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HbA_{1c} and all-cause mortality risk among patients with type 2 diabetes

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Abstract

Background—Several prospective studies have evaluated the association between glycosylated hemoglobin (HbA_{1c}) and death risk among diabetic patients. However, the results have been inconsistent.

Methods—We performed a prospective study which included 13,334 men and 21,927 women with type 2 diabetes. Cox proportional hazards regression models were used to estimate the association of different levels of HbA_{1c} with all-cause mortality.

Results—During a mean follow up of 8.7 years, 4,199 (2,082 men and 2,117 women) patients died. The multivariable-adjusted hazard ratios (HRs) of all-cause mortality associated with different levels of HbA_{1c} at baseline (<6.0%, 6.0-6.9% [reference], 7.0-7.9, 8.0-8.9%, 9.0-9.9%, 10.0-10.9%, and 11.0%) were 1.06, 1.00, 1.10, 0.93, 1.26, 1.18 and 1.31 ($P_{\text{non-linear}} = 0.008$) for men, and 1.21, 1.00, 1.01, 1.08, 1.30, 1.30 and 1.74 ($P_{\text{non-linear}} < 0.001$) for women, respectively. The J-shaped association of HbA_{1c} with all-cause mortality was confirmed among African American and white diabetic patients, patients who were more than 50 years old, never smoked or used insulin. When we used an updated mean value of HbA_{1c}, the J-shaped association of HbA_{1c} with the risk of all-cause mortality did not change.

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Conclusions—Our study demonstrated a J-shaped association between HbA_{1c} and the risk of all-cause mortality among men and women with type 2 diabetes. Both high and low levels of HbA_{1c} were associated with an increased risk of all-cause mortality.

Keywords

mortality; HbA_{1c}; cohort study; type 2 diabetes

1. Introduction

Diabetes is one of the major public health problems worldwide, affecting about 24 million individuals in the US alone [1]. Individuals with diabetes have a 2-4 fold increased risk of all-cause mortality than those without diabetes [2]. Glycosylated hemoglobin (HbA_{1c}) provides a measure of average blood glucose levels over the preceding two to three months and is considered the best measurement of long-term glycemic control among diabetic patients.

Previous observational studies have focused on the association of glycemic control with all-cause mortality, and the majority have showed a positive linear relationship between HbA_{1c} and all-cause mortality [3-6]. However, several other studies suggested an increased risk of all-cause mortality associated with both low normal HbA_{1c} level and high HbA_{1c} level (J or U shaped curve) [7-9]. The UK prospective Diabetes Study (UKPDS) demonstrated a marginally significant lower risk of myocardial infarction (MI) in the intensively treated group [10] and a continued reduction in microvascular risk and the risk of MI and death after an extended post-trial follow-up of 10 years [11]; however, other randomized controlled trials (RCTs) did not show a benefit of intensive glucose control [12-14]. Thus, more epidemiological data are needed. In addition, most epidemiological studies only use a single baseline measurement of HbA_{1c} to predict risk of mortality, which may produce bias. The aim of the present study was to examine the association between levels of HbA_{1c} at baseline and during follow-up with the risk of all-cause mortality among patients with type 2 diabetes in the Louisiana State University Hospital-Based Longitudinal Study (LSUHLS).

2. Materials and Methods

2.1 Study Population

Between 1997 and 2012, the LSU Health Care Services Division (LSUHCS) operated seven public hospitals and affiliated clinics in Louisiana providing quality medical care to the residents of Louisiana regardless of their income or insurance coverage [15-22]. Since 1997, administrative, anthropometric, laboratory (test code, test collection date, test result values, and abnormal flag), clinical diagnosis, and medication data collected at these facilities are available in electronic form for both inpatients and outpatients. Totally there were about 1.6 million patients (35% of the Louisiana population) in the LSU HCS facilities. The LSUHLS was established in 2010 by using these data [15]. We established a cohort of diabetic patients who used LSU HCS hospitals between January 1, 1999 and December 31, 2009, using the International Classification of Diseases (ICD)-9 (code 250). All diabetic patients in the LSU HCS hospitals were diagnosed using the American Diabetes Association (ADA) criteria: a fasting plasma glucose ≥ 7.0 mmol/l, or 2-hour

glucose ≥ 11.1 mmol/l after a 75-g 2-hour oral glucose tolerance test (OGTT); or a patient with one or more classic symptoms plus a random plasma glucose ≥ 11.1 mmol/l [23]. A validation study has been carried out for the diagnosis of diabetes in LSUHSCD hospitals. 20,919 patients from a sample of 21,566 with hospital discharge diagnoses based on ICD codes also had physician-confirmed diabetes using the ADA diabetes diagnosis criteria [23], and the agreement of diabetes diagnosis was 97%.

In the present study, we only included patients who had newly diagnosed diabetes. These patients had used the LSUHSCD system with a mean time of 5.0 years before the diagnosis of diabetes. After excluding patients without at least 2 measurements of any of the required variables for analysis (all variables listed in Table 1), the present study sample included 35,261 patients with type 2 diabetes (19,757 African Americans and 15,504 White Americans; 13,334 men and 21,927 women), who were 30-94 years of age. Among 35,261 participants, 77.4% of patients qualified for free care (by virtue of being low income and uninsured [any individual or family unit whose income is at or below 200% of Federal Poverty Level]), 4.9% of patients were self-pay (uninsured, but incomes not low enough to qualify for free care), 5.1% of patients were covered by Medicaid, 10.4% of patients had Medicare, and 2.2% of patients were covered by commercial insurance. The study and analysis plan were approved by Pennington Biomedical Research Center and LSU Health Sciences Center Institutional Review Boards. We did not obtain informed consent from participants involved in our study because we used anonymized data compiled from electronic medical records.

2.2 Baseline and follow-up measurements

The patient's characteristics, including age of diabetes diagnosis, gender, race/ethnicity, family income, smoking status, types of health insurance, body weight, height, BMI, blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, HbA_{1c}, estimated glomerular filtration rate (eGFR), and medication (antihypertensive drug, cholesterol lowering drug and anti-diabetic drug) within half a year after the diabetes diagnosis (baseline) and during follow-up after the diabetes diagnosis (follow-up) were extracted from the computerized hospitalization records. The updated mean values of HbA_{1c}, LDL cholesterol, BMI, blood pressure and eGFR over time were calculated for each participant from baseline to each year of follow up. For example, at one year the updated mean is the average of the baseline and one year values and at three years it is the average of baseline, one year, two year, and three year values. In the case of an event during follow-up, the period for estimating the updated mean value was from baseline to the year before this event occurred [24]. The average number of HbA_{1c} measurements during the follow-up period was 15.0.

2.3 Prospective follow-up

Follow-up information was obtained from the LSUHLS inpatient and outpatient database by using the unique number assigned to every patient who visits the LSUHSCD hospitals. The diagnosis of all-cause death was the primary endpoint of interest of the study. Mortality outcomes were assessed by linkage with the State Center for Health Statistics at Louisiana's

Office of Public Health (the Louisiana Office of Public Health Vital Records Registry).
Follow-up of each cohort member continued until the date of the death, or June 31, 2013.

2.4 Statistical analysis

The Cox proportional hazard model was used to estimate the association between HbA_{1c} and all-cause mortality. HbA_{1c} was divided into 7 categories (HbA_{1c} <6.0% [42 mmol/mol], 6.0-6.9% [42-52 mmol/mol] [reference], 7.0-7.9% [53-63mmol/mol], 8.0-8.9% [64-74 mmol/mol], 9.0-9.9% [75-85 mmol/mol], 10.0-10.9% [86-96 mmol/mol], and 11.0% [97 mmol/mol]). All analyses were adjusted for age and race (Model 1); age, race, smoking, income, type of insurance, LDL cholesterol, systolic blood pressure, BMI, and eGFR at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses) (Model 2); variables in Model 2, and also for use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents (Model 3). The different categories of HbA_{1c} were included in the models as dummy variables. To avoid the potential bias due to the presence of occult diseases at baseline, additional analyses were carried out excluding the subjects who died during the first two years of follow-up, or excluding patients with a history of coronary heart disease (CHD) or cancer at the time of diagnosis of diabetes. Restricted cubic splines in Cox models were used to test whether there was a dose-response or non-linear associate of HbA_{1c} as a continuous variable with all-cause mortality risk [25]. Non-linear trends were assessed with likelihood-ratio tests of restricted cubic splines [25]. Statistical significance was considered to be $p < 0.05$. All statistical analyses were performed with SAS for Windows, version 9.3 (SAS Institute, Cary, NC).

3. Results

General characteristics stratified by baseline HbA_{1c} are presented in Table 1. During a mean follow-up period of 8.7 years, 4,199 (2,082 men and 2,117 women) patients died. The multivariable-adjusted (Model 3) hazard ratios (HRs) (95% CIs) of all-cause mortality associated with different levels of HbA_{1c} at baseline (<6.0%, 6.0-6.9% [reference], 7.0-7.9%, 8.0-8.9%, 9.0-9.9%, 10.0-10.9%, and 11.0%) were 1.06 (0.92-1.24), 1.00, 1.10 (0.92-1.30), 0.93 (0.75-1.16), 1.26 (1.01-1.58), 1.18 (0.93-1.51) and 1.31 (1.08-1.60) ($P_{\text{non-linear}} = 0.008$) for men, and 1.21 (1.04-1.41), 1.00, 1.01 (0.85-1.20), 1.08 (0.87-1.34), 1.30 (1.03-1.64), 1.30 (1.00-1.69) and 1.74 (1.42-2.13) ($P_{\text{non-linear}} < 0.001$) for women, respectively (Table 2). When patients were divided into 7 groups based on HbA_{1c} levels with the same sample size in each group, there was a J or U-shaped association between HbA_{1c} levels and the risk of all-cause mortality (Online table 1). When HbA_{1c} was considered as a continuous variable by using restricted cubic splines, a nadir of the J-shaped association of HbA_{1c} with all-cause mortality was observed at HbA_{1c} of 6.0-6.9% (Table 2 and Figure 1).

When we did an additional analysis by using an updated mean value of HbA_{1c}, we found the same J-shaped association between HbA_{1c} and the risk of all-cause mortality (Table 2 and Figure 1). The multivariable-adjusted (Model 3) HRs (95% CIs) of all-cause mortality associated with different levels of HbA_{1c} during follow-up (<6.0%, 6.0-6.9%, 7.0-7.9%, 8.0-8.9%, 9.0-9.9%, 10.0-10.9%, and 11.0%) were 1.22 (1.05-1.42), 1.00, 0.89 (0.76-1.06), 1.09 (0.90-1.32), 1.19 (0.95-1.49), 1.31 (1.01-1.71) and 1.48 (1.14-1.93)

($P_{\text{non-linear}} < 0.001$) for men, and 1.30 (1.11-1.51), 1.00, 1.04 (0.88-1.22), 0.94 (0.77-1.16), 1.16 (0.91-1.46), 1.78 (1.37-2.31) and 1.80 (1.34-2.42) ($P_{\text{non-linear}} < 0.001$) for women, respectively (Table 2).

When stratified by race, age, BMI, smoking status, and use of antidiabetic drugs, the trend of a J-shaped association of HbA_{1c} with all-cause mortality was present in most subgroups. But this J-shaped association disappeared, which probably indicated that the effect of HbA_{1c} weakened among patients who were currently smoking (Table 3). When we performed sensitivity analyses by excluding patients who died during the first two years of follow-up (n=435) or excluding patients with a history of CHD or cancer at the diagnosis of diabetes (n=5,608), the multivariable-adjusted J-shaped association of HbA_{1c} with all-cause mortality risk did not change (Online table 2).

4. Discussion

Our study found a J-shaped association of HbA_{1c} at baseline and during follow-up with the risk of all-cause mortality among men and women with type 2 diabetes. A significantly increased risk of all-cause mortality was observed among men with HbA_{1c} <6.0% and HbA_{1c} 11.0%, and among women with HbA_{1c} <6.0% and HbA_{1c} 10.0%, as compared with patients with HbA_{1c} 6.0-6.9%.

Previous studies have focused on the association of HbA_{1c} with all-cause mortality; however, the results were inconsistent. Most of the observational studies suggested a linear and positive association between HbA_{1c} and all-cause mortality [3-6], while others suggested that both low normal HbA_{1c} level and high HbA_{1c} level were associated with an increased risk of all-cause mortality (J or U shaped curve) [7-9]. Major reasons for the inconsistent results of the above studies might include small sample size or small number of deaths, short follow-up time, and different participant characteristics across studies. Until now, there are two systematic reviews evaluating the association between HbA_{1c} and the risk of all-cause mortality among diabetic patients in prospective cohort studies. One systematic review indicated that each 1% increase in HbA_{1c} among diabetic patients might have a 1.15 fold increase in all-cause mortality risk [26]. However, whether low HbA_{1c} would increase all-cause mortality was not suggested in this review because it only assessed HbA_{1c} as a continuous variable for each 1-unit increase of HbA_{1c}. Another systematic review found a significant J-shaped relationship between HbA_{1c} and the risk of all-cause mortality among diabetic patients [27]. However, HbA_{1c} was only divided into 7.5% and <7.5% in this meta-analysis. Our study, conducted in a real clinical population with low income, for the first time revealed a J-shaped relationship between HbA_{1c} and all-cause mortality among patients with type 2 diabetes.

Although clinical trials are better than observational studies to evaluate the association between HbA_{1c} and the risk of all-cause mortality among diabetic patients, whether there is a benefit of intensive glucose control was not confirmed by RCTs. The Sibutramine Cardiovascular OUTcomes (SCOUT) trial indicated that among cardiovascular high-risk patients with type 2 diabetes, increasing HbA_{1c} concentrations increased the risks of cardiovascular adverse outcomes and all-cause mortality, and there was no evidence of

increased risk associated with HbA_{1c} 6.4% [3]. The UKPDS demonstrated a marginally significant lower risk of MI in the intensively treated group during the RCT period [10] and a continued reduction in microvascular risk and the risks of MI and death after an extended post-trial follow-up of 10 years [11]. However, other two RCTs, Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT), did not find any benefits of intensive glucose control on CVD outcomes [13, 14], and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) found an unexpected increase in all-cause and CVD mortality in the intensive glycemic treatment (HbA_{1c} <6.0%) [12]. Two meta-analyses of relevant RCTs indicated that intensive glucose control could reduce the risk of some cardiovascular diseases (such as nonfatal MI and coronary events), but did not reduce the risks of all-cause and CVD-related mortality [28, 29]. The present study, with large sample size and long follow-up time, supported that both low (<6.0% in men and women) and high (10% or 11% in men and women) levels of HbA_{1c} were associated with an increased risk of all-cause mortality among men and women with type 2 diabetes. To make our methodology more rigorous, we have conducted sensitivity analyses by excluding patients who died during the first two years of follow-up or excluding patients with a history of CHD or cancer at the diagnosis of diabetes, and the J-shaped association of HbA_{1c} with all-cause mortality risk did not change. When stratified by race, age, BMI, smoking status, and use of antidiabetic drugs, this J-shaped association of HbA_{1c} with all-cause mortality tended to be present in most subgroups.

Despite no benefit of intensive glucose control from RCTs, the ADA, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) kept the general blood control goal of HbA_{1c} <7% (Class IIB, level of evidence A) for most diabetic patients [30]. The present study found that the lowest mortality rate was among diabetic patients with HbA_{1c} 6.0-6.9% at baseline (new-onset diabetes), and HbA_{1c} 6.0-7.9% during follow-up. Two other cohort studies demonstrating the similar J-shaped association between HbA_{1c} and all-cause mortality also suggested that the lowest mortality rate was found among patients with HbA_{1c} 6.5-6.9% for new-onset diabetes [9], and with a median HbA_{1c} of 7.5% for long-standing diabetes (mean of diabetes duration >5 years) [8]. Based on results from the RCTs, the present study and above two epidemiological studies, the best range of HbA_{1c} seems to be 6.0-6.9% for new-onset diabetes and 6.0-7.9% for long-standing diabetes.

The mechanism for the relationship between elevated blood glucose levels and high mortality has been well explained. Diabetic complications are the major causes of death in persons with diabetes and the theories of diabetic complications caused by hyperglycemia mainly include the toxic effects of hyperglycemia and its pathophysiological derivatives (such as oxidants, hyperosmolarity, or glycation products) on tissues directly and a sustained alteration in cell signaling pathways (such as changes in phospholipids or kinases) induced by the products of glucose metabolism [31]. Reasons for very low HbA_{1c} associated with an increased risk of all-cause mortality are not clear now. The most likely culprit has been hypoglycemia, even though the post hoc analyses of ACCORD data have suggested that this is not the case [32, 33]. Indeed some other studies supported this hypothesis, such as the Veterans Affairs Study which suggested more than one episode of severe hypoglycemia was

associated with an 88% rise in the risk for sudden death [34]. Future studies are needed to confirm or explore the mechanism of low HbA_{1c} with an increased risk of all-cause mortality.

There were several strengths of our study, including the large sample size, long follow-up time, and the use of administrative databases to avoid differential recall bias. We used baseline HbA_{1c} levels and updated mean values, which could avoid potential bias from a single baseline measurement. Besides, our study subjects were not volunteers, but rather represent a real clinical population, which makes the results very pertinent to the clinical population of people with low income and with type 2 diabetes. In addition, participants in the present study used the same public health care system which minimized the influence from the accessibility to health care. There were also some limitations. First, our analysis was not performed on a representative sample of the population which limited the generalizability of this study; however, LSUHCS hospitals were public hospitals and covered over 1.6 million patients, most of whom were low income persons in Louisiana. The results of the present study would have wide applicability for the population with low income and without health insurance in the US. Second, we did not have information on cause-specific deaths and could not assess cardiovascular mortality as a separate end-point. Third, even though our analyses adjusted for an extensive set of confounding factors, residual confounding due to measurement error in the assessment of confounding factors, unmeasured factors such as physical activity, education, and dietary factors, cannot be excluded.

In conclusion, our study demonstrated a J-shaped association of HbA_{1c} with the risk of all-cause mortality risk among men and women with type 2 diabetes. Both high and low levels of HbA_{1c} were associated an increased risk of all-cause mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. We performed a prospective study including 35261 patients with type 2 diabetes.
2. Our study subjects represented a real clinical population with low income.
3. A J-shaped association of HbA1c with death was found among diabetic patients.
4. Both low and high HbA1c will increase death risk.

Figure 1.

Hazard ratios for all-cause mortality based on different levels of HbA_{1c} at baseline and during follow-up. Adjusted for age, race, types of insurance, income, smoking, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, glomerular filtration rate, use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents.

Table 1
Baseline characteristics according to HbA_{1c} categories of patients with type 2 diabetes

	HbA _{1c} (%) (mmol/mol)							P
	<6.0 (42)	6.0-6.9 (42-52)	7.0-7.9 (53-63)	8.0-8.9 (64-74)	9.0-9.9 (75-85)	10.0-10.9 (86-96)	11.0 (97)	
No. of participants	9,417	9,217	4,952	3,119	2,379	1,867	4,310	-
No. of deaths	1,127	1,039	646	368	283	231	505	0.114
Race/Ethnicity (%)								<0.001
African American	47.3	56.4	56.1	57.0	56.5	59.3	71.8	
White	52.7	43.6	43.9	43.0	43.5	40.7	28.2	
Male (%)	37.5	33.3	35.5	36.7	41.4	46.6	45.9	<0001
Age, yr	53.9 (0.1)	54.3 (0.1)	52.8 (0.1)	50.8 (0.2)	49.3 (0.2)	48.5 (0.2)	47.9 (0.2)	<0.001
Income, \$/family	19,714 (280)	19,684 (282)	19,692 (383)	19,056 (483)	18,860 (554)	18,815 (626)	17,794 (418)	0.005
Body mass index, kg/m ²	33.6 (0.1)	35.3 (0.1)	35.1 (0.1)	34.3 (0.1)	34.1 (0.2)	33.8 (0.2)	32.5 (0.1)	<0.001
Systolic blood pressure, mm Hg	141 (0.2)	144 (0.2)	146 (0.3)	146 (0.4)	147 (0.5)	147 (0.6)	145 (0.4)	<0.001
Low-density lipoprotein cholesterol, mg/dL	110 (0.4)	110 (0.4)	111 (0.6)	112 (0.7)	111 (0.8)	115 (0.9)	118 (0.6)	<0.001
Glomerular filtration rate (mL/min/1.73 m ²) (%)								<0.001
90	37.9	40.8	45.0	51.9	56.0	57.9	60.9	
60-89	46.4	44.1	39.9	35.8	33.9	32.0	30.4	
30-59	13.7	13.6	13.3	10.8	8.6	9.2	7.9	
5-29	1.3	1.1	1.3	1.2	1.3	0.9	0.6	
<15	0.8	0.5	0.5	0.3	0.3	0.2	0.2	<0.001
Smoking status (%)								
Never smoking	63.6	69.1	68.4	66.2	64.5	63.5	62.3	
Past smoking	7.5	7.1	6.8	7.6	8.2	7.8	6.6	
Current smoking	29.0	23.8	24.8	26.2	27.3	28.7	31.1	
Type of insurance (%)								<0.001
Free	74.9	76.3	76.1	79.9	79.2	81.5	81.4	
Self-pay	4.1	4.2	4.4	5.1	5.6	6.1	8.1	
Medicaid	5.4	5.0	5.4	4.1	5.5	5.3	5.3	
Medicare	13.2	12.3	11.8	8.5	7.2	5.7	3.9	
Commercial	2.4	2.4	2.3	2.5	2.6	1.5	1.4	

	HbA _{1c} (%) (mmol/mol)							P
	<6.0 (42)	6.0-6.9 (42-52)	7.0-7.9 (53-63)	8.0-8.9 (64-74)	9.0-9.9 (75-85)	10.0-10.9 (86-96)	11.0 (97)	
Patient status (%)								<0.001
Outpatient only	47.7	49.5	48.1	48.0	44.0	43.1	41.0	
Outpatient and inpatient	52.3	50.5	51.9	52.0	56.0	56.9	59.1	
Uses of medications (%)								
Glucose-lowering medication								<0.001
Oral hypoglycemic agents	33.7	44.1	39.0	29.1	24.3	23.2	20.1	
Insulin	8.5	20.4	35.1	45.2	53.5	53.1	58.0	
Lipid-lowering medication	53.9	58.3	58.2	56.7	58.2	57.1	54.8	<0.001
Antihypertensive medication	72.3	73.6	72.8	71.5	74.3	72.4	72.9	0.140

Values represent means (SE) or percentages. All continuous data adjusted for age, gender and race (age was adjusted for gender and race).

Table 2
Hazard ratios for all-cause mortality according to different levels of HbA_{1c} at baseline and during follow-up among patients with type 2 diabetes

		HbA _{1c} (%) (mmol/mol)							
		<6.0 (<42)	6.0-6.9 (42-52)	7.0-7.9 (53-63)	8.0-8.9 (64-74)	9.0-9.9 (75-85)	10.0-10.9 (86-96)	11.0 (97)	
Male									
<i>Baseline</i>									
No. of participants		3,532	3,067	1,757	1,146	984	869	1,979	
No. of cases		567	516	302	175	141	124	257	
Person-years		26,526	25,390	15,176	10,193	8,455	7,527	16,093	
<i>HR (95% CI)</i>									
Model 1		1.15 (1.02-1.29)	1.00	1.03 (0.89-1.18)	0.98 (0.83-1.17)	1.11 (0.92-1.33)	1.17 (0.96-1.42)	1.32 (1.13-1.54)	
Model 2		1.17 (1.01-1.36)	1.00	1.09 (0.92-1.30)	0.97 (0.79-1.21)	1.24 (0.99-1.54)	1.26 (0.99-1.60)	1.41 (1.17-1.71)	
Model 3		1.06 (0.92-1.24)	1.00	1.10 (0.92-1.30)	0.93 (0.75-1.16)	1.26 (1.01-1.58)	1.18 (0.93-1.51)	1.31 (1.08-1.60)	
<i>Follow-up</i>									
No. of participants		3,031	3,256	2,446	1,713	1,162	787	939	
No. of cases		547	518	368	244	159	109	137	
Person-years		21,525	26,372	21,446	15,244	10,316	6,862	7,596	
<i>HR (95% CI)</i>									
Model 1		1.47 (1.30-1.66)	1.00	0.93 (0.81-1.06)	1.03 (0.88-1.20)	1.15 (0.96-1.38)	1.37 (1.10-1.69)	1.81 (1.49-2.20)	
Model 2		1.44 (1.25-1.67)	1.00	0.91 (0.77-1.07)	1.18 (0.98-1.42)	1.32 (1.06-1.63)	1.50 (1.16-1.94)	1.82 (1.41-2.35)	
Model 3		1.22 (1.05-1.42)	1.00	0.89 (0.76-1.06)	1.09 (0.90-1.32)	1.19 (0.95-1.49)	1.31 (1.01-1.71)	1.48 (1.14-1.93)	
Female									
<i>Baseline</i>									
No. of participants		5,885	6,150	3,195	1,973	1,395	998	2,331	
No. of cases		567	516	302	175	141	124	257	
Person-years		26,526	25,390	15,176	10,193	8,455	7,527	16,093	
<i>HR (95% CI)</i>									
Model 1		1.29 (1.15-1.46)	1.00	1.16 (1.01-1.33)	1.18 (1.00-1.39)	1.36 (1.13-1.64)	1.55 (1.25-1.91)	1.92 (1.65-2.24)	
Model 2		1.30 (1.12-1.50)	1.00	1.02 (0.86-1.21)	1.16 (0.94-1.43)	1.43 (1.14-1.79)	1.51 (1.16-1.96)	1.95 (1.61-2.37)	
Model 3		1.21 (1.04-1.41)	1.00	1.01 (0.85-1.20)	1.08 (0.87-1.34)	1.30 (1.03-1.64)	1.30 (1.00-1.69)	1.74 (1.42-2.13)	

		HbA _{1c} (%) (mmol/mol)							
		<6.0 (<42)	6.0-6.9 (42-52)	7.0-7.9 (53-63)	8.0-8.9 (64-74)	9.0-9.9 (75-85)	10.0-10.9 (86-96)	11.0 (97)	
<i>Follow-up</i>									
No. of participants		5,192	6,400	4,012	2,479	1,660	1,059	1,125	
No. of cases		539	579	386	224	159	118	112	
Person-years		40,144	55,568	38,516	24,504	16,743	10,619	10,428	
HR (95% CI)									
Model 1		1.40 (1.24-1.57)	1.00	1.07 (0.94-1.22)	1.14 (0.97-1.33)	1.34 (1.12-1.60)	1.86 (1.52-2.28)	2.16 (1.75-2.67)	
Model 2		1.48 (1.28-1.72)	1.00	1.11 (0.94-1.30)	1.10 (0.90-1.34)	1.35 (1.08-1.69)	2.08 (1.62-2.68)	2.27 (1.71-3.03)	
Model 3		1.30 (1.11-1.51)	1.00	1.04 (0.88-1.22)	0.94 (0.77-1.16)	1.16 (0.91-1.46)	1.78 (1.37-2.31)	1.80 (1.34-2.42)	
Total									
<i>Baseline</i>									
No. of participants		9,417	9,217	4,952	3,119	2,379	1,867	4,310	
No. of cases		1,134	1,032	604	350	282	248	514	
Person-years		53,052	50,780	30,352	20,386	16,910	15,054	32,186	
HR (95% CI) *									
Model 1		1.23 (1.13-1.33)	1.00	1.09 (0.99-1.21)	1.08 (0.96-1.22)	1.23 (1.08-1.41)	1.35 (1.17-1.56)	1.60 (1.43-1.78)	
Model 2		1.24 (1.12-1.38)	1.00	1.06 (0.93-1.19)	1.07 (0.92-1.24)	1.34 (1.14-1.57)	1.39 (1.16-1.66)	1.67 (1.45-1.91)	
Model 3		1.15 (1.03-1.28)	1.00	1.06 (0.93-1.19)	1.01 (0.87-1.17)	1.29 (1.10-1.52)	1.25 (1.05-1.50)	1.52 (1.32-1.75)	
<i>Follow-up</i>									
No. of participants		8,223	9,656	6,458	4,192	2,822	1,846	2,064	
No. of cases		1,086	1,097	754	468	318	227	249	
Person-years		61,669	81,940	59,962	39,748	27,059	17,481	18,024	
HR (95% CI) *									
Model 1		1.44 (1.32-1.57)	1.00	1.00 (0.91-1.09)	1.08 (0.97-1.21)	1.24 (1.09-1.41)	1.60 (1.38-1.85)	1.98 (1.72-2.29)	
Model 2		1.48 (1.34-1.64)	1.00	1.01 (0.90-1.13)	1.15 (1.01-1.32)	1.36 (1.16-1.59)	1.77 (1.48-2.12)	2.05 (1.69-2.47)	
Model 3		1.27 (1.14-1.42)	1.00	0.96 (0.86-1.08)	1.03 (0.89-1.18)	1.19 (1.01-1.40)	1.52 (1.26-1.83)	1.64 (1.35-1.99)	

Model 1 adjusted for age and race.

Model 2 adjusted for age, race, types of insurance, income, smoking, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, and glomerular filtration rate at baseline (in baseline analyses) and during follow-up (in the follow-up analyses).

Model 3 adjusted for variables in Model 2, and also for use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents at baseline (in baseline analyses) and during follow-up (in the follow-up analyses).

* Gender was additional adjusted in Model 1, 2, 3 among the total patients.

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Hazard ratio for all-cause mortality according to different levels of HbA_{1c} at baseline and during follow-up among various subpopulations

Table 3

	HbA _{1c} (%) (mmol/mol)						
	<6.0(<42)	6.0-6.9(42-52)	7.0-7.9(53-63)	8.0-8.9(64-74)	9.0-9.9(75-85)	10.0-10.9(86-96)	11.0(97)
Baseline							
<i>Race</i>							
African American	1.30 (1.11-1.52)	1.00	1.06 (0.88-1.27)	1.06 (0.85-1.31)	1.31 (1.05-1.64)	1.31 (1.02-1.68)	1.44 (1.20-1.74)
White American	1.05 (0.91-1.21)	1.00	1.07 (0.90-1.26)	0.97 (0.78-1.20)	1.29 (1.02-1.62)	1.21 (0.94-1.57)	1.67 (1.34-2.08)
<i>Age groups, yr</i>							
<60	1.03 (0.89-1.19)	1.00	1.07 (0.91-1.26)	0.89 (0.73-1.07)	1.18 (0.97-1.43)	1.10 (0.89-1.36)	1.33 (1.13-1.56)
60-94	1.21 (1.04-1.40)	1.00	1.00 (0.83-1.21)	1.12 (0.87-1.44)	1.16 (0.86-1.57)	1.15 (0.81-1.65)	1.16 (0.83-1.63)
<i>Body mass index, kg/m²</i>							
<30	1.09 (0.93-1.27)	1.00	0.86 (0.71-1.05)	0.95 (0.75-1.19)	1.34 (1.05-1.71)	0.95 (0.70-1.27)	1.37 (1.12-1.68)
30	1.13 (0.98-1.31)	1.00	1.20 (1.02-1.40)	1.07 (0.88-1.31)	1.28 (1.03-1.58)	1.55 (1.23-1.94)	1.62 (1.34-1.97)
<i>Smoking status</i>							
Never	1.27 (1.11-1.45)	1.00	1.16 (1.00-1.35)	1.15 (0.95-1.39)	1.43 (1.17-1.76)	1.42 (1.13-1.77)	1.59 (1.33-1.91)
Ever	1.90 (1.21-99)	1.00	1.28 (0.76-2.15)	0.90 (0.44-1.87)	1.38 (0.74-2.55)	1.81 (0.92-3.58)	2.38 (1.35-4.21)
Current	0.88 (0.73-1.06)	1.00	0.83 (0.66-1.06)	0.79 (0.60-1.04)	1.07 (0.80-1.43)	0.89 (0.64-1.23)	1.28 (1.01-1.62)
<i>Using glucose-lowering agents</i>							
No	1.05 (0.91-1.22)	1.00	1.23 (1.01-1.51)	1.02 (0.78-1.33)	1.49 (1.11-2.02)	1.30 (0.95-1.79)	1.74 (1.37-2.22)
Oral hypoglycemic agents	1.11 (0.91-1.35)	1.00	0.88 (0.69-1.11)	0.95 (0.68-1.33)	1.13 (0.77-1.66)	1.12 (0.73-1.71)	1.16 (0.82-1.66)
Insulin	1.61 (1.26-2.06)	1.00	1.11 (0.90-1.36)	1.06 (0.84-1.34)	1.32 (1.05-1.67)	1.34 (1.03-1.75)	1.60 (1.29-1.98)
Follow-up							
<i>Race</i>							
African American	1.37 (1.17-1.61)	1.00	0.89 (0.75-1.06)	1.06 (0.87-1.29)	1.18 (0.95-1.47)	1.40 (1.09-1.79)	1.33 (1.03-1.71)
White American	1.20 (1.04-1.38)	1.00	1.04 (0.89-1.22)	0.98 (0.80-1.20)	1.21 (0.94-1.55)	1.66 (1.26-2.20)	2.23 (1.63-3.06)
<i>Age groups, yr</i>							
<60	1.27 (1.09-1.48)	1.00	1.07 (0.91-1.25)	0.95 (0.80-1.13)	1.15 (0.95-1.39)	1.32 (1.07-1.63)	1.33 (1.07-1.65)
60-94	1.20 (1.03-1.40)	1.00	0.79 (0.66-0.95)	1.04 (0.82-1.32)	0.85 (0.59-1.23)	1.38 (0.86-2.21)	1.60 (0.92-2.80)
<i>Body mass index kg/m²</i>							
<30	1.23 (1.05-1.44)	1.00	0.95 (0.79-1.14)	1.03 (0.83-1.29)	1.24 (0.97-1.59)	1.04 (0.77-1.41)	1.51 (1.15-1.98)

		HbA _{1c} (%) (mmol/mol)						
		<6.0(<42)	6.0-6.9(42-52)	7.0-7.9(53-63)	8.0-8.9(64-74)	9.0-9.9(75-85)	10.0-10.9(86-96)	11.0(97)
30		1.21 (1.04-1.40)	1.00	0.98 (0.84-1.14)	1.04 (0.87-1.25)	1.17 (0.94-1.45)	2.01 (1.59-2.55)	1.59 (1.20-2.12)
Smoking status								
Never		1.32 (1.15-1.51)	1.00	1.00 (0.87-1.16)	1.00 (0.83-1.19)	1.29 (1.05-1.59)	1.69 (1.34-2.14)	1.65 (1.27-2.15)
Ever		2.13 (1.33-3.41)	1.00	0.85 (0.51-1.40)	1.10 (0.64-1.92)	1.74 (0.97-3.15)	2.06 (0.97-4.38)	2.01 (0.88-4.61)
Current		1.09 (0.90-1.33)	1.00	0.91 (0.73-1.14)	1.07 (0.84-1.37)	0.94 (0.70-1.26)	1.19 (0.85-1.67)	1.57 (1.14-2.16)
Using glucose-lowering agents								
No		1.09 (0.94-1.26)	1.00	1.19 (0.98-1.44)	1.16 (0.91-1.47)	1.23 (0.90-1.68)	1.93 (1.38-2.71)	2.05 (1.48-2.84)
Oral hypoglycemic agents		1.60 (1.32-1.94)	1.00	1.03 (0.83-1.29)	1.01 (0.72-1.44)	1.38 (0.91-2.09)	1.32 (0.74-2.36)	0.69 (0.30-1.57) *
Insulin		1.87 (1.40-2.50)	1.00	0.77 (0.63-0.94)	0.89 (0.72-1.10)	1.03 (0.82-1.31)	1.29 (0.99-1.67)	1.49 (1.13-1.98)

Adjusted for age, race, types of insurance, income, smoking, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, glomerular filtration rate, use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents at baseline (in baseline analyses) and during follow-up (in the follow-up analyses), other than the variable for stratification.

*There were only 7 deaths in this group.