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ORIGINAL ARTICLE

Haemoglobin A1c variability is a strong, independent predictor of all-cause mortality in patients with type 2 diabetes

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Aims: To evaluate various measures of haemoglobin (Hb) A1c variability, compared with average HbA1c, as independent predictors of mortality.

Materials and Methods: The Renal Insufficiency And Cardiovascular Events Italian multicentre study enroled 15 733 patients with type 2 diabetes from 19 diabetes clinics during 2006-2008. A total of 3 to 5 HbA1c measures, obtained during the 2-year period before enrolment, were available from 9 centres (8290 patients) and were used to calculate average HbA1c (HbA1c -MEAN) and HbA1c variability, measured as intra-individual standard deviation (HbA1c-SD), SD adjusted for the number of HbA1c assessments (HbA1c-AdjSD) and coefficient of variation (HbA1c-CV), that is, the HbA1c-SD to HbA1c-MEAN ratio. Vital status on October 31, 2015 was retrieved for 8252 patients (99.5%).

Results: The measures of HbA1c variability increased according to quartiles of HbA1c-MEAN and vice versa. HbA1c-MEAN and measures of HbA1c variability were associated with all-cause mortality; however, the strength of association of HbA1c-MEAN was lower than that of HbA1c -SD, HbA1c-CV or HbA1c-AdjSD, and disappeared after adjusting for confounders and any of the measures of HbA1c variability. Mortality increased with quartiles of HbA1c-MEAN, HbA1c -SD, HbA1c-CV and HbA1c-AdjSD, but only the association with HbA1c variability measures remained after adjustment for confounders and/or each other measure. In the fully adjusted model, mortality risk was lower for HbA1c-SD below the median and higher for HbA1c-SD above the median, regardless of whether HbA1c-MEAN was below or above the median.

Conclusions: HbA1c variability is a strong, independent predictor of all-cause mortality in type 2 diabetes and appears to be even more powerful than average HbA1c in predicting mortality.

KEYWORDS

all-cause mortality, cardiovascular risk factors, complications, HbA1c, type 2 diabetes, variability

*A complete list of RIACE Investigators can be found online in Supporting Information (Appendix S1).

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1 | INTRODUCTION

Two milestone intervention trials have provided compelling evidence that intensive glycaemic control is effective in preventing microvascular and macrovascular complications in both type 1[1] and type 2[2] diabetes. Post hoc analyses of these trials showed that long-term glycaemic exposure, expressed as the updated mean of haemoglobin (Hb) A1c levels over time, is the main risk factor for development of complications,[3,4] and that the average HbA1c level explained virtually all of the difference in risk of complications between the intensive and conventional treatment groups.[5] However, it has been suggested that adverse outcomes in diabetic individuals may be related also to the variability in glycaemic control, which includes glucose variability and HbA1c variability.

Glucose variability relates to within-day fluctuations in glycaemia, with alternations in peaks, especially post-prandial,[6] and in troughs, which may fall into the hypoglycaemic range.[7] Both hyperglycaemic and hypoglycaemic episodes may trigger a pro-inflammatory, pro-oxidant and pro-coagulant response,[8,9] thus favouring the development and progression of complications. However, despite its biological plausibility, the detrimental effect of glucose variability is still a matter of debate because of the conflicting results of existing studies.[10,11]

Conversely, HbA1c variability relates to changes in HbA1c from one visit to the next. Although the underlying mechanisms are less clear, the experimental evidence supporting a role for HbA1c variability in the development of complications is more robust than that for glucose variability, as shown by two recent meta-analyses.[12,13] In detail, studies in patients with type 1 diabetes[14–17] consistently showed that HbA1c variability is an independent risk factor for microvascular complications, and one such study also found a relation with cardiovascular disease (CVD),[16] even after adjusting for average HbA1c. Studies in subjects with type 2 diabetes were concordant in reporting an independent association of HbA1c variability with diabetic kidney disease (DKD), especially albuminuric DKD,[18–21] whereas conflicting results were obtained for diabetic retinopathy (DR)[20,22] and CVD.[23,24] Finally, a few studies reported an association of HbA1c variability with mortality, independent of average HbA1c.[25–28]

We used the large cohort of the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study (NCT00715481; www.ClinicalTrials.gov) to evaluate various measures of HbA1c variability, compared with average HbA1c, as independent predictors of mortality in patients with type 2 diabetes.

2 | MATERIALS AND METHODS

2.1 | Design

The RIACE study is an observational, prospective, multicentre, cohort study on the impact of estimated glomerular filtration rate (eGFR) on morbidity and mortality in patients with type 2 diabetes.[29] The study was conducted in accordance with the Declaration of Helsinki. It was approved by the locally appointed ethics committees, and participants gave informed consent.

2.2 | Subjects

The RIACE population consists of 15 933 Caucasian non-dialytic patients with type 2 diabetes, consecutively visiting 19 hospital-based, tertiary referral, diabetes clinics of the National Health Service throughout Italy (Appendix S1) during the years 2006-2008. Because of missing or implausible values, 160 patients were excluded, and the data from the remaining 15 773 subjects were analysed. Traditional CVD risk factors and complications were determined as part of the baseline assessment, using a standardized protocol across participating centres.[29]

The present study analysed data from 9 centres, among the 19 participating centres, that provided HbA1c measures obtained during the 2-year period prior to enrolment.[20] Of the 10 737 patients enrolled in these centres, 8290 patients (77.2%; 52.6% of the entire RIACE cohort) had 3 to 5 HbA1c values, including those obtained at enrolment, thus allowing the assessment of HbA1c variability; the remaining 2447 subjects with 1 (n = 922) or 2 (n = 1525) HbA1c measure(s) were excluded from analysis. The pre-specified working hypothesis was that HbA1c variability is an independent predictor of all-cause mortality beyond average HbA1c.

2.3 | All-cause mortality

The vital status of study subjects on October 31, 2015 was verified by interrogating the Italian Health Card database (http://sistemats1.sanita.finanze.it/wps/portal/) which provides updated information on all current Italian residents.

2.4 | HbA1c variability

HbA1c was measured by HPLC using DCCT-aligned methods. As reference intervals were slightly different among centres (ie, the upper limit varied from 5.7% to 6.2%), the results from different laboratories were harmonized post-analytically by normalization to an upper limit of 6.0%, using the following formula: measured HbA1c × 6.0/upper

limit of the reference interval for each centre. Average HbA1c and HbA1c variability were calculated retrospectively for each patient as the intra-individual mean (HbA1c-MEAN) and standard deviation (HbA1c-SD), respectively, of 4.52 ± 0.76 HbA1c values obtained during the 2-year period preceding recruitment, including the enrolment visit. As few values would make the SD apparently greater than many values, HbA1c-SD was adjusted for the number of HbA1c assessments according to the formula: HbA1c -adjSD = SD/√[n/(n-1)].[14,16,20] Furthermore, as a normalized measure of variability, the coefficient of variation of HbA1c (HbA1c-CV) was calculated as the HbA1c-SD to HbA1c-MEAN ratio to correct for larger SDs resulting from higher absolute HbA1c-MEAN values.[15,20]

2.5 | Traditional CVD risk factors

Study subjects underwent a structured interview to collect the following information: age at the time of interview, smoking status (never, former, current), known diabetes duration, co-morbidities and current glucose-, lipid- and blood pressure (BP)-lowering therapy.[29]

Body mass index (BMI) was calculated from weight and height. Waist circumference was measured in 4618 subjects and was estimated in the remaining 11 155 individuals, using the log-transformed BMI values, as previously described.[30] BP was measured with a sphygmomanometer, with patients seated with the arm at the heart level. Hypertension was defined as systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 and/or anti-hypertensive treatment.[29]

Triglycerides and total and HDL cholesterol were determined in fasting blood samples by colorimetric enzymatic methods. Non-HDL cholesterol was calculated by the formula: total cholesterol – HDL cholesterol, and LDL cholesterol was calculated by the Friedewald formula. Dyslipidaemia was defined as LDL cholesterol ≥2.59 mmoL/L and/or treatment with lipid-lowering agents.[29]

2.6 | Complications

The presence of DKD was assessed by measuring albuminuria and serum creatinine, as previously detailed.[29,31] The albumin excretion rate (AER) was obtained from 24-hour urine collections or was calculated from the albumin-to-creatinine ratio in early-morning, first-voided urine samples, using a conversion formula developed in patients with type 1 diabetes and preliminarily validated in a subgroup of RIACE participants. Albuminuria was measured in fresh urine samples by immunonephelometry or immunoturbidimetry, in the absence of interfering clinical conditions. For each patient, 1 to 3 measurements were obtained; in cases of multiple measurements, the geometric mean of 2 or 3 values was used for analysis. In subjects with multiple measurements (4062 with at least 2 and 2310 with 3 values), the concordance rate between the first value and the geometric mean was >90% for all albuminuria categories.[31] Serum (and urine) creatinine was measured using the modified Jaffe method, and eGFR was calculated using the CKD Epidemiology Collaboration equation, with the mean serum creatinine value in cases of multiple measures.[29,31] Patients were then classified into categories of albuminuria (A1-A3) and eGFR (G1-G5) and were assigned to one of the following DKD phenotypes: no DKD (ie, A1G1-A1G2), albuminuria alone (albuminuric DKD with preserved eGFR, ie. A2G1-A2G2-A3G1-A3G2), reduced eGFR alone (non-albuminuric DKD, ie, A1G3-A1G4-A1G5), or both albuminuria and reduced eGFR (albuminuric DKD with reduced eGFR, ie, A2G3-A2G4-A2G5-A3G3-A3G4-A3G5), as previously reported.[29]

In each centre, the presence of DR was assessed by an expert ophthalmologist by dilated fundoscopy. Patients with mild or moderate non-proliferative DR were classified as having non-advanced DR, whereas those with severe non-proliferative DR, proliferative DR or maculopathy were grouped into the advanced DR category. DR grade was assigned based on the worse eye.[29]

Previous major acute CVD events, including myocardial infarction, stroke, foot ulcer/gangrene/amputation and coronary, carotid and lower limb revascularization, were adjudicated based on hospital discharge records by an ad hoc committee in each centre.[29]

2.7 | Statistical analysis

Data are expressed as the mean ±SD or median (interquartile range) for continuous variables, and the number of cases (percentage) for categorical variables. Continuous variables were compared by 1-way ANOVA, for normally distributed variables, or by the Kruskal-Wallis test, in cases of variables with a skewed distribution. Pearson's chi-squared test was applied to categorical variables.

Patients were stratified by quartiles of HbA1c-MEAN, HbA1c -SD, HbA1c-AdjSD and HbA1c-CV values. In addition, they were classified into 4 HbA1c variability categories based on HbA1c-MEAN and HbA1c-SD levels below or above population median values, that is, (1) both below median, (2) HbA1c-MEAN below and HbA1c-SD above median, (3) HbA1c-MEAN above and HbA1c-SD below median and (4) both above median.[15,20]

Kaplan-Meier survival curves for all-cause mortality were calculated according to quartiles of HbA1c-MEAN, HbA1c-SD, HbA1c-CV or HbA1c-AdjSD, or to the above categories of HbA1c variability. Differences in survival rates were analysed using the log-rank statistic. Survival analyses were performed by Cox proportional hazards regression according to (1) HbA1c-MEAN, HbA1c-SD, HbA1c-CV, or HbA1c-AdjSD as continuous variables; (2) quartiles of HbA1c-MEAN, HbA1c-SD, HbA1c-CV or HbA1c-AdjSD; and (3) HbA1c variability categories. Analyses were adjusted for baseline age and gender (model 1) or age and gender plus smoking habits, known disease duration, anti-hyperglycaemic treatment, triglycerides, HDL cholesterol, dyslipidaemia, hypertension, DKD phenotype, DR grade, history of major acute CVD events and cancer (model 2). Survival analyses by HbA1c-MEAN or quartiles of HbA1c-MEAN (both models 1 and 2) were further adjusted for HbA1c-SD, HbA1c-CV or HbA1c-AdjSD or for quartiles of these measures, respectively. The results of these analyses were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

All P values were 2-sided, and a $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois).

3 | RESULTS

Valid information concerning vital status on October 31, 2015 was retrieved for 8252 patients, that is, 99.5% of the 8290 RIACE participants for whom 3 to 5 HbA1c values were available. At the time of the census, 6239 (75.6%) patients were alive and 2013 (24.4%) subjects were deceased. The duration of follow-up was 7.35 ±2.08 years.

The baseline clinical features of subjects with 3 to 5 available HbA1c values were similar to those of subjects with fewer than 3 HbA1c values available (not shown). The measures of HbA1c variability increased according to the quartiles of HbA1c-MEAN and vice versa. In addition, CVD risk factors and the prevalence of complications and treatments increased according to the quartiles of HbA1c-MEAN and HbA1c-SD, with the exception of diabetes duration and the prevalence of female gender, dyslipidaemia, hypertension, non-advanced DR and CVD, which did not increase with increasing HbA1c-SD quartiles (Tables S1 and S2). The results for quartiles of HbA1c-CV (and of HbA1c-AdjSD) were similar to those of quartiles of HbA1c-SD (not shown), suggesting that differences among HbA1c-SD quartiles were not solely attributable to differences in absolute HbA1c-MEAN values.

TABLE 1 All-cause mortality by HbA1c-MEAN and measures of HbA1c variability

Model 1 Not adjusted for each other	HR	95% CI	*P*
HbA1c-MEAN	1.162	1.120-1.205	<.0001
HbA1c-SD	1.495	1.381-1.618	<.0001
HbA1c-CV	1.034	1.027-1.042	<.0001
HbA1c-AdJSD	1.601	1.461-1.754	<.0001
Adjusted for each other	HR	95% CI	*P*
HbA1c-MEAN	1.097	1.053-1.143	<.0001
HbA1c-SD	1.367	1.248-1.496	<.0001
HbA1c-MEAN	1.124	1.082-1.167	<.0001
HbA1c-CV	1.028	1.021-1.036	<.0001
HbA1c-MEAN	1.094	1.050-1.140	<0001
HbA1c-AdJSD	1.444	1.301-1.604	<.0001
Model 2			
Not adjusted for each other	HR	95% CI	*P*
HbA1c-MEAN	1.048	1.006-1.092	.024
HbA1c-SD	1.335	1.223-1.457	<.0001
HbA1c-CV	1.027	1.019-1.035	<.0001
HbA1c-AdJSD	1.404	1.270-1.553	<.0001
Adjusted for each other	HR	95% CI	*P*
HbA1c-MEAN	–	–	–
HbA1c-SD	1.335	1.223-1.457	<.0001
HbA1c-MEAN	–	–	–
HbA1c-CV	1.027	1.019-1.035	<.0001
HbA1c-MEAN	–	–	–
HbA1c-AdJSD	1.404	1.270-1.553	<.0001

Abbreviations: CI, confidence interval; HbA1c-AdjSD, adjusted SD of HbA1c; HbA1c, haemoglobin A1c; HbA1c-CV, coefficient of variation of HbA1c; HbA1c-MEAN, average HbA1c; HbA1c-SD, standard deviation of HbA1c; HR, hazard ratio. Survival analysis by Cox proportional hazards regression according to HbA1c-MEAN and measures of HbA1c variability (HbA1c-SD, HbA1c-CV and HbA1c-AdjSD), adjusted for age and gender (model 1) and for multiple confounders (model 2), not adjusted or further adjusted for each other (ie, HbA1c-MEAN for each measure of HbA1c variability).

Both HbA1c-MEAN and measures of HbA1c variability were associated with all-cause mortality in the unadjusted Cox regression analysis (not shown) after adjustment for age and gender (model 1) and multiple confounders (model 2), but the strength of association of HbA1c-MEAN was lower than that of HbA1c-SD, HbA1c-CV or HbA1c-AdjSD (Table 1). However, when adjusting for both multiple confounders and each other, only measures of HbA1c variability remained as significant correlates of mortality (Table 1). Kaplan-Meier curves (not shown) and unadjusted Cox proportional hazards regression (Table 2) showed that mortality increased with the quartiles of HbA1c-MEAN, HbA1c-SD, HbA1c-CV and HbA1c-AdjSD; these relationships remained after adjusting for age and gender (model 1), but not for multiple confounders (model 2) in the case of HbA1c-MEAN. Similar results were obtained with further adjustment for each other measure, with only the quartiles of HbA1c-SD, HbA1c-CV and HbA1c-AdjSD correlating in a stepwise manner with mortality (Figure 1).

The CVD risk profile was the worst and the prevalence of complications, with the exception of non-albuminuric DKD, was the highest in subjects with both HbA1c-MEAN and HbA1c-SD above the median, whereas they were the best and lowest, respectively, in subjects with both values below the median. Individuals with 1 measure above and 1 measure below the median were similar with respect to several features, with the exception of longer duration of diabetes and higher prevalence of female gender, dyslipidaemia, hypertension, insulin, lipid-lowering and anti-hypertensive treatment, DR and CVD in patients with HbA1c-MEAN above and HbA1c-SD below the median than in those with HbA1c-MEAN below and HbA1c-SD above the median (Table 3).

Kaplan-Meier curves (Figure 2A) and unadjusted Cox proportional hazards regression (Figure 2B) showed that mortality was lowest in subjects with both HbA1c-MEAN and HbA1c-SD below the median and was highest in those with both of these values above the median, whereas it was similar in subjects with 1 value above and the other below the median. When adjusting for age and gender (Figure 2C), the curves of the latter 2 groups separated, with a higher mortality risk in individuals with HbA1c-MEAN below and HbA1c-SD above the median than in those with HbA1c-MEAN above and HbA1c-SD below the median. When adjusting for multiple confounders (Figure 2D), mortality risk was lower in subjects with HbA1c-SD below the median and higher in those with HbA1c-SD above the median, regardless of whether HbA1c-MEAN was below or above the median. The results of Cox regression analysis according to categories of HbA1c variability are presented in Table S3.

4 | DISCUSSION

This study provides compelling evidence that HbA1c variability, regardless of whether it is measured as HbA1c-SD, HbA1c-CV or HbA1c-AdjSD, is a strong and independent predictor of total mortality in patients with type 2 diabetes. It also shows that HbA1c variability is apparently more powerful than average HbA1c in predicting all-cause mortality, as HbA1c-MEAN was no longer associated with mortality

TABLE 2 All-cause mortality by quartiles of HbA1c-MEAN and of measures of HbA1c variability

				Adjusted					
	Unadjusted			Model 1			Model 2		
Variables	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
HbA1c-MEAN			<.0001			<.0001			
Quartile I	1.000	–	-	1.000	-	–			
Quartile II	1.116	0.979-1.273	.101	1.026	0.900-1.170	.700			
Quartile III	1.257	1.106-1.428	<.0001	1.171	1.030-1.332	.016			
Quartile IV	1.527	1.349-1.729	<.0001	1.493	1.318-1.690	<.0001			
HbA1c-SD			.001			<.0001			<.0001
Quartile I	1.000	–	-	1.000	–	–	1.000	–	–
Quartile II	1.185	1.039-1.352	.011	1.206	1.058-1.376	.005	1.124	0.985-1.284	.084
Quartile III	1.412	1.244-1.604	<.0001	1.490	1.312-1.693	<.0001	1.306	1.147-1.487	<.0001
Quartile IV	1.429	1.259-1.623	<.0001	1.779	1.566-2.021	<.0001	1.441	1.262-1.645	<.0001
HbA1c-CV			<.0001			<.0001			<.0001
Quartile I	1.000	–	-	1.000	–	–	1.000	–	–
Quartile II	1.118	0.981-1.275	094	1.196	1.050-1.364	.007	1.153	1.011-1.315	.033
Quartile III	1.397	1.233-1.584	<.0001	1.521	1.341-1.724	<.0001	1.354	1.192-1.537	<.0001
Quartile IV	1.321	1.163-1.499	<.0001	1.692	1.490-1.922	<.0001	1.452	1.274-1.654	<.0001
HbA1c-AdjSD			<.0001			<.0001			<.0001
Quartile I	1.000	–	–	1.000	–	–	1.000	–	–
Quartile II	1.191	1.044-1.359	.009	1.204	1.056-1.374	<.0001	1.127	0.987-1.287	.078
Quartile III	1.409	1.240-1.601	<.0001	1.475	1.298-1.676	<.0001	1.281	1.125-1.460	<.0001
Quartile IV	1.458	1.284-1.656	<.0001	1.787	1.573-2.031	<.0001	1.445	1.266-1.650	<.0001

Abbreviations: HbA1c, haemoglobin A1c,; HbA1c-MEAN, average HbA1c; HbA1c-SD, standard deviation of HbA1c; HbA1c-CV, coefficient of variation of HbA1c; HbA1c-AdjSD, adjusted SD of HbA1c; HR, hazard ratio; CI, confidence interval. Survival analysis by Cox proportional hazards regression according to quartiles of HbA1c-MEAN, HbA1c-SD, HbA1c-CV, and HbA1c-AdjSD, unadjusted or adjusted for age and gender (model 1) or multiple confounders (model 2).

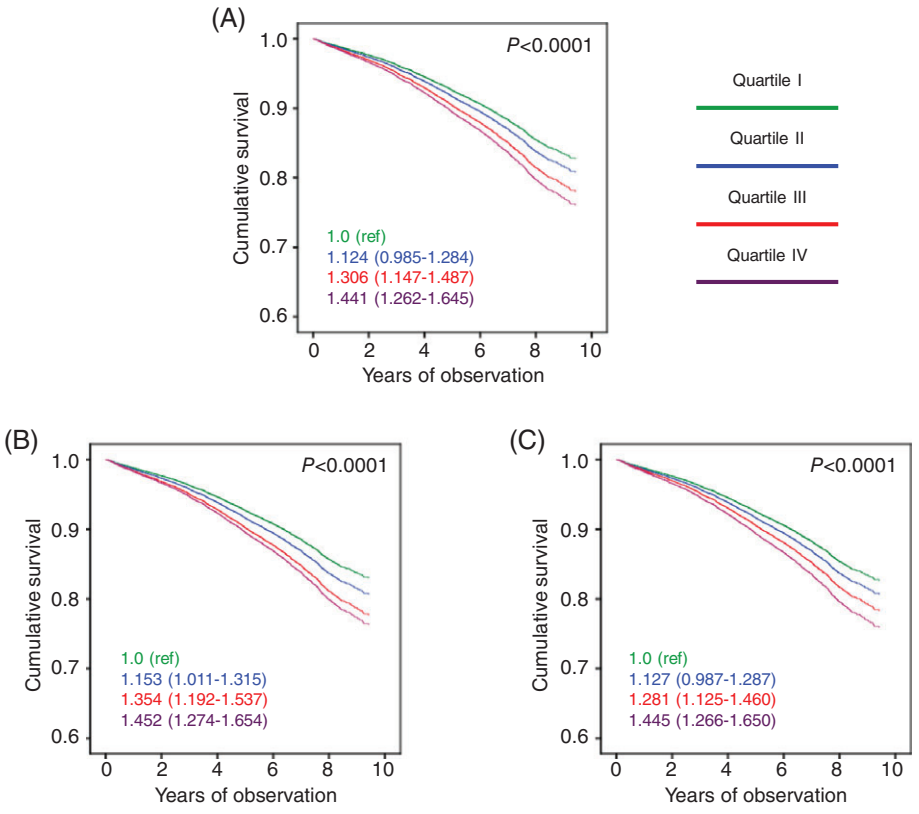

FIGURE 1 Cox proportional hazards regression according to quartiles of HbA1c-SD A, HbA1c-CV B, and HbA1c-AdjSD D, adjusted for HbA1c-MEAN and multiple confounders. HRs (95% CI) for mortality are shown for each quartile of measures of HbA1c variability. Abbreviations: HbA1c-AdjSD, adjusted HbA1c-SD; HbA1c-CV, coefficient of variation of HbA1c; HbA1c-SD, standard deviation of HbA1c; HbA1c, haemoglobin A1c; HbA1c-MEAN, average HbA1c; HR, hazard ratio; CI, confidence interval

TABLE 3 Clinical features by categories of HbA1c variability

Variables	Groups				
	HbA1c-MEAN$_{below}$		HbA1c-MEAN$_{above}$		
	HbA1c-SD$_{below}$	HbA1c-SD$_{above}$	HbA1c-SD$_{below}$	HbA1c-SD$_{above}$	*P**
n (%)	2767 (33.5)	1362 (16.5)	1360 (16.5)	2763 (33.5)	
HbA1c-MEAN, % (mmol Mol^{-1})	6.70 ±0.58 (49.7 ± 6.3)	6.91 ±0.51 (52.0 ± 5.6)	8.34 ±0.73 (67.7 ± 8.0)	8.77 ±0.97 (72.3 ± 10.6)	
HbA1c-SD, % (mmol Mol^{-1})	0.27 ±0.10 (3.0 ±1.1)	0.76 ±0.32 (8.3 ± 3.5)	0.32 ±0.09 (3.5 ±1.0)	0.98 ± ±0.56 (10.7 ±6.1)	
HbA1c-AdjSD, % (mmol Mol^{-1})	0.24 ±0.09 (2.6 ±1.0)	0.66 ±0.27 (7.2 ± 3.0)	0.28 ±0.08 (3.1 ±0.9)	0.86 ±0.48 (9.4 ±5.2)	
HbA1c-CV, %	4.08 ±1.46	10.97 ± 4.60	3.81 ±1.13	11.13 ±6.10	
Deaths, n (%)	560 (20.2)	334 (24.6)	335 (24.6)	784 (28.4)	<.0001
Age, years	68.0 ± 9.7	66.7 ±10.1	69.7 ±9.2	67.2 ±10.1	<.0001
Male gender, n (%)	1620 (58.5)	833 (61.2)	673 (49.5)	1578 (57.1)	<.0001
Diabetes duration, years	11.0 (5.0-21.0)	9.0 (4.0-18.0)	19.0 (12.0-27.0)	15.0 (9.0-24.0)	<.0001
Smoking, n (%)					<.0001
Never	1475 (53.3)	688 (50.5)	781 (57.4)	1518 (54.9)	
Former	906 (32.7)	449 (33.0)	404 (29.7)	783 (28.3)	
Current	386 (14.0)	225 (16.5)	175 (12.9)	462 (16.7)	
BMI, kg·m^{-2}	28.3 ± 4.7	29.0 ± 5.1	28.5 ± 5.1	29.5 ±5.2	<.0001
Waist circumference, cm	101.1 ± 9.6	102.7 ± 10.4	101.3 ± 10.2	103.6 ±10.6	<.0001
Triglycerides, mmolċl^{-1}	1.22 (0.90-1.70)	1.31 (0.97-1.83)	1.30 (0.93-1.84)	1.42 (1.03-2.05)	<.0001
Total cholesterol, mmol·l^{-1}	4.74 ±0.90	4.72 ±0.93	4.76 ±0.91	4.77 ±0.99	.423
HDL cholesterol, mmol·l^{-1}	1.34 ±0.36	1.29 ±0.35	1.32 ±0.34	1.26 ±0.34	<.0001
LDL cholesterol, mmol·l^{-1}	2.77 ±0.77	2.75 ±0.81	2.76 ±0.78	2.75 ±0.85	.885
Non-HDL cholesterol, mmol·l^{-1}	3.40 ±0.85	3.44 ±0.90	3.45 ±0.88	3.51 ±0.96	<0001
Dyslipidaemia, n (%)	2311 (83.5)	1113 (81.7)	1163 (85.5)	2281 (82.6)	.039
Systolic BP, mm Hg	138.6 ±17.9	141.6 ±17.8	138.4 ±18.0	140.3 ±19.0	<.0001
Diastolic BP, mm Hg	78.2 ±9.0	78.6 ±8.9	78.8 ±9.2	78.7 ±9.6	.159
Pulse pressure, mm Hg	60.4 ±16.0	62.9 ±15.8	59.6 ±15.8	61.6 ±16.4	<.0001
Hypertension, n (%)	2340 (84.6)	1141 (83.8)	1223 (89.9)	,372 (85.8)	<.0001
Anti-hyperglycaemic treatment, n (%)					<.0001
Lifestyle	643 (23.2)	131 (9.6)	41 (3.0)	60 (2.2)	
Non-insulin	1794 (64.8)	1019 (74.8)	865 (63.6)	1628 (58.9)	
Insulin	330 (11.9)	212 (15.6)	454 (33.4)	1075 (38.9)	
Lipid-lowering treatment, n (%)	1369 (49.5)	609 (44.7)	720 (52.9)	198 (50.6)	<.0001
Anti-hypertensive treatment, n (%)	2019 (73.0)	967 (71.0)	1034 (76.0)	2034 (73.6)	.027
ACE-I/ARB treatment, n (%)	1614 (58.1)	789 (57.7)	873 (63.9)	1715 (61.7)	<.0001
Albuminuria, mg day^{-1}	11.3 (6.0-24.5)	13.4 (6.9-29.9)	13.6 (6.9-32.9)	16.3 (7.5-46.8)	<.0001
Serum creatinine, μMol·l^{-1}l	83.9 ± 35.5	86.2 ± 3 9.6	83.0 ± 26.4	86.1 ± 32.3	.007
eGFR, mlċmin^{-1}ċ1.73 m^{-2}	79.4 ± 19.1	76.4 ± 19.5	80.1 ±21.2	77.6 ±21.0	<.0001
DKD phenotype					<.0001
No DKD	1922 (69.5)	879 (64.5)	829 (61.0)	1555 (56.3)	
Albuminuric DKD with preserved eGFR	420 (15.2)	238 (17.5)	252 (18.5)	640 (23.2)	
Non-albuminuric DKD	250 (9.0)	146 (10.7)	166 (12.2)	283 (10.2)	
Albuminuric DKD with reduced eGFR	175 (6.3)	99 (7.3)	113 (8.3)	285 (10.3)	
DR, n (%)					<.0001
No DR	2333 (84.3)	1135 (83.3)	884 (65.0)	1890 (68.4)	
Non-advanced DR	300 (10.8)	142 (10.4)	321 (23.6)	503 (18.2)	
Advanced DR	134 (4.8)	85 (6.2)	155 (11.4)	370 (13.4)	
Any CVD, n (%)	612 (22.1)	279 (20.5)	423 (31.1)	802 (29.0)	<.0001
Any cancer, n (%)	157 (5.7)	101 (7.4)	78 (5.7)	146 (5.3)	.049

Abbreviations: ACE-I/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HbA1c-MEAN, average HbA1c; HbA1c-SD, standard deviation of HbA1c; MEAN$_{above}$/SD$_{above}$, HbA1c-MEAN above the median/HbA1c-SD above the median; MEAN$_{above}$/SD$_{below}$, HbA1c-MEAN above the median/HbA1c-SD below the median; MEAN$_{below}$/SD$_{above}$, HbA1c-MEAN below the median/HbA1c-SD above the median; MEAN$_{below}$/SD$_{below}$, HbA1c-MEAN below the median/HbA1c-SD below the median. Main baseline clinical characteristics of subjects with vital status information stratified according to HbA1c-MEAN and HbA1c-SD above and below the cohort median values. Values are given as mean ± SD or median (interquartile range) for continuous variables and n (%) for categorical variables; *P values for comparison between groups using one-way ANOVA for parametric or the corresponding Kruskal-Wallis test for non-parametric continuous variables and the χ^2 test for categorical variables.

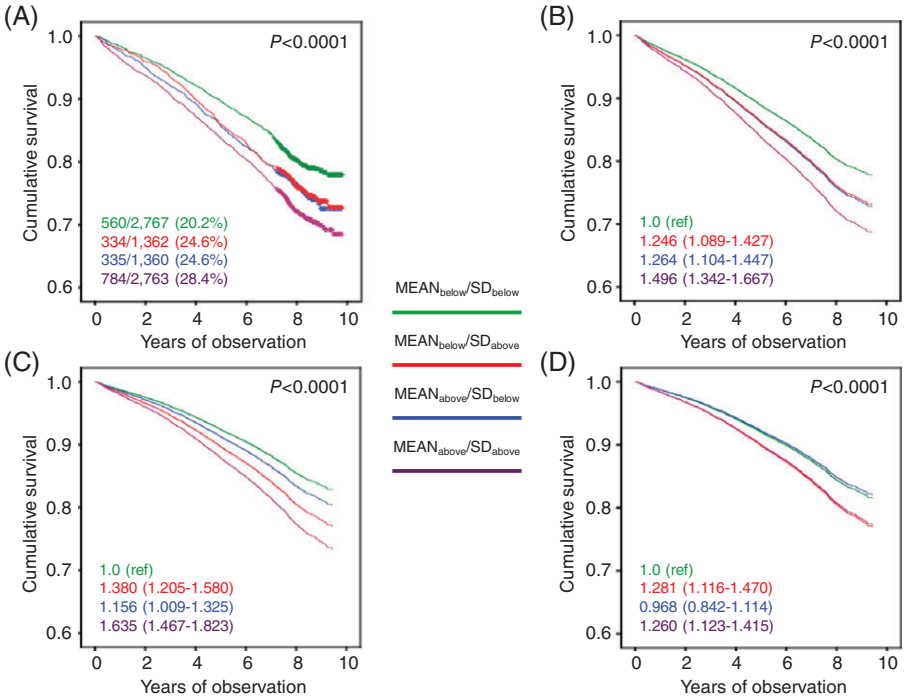

FIGURE 2 Cumulative survival by Kaplan-Meier analysis A, and Cox proportional hazards regression, unadjusted B, and adjusted for age and gender C, and multiple confounders D, according to categories of HbA1c variability. Number (percentage) of deaths or HRs (95% CI) for mortality are shown for each category of HbA1c variability. Abbreviations: CI, confidence interval; HbA1c, haemoglobin A1c; HR, hazard ratio; $MEAN_{below}/SD_{below}$, average HbA1c below the median/standard deviation of HbA1c below the median; $MEAN_{below}/SD_{above}$, HbA1c-MEAN below the median/HbA1c-SD above the median; $MEAN_{above}/SD_{below}$, HbA1c-MEAN above the median/HbA1c-SD below the median; $MEAN_{above}/SD_{above}$, HbA1c-MEAN above the median/HbA1c-SD above the median

after adjusting for any measure of HbA1c variability in the fully adjusted model. The independent association of HbA1c variability with all-cause mortality is consistent with a post hoc analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial[27] and two previous retrospective studies of limited size, which also found no correlation between HbA1c-MEAN and mortality after adjusting for HbA1c-SD or HbA1c-CV.[25,26] In addition, our findings are consistent with studies reporting a relationship between visit-to-visit (day-to-day) variations in fasting glucose and mortality,[27,32] including the recent Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE).[33,34]

The most intriguing and original finding of our study was that the relationship between HbA1c-MEAN and all-cause mortality was greatly reduced and that the relationship with quartiles of HbA1c-MEAN disappeared also after adjusting for complications (and other CVD risk factors and cancer), whereas that between measures of HbA1c variability and quartiles of these measures did not. In addition, in the fully adjusted model, there was no effect on mortality of HbA1c-MEAN, below or above the median, whereas mortality risk was dependent on whether HbA1c-SD was below or above the median. These findings might imply that the impact of average HbA1c on the risk of all-cause mortality is lower than that of HbA1c variability and is mediated predominantly through its effect that favours the development of long-term complications. Conversely, HbA1c variability seems to affect mortality risk to a greater extent than does HbA1c-MEAN and beyond the previously reported effect on complications,[12–23] which was found to be even stronger than that of HbA1c-MEAN for (albuminuric) DKD.[20] However, the higher prevalence of advanced DR and CVD in subjects with high HbA1c-MEAN than in those with high HbA1c-SD suggests that this heavier burden of non-renal complications, particularly CVD, may have masked the influence of average HbA1c on the risk of mortality in regression models. Of note, our results concerning the impact of HbA1c-MEAN and HbA1c-SD, below or above the median, on mortality are in contrast to those concerning DKD in subjects with type 1 diabetes from the FinnDiane Study[15] and in patients with type 2 diabetes from the RIACE study,[20] both of which show that the risk of (albuminuric) DKD was similar in those with 1 measure above and the other below the median. This discrepancy may support the interpretation that the independent effect of HbA1c variability on mortality is not mediated through its effect that favours DKD.

Another interesting observation of our study is the absence of impact of low HbA1c-MEAN on mortality, as the lowest quartile of HbA1c-MEAN was associated with the lowest mortality risk, with or without adjustment for HbA1c variability. This finding is at odds with previous reports showing a J-curve effect of HbA1c on the risk of mortality,[35] although other surveys failed to detect this effect.[36] In addition, our observation is in contrast to studies reporting that the impact of HbA1c variability on mortality was higher in subjects with relatively low HbA1c-MEAN,[25] or significantly increased only in those with initial HbA1c below 8%.[28] However, patients falling within the lowest quartile of HbA1c-MEAN had an average HbA1c of 6.32%, with only 421 (20.4%) subjects showing values below 6%, and 125 (6.1%) of them using insulin and/or secretagogues. Therefore, it cannot be excluded that, below a certain cut-off value of HbA1c-MEAN, this detrimental effect of low values on survival might also have been detected in the RIACE cohort.

Although this and other studies[12–23,25–28] have provided strong evidence in favour of an independent association of the HbA_{1c} change from one visit to the next with unfavourable outcomes (including mortality), it remains unclear whether this association reflects a causal relationship or, rather, depends on confounding factors that characterize subjects with high HbA1c variability. A possible mechanism underlying a promoting effect of HbA1c variability on mortality is that

periods of sustained hyperglycaemia and higher HbA1c levels may be "remembered" during subsequent periods of normoglycaemia and lower HbA1c values,[20] because of the induction of long-lasting epigenetic changes.[37] Moreover, during periods of higher HbA1c levels, patients may accumulate an excess risk, as the result of the exponential or logarithmic relation of rising HbA1c values with adverse outcomes,[4,38] which may also cause the arithmetic mean of HbA1c to underestimate the risk, which is better captured by HbA1c variability. However, the independent effect of HbA1c variability on mortality risk might also mirror (1) the poor compliance with medication and self-management, (2) the presence of multiple co-morbidities and related treatments that increase insulin resistance and, hence, CVD risk, and (3) the poor quality of life and lack of support.[13,15,39,40] These conditions might all also confer an increased risk of severe hypoglycaemia, which was shown, in the DEVOTE trial, to be associated with higher fasting glucose variability[36] and to be temporally related to mortality.[37] Unfortunately, it is difficult to design intervention trials to demonstrate a cause-effect relationship between HbA1c variability and mortality in diabetic individuals.

Strengths of this study include the large size of the cohort, the analysis of a contemporary real-life dataset and the completeness of baseline and follow-up data. A limitation might be that HbA1c variability was assessed retrospectively, over a 2-year period before enrolment, using 3 to 5 HbA1c measurements, performed, without prespecified intervals, as a part of standard care. However, a 2-year observation period and 3 to 5 measurements were found to be sufficient to assess HbA1c variability,[28] or to provide results that are superimposable upon those derived from longer periods[19] or more numerous HbA1c values.[18] Furthermore, intervals between measurements ranged only from 6 to 9 months, and HbA1c-AdjSD was used to account for the difference in the number of measures. Another limitation is that patients attending tertiary referral outpatient diabetes clinics do not represent the totality of individuals with type 2 diabetes in Italy, as a proportion of them are followed elsewhere; therefore, the study findings may not be applicable to the general ambulatory diabetes population. In fact, patients who are referred to such centres are usually more complicated and, hence, at a higher risk of mortality and of variable glucose control. Finally, potential methodological limitations have been addressed in previous RIACE reports.[20,24,29–31]

In conclusion, HbA1c variability is a strong independent predictor of all-cause mortality in patients with type 2 diabetes and appears to be more powerful than average HbA1c in predicting all-cause mortality. Further studies are required to understand whether HbA1c variability acts as a mediator or is an innocent bystander in this relationship.

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Conflict of interest

Dr. Orsi reported personal fees from Abbot, Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Lifescan, Novo Nordisk, Sanofi-Aventis, and Takeda. Dr. Solini reported receiving a grant from Astra Zeneca and personal fees from Boehringer Ingelheim and Eli Lilly. Dr. Bonora reported receiving grants from Astra-Zeneca, Novo Nordisk, Roche, and Takeda and personal fees from Abbot, Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, Roche, Sanofi-Aventis, and Takeda. Dr. Morano reported receiving personal fees from Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, and Takeda. Dr. Nicolucci reported receiving grants from Artsana, Astra-Zeneca, Eli Lilly, Novo Nordisk, and Sanofi-Aventis and personal fees from Eli Lilly and Novo Nordisk. Dr. Penno reported receiving personal fees from Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, and Merck Sharp & Dohme. Dr. Pugliese reported receiving personal fees from Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mylan, Shire, Sigma-Tau, and Takeda. No other disclosures were reported.

Author contributions

All authors contributed significantly to the submitted manuscript. EO, AS, AN, GPe, and GPu designed the study. All authors contributed to the acquisition, analysis, or interpretation of the data for the work. EO and GPu drafted the manuscript. AS, EB, CF, RT, MV, FC, GG, SM, AN, and GPe revised the manuscript critically for essential intellectual content. All authors read and approved the submitted manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

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

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