23 (1.17–1.29)	1.30 (1.19–1.42)	1.16 (1.08–1.25)	1.12 (1.02–1.24)
>7.33–11.40	1.31 (1.23–1.38)	1.37 (1.23–1.50)	1.23 (1.14–1.33)	1.14 (1.02–1.28)
>11.40–16.64	1.46 (1.38–1.55)	1.56 (1.40–1.73)	1.32 (1.21–1.44)	1.12 (0.99–1.27)
>16.64	1.53 (1.42–1.64)	1.70 (1.50–1.93)	1.36 (1.22–1.51)	1.09 (0.94–1.26)

All models mutually adjust for HbA_{1c} measures plus age, age^2, sex, duration of DM, index of multiple deprivation, smoking, and BMI. During follow-up, N = 25,927 (44.1%) have any emergency hospital admission, 8,192 (13.9%) have an admission for infection, 11,798 (20.1%) have a cardiovascular admission, and 6,018 (10.2%) have an admission for CAD or IS. *Average of the previous four annual means (2006, 2007, 2008, and 2009). †Mean annual slope from the linear regression of all measurements in the previous 4 years. ‡CoV derived from the mean and SD of all measurements in the previous 4 years. Note that all cutoffs correspond to the following percentiles: 10th, 25th, 50th, 75th, and 90th.

study (with average HbA_{1c}, mostly defined using absolute levels).

Nevertheless, our results are broadly similar to two other recent studies: one a cohort study from Italy (Renal Insufficiency And Cardiovascular Events [RIACE]) (30) and the other an analysis of U.K. data from a different primary care data set (16). The Italian study (15,000 T2DM patients) shared many similar conclusions, particularly that HbA_{1c} variability was a stronger predictor of all-cause mortality than mean HbA_{1c} and that trajectory was not associated with mortality after adjustment for variability. They also found an impact of variability at both higher and lower levels of mean HbA_{1c}, although, unlike our results, they found no J-shape association between average HbA_{1c} and risk. The large (n = 54,000) U.K. primary care cohort study among older people (>70) in the U.K. found mortality risks of similar magnitude (approximately a two times increase), with average HbA_{1c} only important at higher levels, >9% (75 mmol/mol) (16). Unlike our study, these authors also reported independent associations between HbA_{1c} trajectory and mortality. They defined "variability" as an absolute change in HbA_{1c} of at least 0.5%, which might potentially classify individuals with frequent smaller changes as "stable" who would be classified as more "variable" using our CoV measurement; this might explain why trajectory seemed to have stronger associations with poor outcomes in their analysis. Our study also showed that variability is important in younger people with T2DM as well as older people.

Our results feature key areas of disagreement with other recent studies. A large cohort study of U.S. Veterans Affairs patients (~58,000 T2DM patients) identified increased risks of mortality, hospitalization, and myocardial infarction associated with increasing variability, but they seemed lower in magnitude, with average HbA_{1c} remaining more strongly associated (15). This study included mostly older white men (mean age 65 years), not representative of broader populations, and could not adjust for some key confounders such as DM duration, strongly related to average HbA_{1c} in our data set, and did not use statistically comparable categories to compare average and variability in HbA_{1c}. In a very large primary care–based Chinese cohort (~90,000 T2DM patients), linear associations were found for variability in HbA_{1c} with cardiovascular and all-cause mortality, but these were only significant in younger people, <65 years of age (31). Baseline assessments of HbA_{1c} were not clearly made before measurement of outcomes, and this potentially introduces a risk of "reverse causality" for older people where stronger associations with variability were observed. In a small cohort of older people with long-standing T2DM from Rio de Janiero, variability was found to be a better predictor of microvascular complications than average HbA_{1c} but only when average levels were relatively low (<7.5% [58.5 mmol/mol]). The somewhat conflicting results of these key studies have possibly also led to some inertia in developing guidelines that more explicitly address HbA_{1c} stability in T2DM patients.

Key Strengths and Limitations

The key strengths of our study are the large and representative data set that was used. We included both younger and older people with prevalent T2DM and measured variability, average, and

trajectory of HbA_{1c} over a 4-year time period using comparable categories before assessing outcomes. This is important in assessing causality, since many DM complications (e.g., infections, cardiovascular events) themselves interfere with HbA_{1c} control and alter HbA_{1c} levels, potentially leading to reverse causality (22). While we designed our study to ensure that HbA_{1c} variables were measured prior to the occurrence of any key outcome, the limitation here is that these measurements become out-of-date over the lengthy follow-up (up to 6 years). To address this, we carried out a sensitivity analysis that incorporated time-updated HbA_{1c} values. This strengthened the importance of variability as a predictor of all-cause mortality, with average HbA_{1c} no longer showing an effect. While time-updated analyses appear more credible, they also run a greater risk of reverse causality; i.e., HbA_{1c} may become more variable in the final years before death due to functional, physical, or cognitive decline. However, in an analysis of individuals with at least 2-year survival after baseline, we found no evidence of reverse causality. We did not find strong evidence of an impact of trajectory (direction of trends in HbA_{1c}) on mortality or hospitalization risks after adjustment for variability. However, our study design only measured trajectory over a 4-year time period, which may be insufficient to fully characterize this for most people. Our results were robust to adjustment for key confounders measured at baseline, and we were able to adjust for more potential confounders than previous studies. However, residual confounding remains a potential explanation for our findings. In particular, we were unable to adjust for other lifestyle factors that might be important (e.g., exercise, diet) and also for adherence to treatment. Most of our covariates are likely to be relatively stable over the study period, but medication use may vary, and therefore reported associations based on baseline usage may be attenuated. We were unable to consider newer classes of anti-DM medications (e.g., sodium–glucose cotransporter 2 or glucagon-like peptides) that may be beneficial in promoting stability, as too few patients were taking these drugs during the baseline period (2006–2009), though this could be possible in the future. Our primary analyses excluded a significant number of patients who did not have at least one measurement of HbA_{1c} in each year of the 4-year baseline period. This was done in order to develop a more robust measurement of variability and to avoid biasing estimates of variability toward patients who may have had a lot of measurements taken close to a health event (e.g., infection [16], CVD episode [32], or medication change that might influence this parameter) but not at other times. However, in a less restrictive sensitivity analysis including any patient with at least four measurements (>90% of the total eligible) at any time during the baseline period, results were almost identical. As there were virtually no other missing data, we believe our findings are likely representative of most patients with T2DM. However, 6% of the cohort died during the baseline period, and also younger, more recently diagnosed patients were less likely to be included, as they may not have had four serial measurements before 1 January 2010. Our definition of hypoglycemia is highly specific and likely to have missed milder episodes that occur and are resolved by the patient or with assistance from carers/family and are not recorded. However, more severe hypoglycemia requiring medical care would be expected to present in secondary care (either through accident and emergency attendance or hospital admission) and have been reported to primary care, and so captured in our data set, and may also be more strongly associated with poor outcomes. Most previous larger studies using HbA_{1c} to assess variability have not been able to adjust for hypoglycemia. Finally, our article is based entirely on observational data and so cannot consider the extent to which any risks might be reversible if variability were reduced.

Clinical Implications and Mechanisms

A detailed analysis of mechanisms by which longer-term variability might increase mortality risk is beyond the scope of this study. Adjustments for severe hypoglycemia did not affect estimates of the strength of associations between poor outcomes and average HbA_{1c} but somewhat attenuated the magnitude of our variability estimates, though they remained statistically and clinically significant. Associations between mortality and average HbA_{1c} were attenuated after adjustment for treatment, but this was not the case for CoV, which may suggest different mechanisms of action. Any increases in CoV raised mortality risk in our analyses, while higher average HbA_{1c} had an effect only among the highest 10% of the distribution. Elevated average HbA_{1c} was more strongly associated with CAD and IS deaths, and particularly CAD and IS hospitalizations, where the association with CoV was completely attenuated and only average levels appeared predictive. Strong associations of average HbA_{1c} with CAD and myocardial infarction were also observed recently in the UK Biobank data (28) and the Veterans Affairs study (15). Few other studies have been sufficiently powered to assess associations among HbA_{1c} average, variability, and CVD subcodes, but this suggests that a focus on CVD as an outcome could be incomplete. HbA_{1c} has known associations with both preprandial glucose levels and atherosclerosis but is poorly correlated with postprandial glucose (33,34) and provides an incomplete measure of acute glucose excursions. Other measures including blood glucose variability may therefore be important to support DM management better (33,34), though HbA_{1c} measurements are the mainstay of DM management in primary care in the U.K.

Higher levels of HbA_{1c} variability could potentially reflect many different patient and service level factors. Our study identified that higher variability was associated with many patient characteristics that might be related to patient adherence with DM management, such as smoking, higher BMI, male sex, younger age, and higher levels of socioeconomic deprivation. However, we are not aware of evidence that HbA_{1c} variability is directly related to treatment adherence and could not assess this. Other factors that may increase variability might include poor social support, infections, and cardiovascular events (35) and/or potentially a more severe, rapidly progressing form of DM (36). Nevertheless, variability in HbA_{1c} could be easily measured in U.K. primary care, and likely elsewhere, since multiple measurements of HbA_{1c} are available in routine practice for most patients. They could thus inform decisions based on finer assessments of future risk.

Our data suggest that for T2DM patients with lower or moderately raised average HbA_{1c} (<9% in our cohort), mortality risk might be reduced more by promoting stability than reductions in

chronic levels, and even at higher average levels stability remains important. There were already evidence, guidelines, and analyses supporting more relaxed targets for average HbA_{1c} among older people (37) and also for people with significant comorbidity or frailty (16,38–40). Our results may suggest this could also be appropriate for younger people, but this requires confirmation in RCTs. We included mainly prevalent cases of DM, some of whom had already been diagnosed with DM for many years, and considered only mortality and unplanned hospital admissions over a relatively short term. Importantly, smaller elevations in average HbA_{1c} increased the risk of CAD and IS hospitalizations and mortality in our data, and only average was predictive of first hospitalization for CAD and IS. High-quality randomized evidence has identified benefits from tighter control (to <7% HbA_{1c} [53 mmol/mol]) among individuals with newly diagnosed DM, particularly for microvascular outcomes (3), though benefits for cardiovascular outcomes and all-cause mortality has been less clear-cut (5,6). These findings also strongly support a focus on average chronic levels. Our study highlights the need for individualized targets but suggests a need to focus on stability as well as a lower target level for many people living with T2DM.

Conclusion

Variability in HbA_{1c} was more important than average level in predicting mortality among people with prevalent T2DM in U.K. primary care. Average level remained important, though, particularly at higher levels of HbA_{1c} (e.g., >9% [75 mmol/mol]), and both high average and linearly increasing variability were important for predicting first unplanned hospital admission and cardiovascular mortality. Current guidelines promote both lower levels of HbA_{1c} and stability of HbA_{1c}, but tend to prioritize the former, while our analyses generally suggest that more importance should be given to stability for many patients. Measurements of variability could be incorporated into primary care consultations to guide risk assessment also.

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The interpretation and conclusions contained in this report are those of the authors alone.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. J.A.C., I.M.C., and D.G.C. contributed to the development of study methodology. J.A.C. and D.G.C. contributed to study conceptualization. I.M.C. acquired data and performed statistical analysis. T.H. and S.D. provided clinical input. J.A.C., I.M.C., T.H., S.D., and D.G.C. contributed to interpretation of results and drafting of the manuscript and approved the final version. I.M.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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