ORIGINAL RESEARCH

Diabetes Mellitus–Related All-Cause and Cardiovascular Mortality in a National Cohort of Adults

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Background—Diabetes mellitus is a risk factor for cardiovascular disease (CVD) and has been associated with 2- to 4-fold higher mortality. Diabetes mellitus–related mortality has not been reassessed in individuals receiving routine care in the United States in the contemporary era of CVD risk reduction.

Methods and Results—We retrospectively studied 963 648 adults receiving care in the US Veterans Affairs Healthcare System from 2002 to 2014; mean follow-up was 8 years. We estimated associations of diabetes mellitus status and hemoglobin A1c (HbA1c) with all-cause and CVD mortality using covariate-adjusted incidence rates and multivariable Cox proportional hazards regression. Of participants, 34% had diabetes mellitus. Compared with nondiabetic individuals, patients with diabetes mellitus had 7.0 (95% CI, 6.7–7.4) and 3.5 (95% CI, 3.3–3.7) deaths/1000-person-years higher all-cause and CVD mortality, respectively. The age-, sex-, race-, and ethnicity-adjusted hazard ratio for diabetes mellitus–related mortality was 1.29 (95% CI, 1.28–1.31), and declined with adjustment for CVD risk factors (hazard ratio, 1.18 [95% CI, 1.16–1.19]) and glycemia (hazard ratio, 1.03 [95% CI, 1.02–1.05]). Among individuals with diabetes mellitus, CVD mortality increased as HbA1c exceeded 7% (hazard ratios, 1.11 [95% CI, 1.08–1.14], 1.25 [95% CI, 1.22–1.29], and 1.52 [95% CI, 1.48–1.56] for HbA1c 7%–7.9%, 8%–8.9%, and ≥9%, respectively, relative to HbA1c 6%–6.9%). HbA1c 6% to 6.9% was associated with the lowest mortality risk irrespective of CVD history or age.

Conclusions—Diabetes mellitus remains significantly associated with all-cause and CVD mortality, although diabetes mellitus–related excess mortality is lower in the contemporary era than previously. We observed a gradient of mortality risk with increasing HbA1c >6% to 6.9%, suggesting HbA1c remains an informative predictor of outcomes even if causality cannot be inferred. **(*J Am Heart Assoc*. 2019;8:e011295. DOI:10.1161/JAHA.118.011295.)**

Key Words: diabetes mellitus • mortality • cardiovascular disease

Diabetes mellitus affects nearly 10% of adults in the United States,[1,2] is a significant risk factor for cardiovascular disease (CVD), chronic kidney disease, and numerous other complications,[3] and is associated with all-cause and CVD mortality.[4–8] Indeed, myocardial infarction is the leading cause of death among individuals with diabetes mellitus.[4] Accordingly, the clinical care of patients with diabetes mellitus has 2 broad goals: improving glycemic control to reduce diabetic complications[9–11] and modifying risk factors for complications, in particular those associated with CVD.[12]

Observational studies preceding contemporary CVD risk reduction strategies reported 3- to 4-fold higher all-cause and CVD mortality in participants with diabetes mellitus compared with those without diabetes mellitus.[13–16] More recently, analyses of the National Health and Nutrition Examination Survey and the National Health Interview Survey demonstrated reductions in CVD mortality in individuals with and

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Accompanying Figure S1 and Tables S1 through S8 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011295

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Received October 22, 2018; accepted January 2, 2019.

Clinical Perspective

What Is New?

- In this national cohort of US adults, diabetes mellitus was associated with a 16% increase in all-cause and an 18% increase in cardiovascular mortality.
- Among those with diabetes mellitus, a hemoglobin A1c of 6% to 6.9% was associated with lowest mortality, irrespective of age or prior cardiovascular disease.
- Diabetes mellitus–related excess mortality is lower than found in studies from the 1980s and 1990s.

What Are the Clinical Implications?

- Diabetes mellitus remains associated with increased mortality, but the association is attenuated by cardiovascular risk factor control.
- A hemoglobin A1c of 6% to 6.9% was associated with the lowest mortality among those with diabetes mellitus in a national, integrated healthcare system.
- Hemoglobin A1c is associated with mortality, irrespective of a causal mechanism, so it remains an informative marker of risk for patients with diabetes mellitus.

without diabetes mellitus in the United States across successive survey periods spanning the 1970s to 2000, suggesting temporal improvements in overall CVD care.[5,6] Similarly, analyses of diabetes mellitus–related care in the United States showed improvements in CVD risk factor control and preventive practices from 1990 to 2010,[17] as well as declines in the rates of diabetes mellitus–related complications.[18] In Europe, recent studies using clinical registry data have provided contemporary estimates of diabetes mellitus–related mortality in the context of national health systems in several European nations.[7,8,19–21] These studies demonstrate improved but persistent diabetes mellitus–related excess mortality despite improvements in CVD risk factor management. An analysis aimed at updating estimates of diabetes mellitus–related mortality for patients receiving routine clinical care in the United States is needed.

This study evaluated the association between type 2 diabetes mellitus and all-cause and CVD mortality, accounting for CVD risk factors, in a large, national contemporary US cohort receiving care in an integrated healthcare system. We also examined the association between hemoglobin A1c (HbA1c) and mortality among individuals with diabetes mellitus, whether this association varied by CVD history or age, and its stability over short- and long-term time horizons. Understanding the relationships between diabetes mellitus status and HbA1c with all-cause and CVD mortality in a contemporary healthcare setting in the United States could inform optimal CVD risk reduction and diabetes mellitus management strategies.

Methods

The data and all statistical code that support the findings of this study are available on reasonable request to the corresponding author. Because of the sensitive nature of the clinically derived data collected for this study, requests for data must be from qualified researchers with approved human subjects research protocols.

Study Population

This study included individuals receiving routine primary care in the US Department of Veterans Affairs Healthcare System (VA), defined as those who had at least 4 VA primary care provider visits from 2002 through 2003. We included individuals for whom diabetes mellitus status could be established and for whom baseline age, sex, race, ethnicity, non–high-density lipoprotein cholesterol, systolic blood pressure (SBP), smoking status, body mass index (BMI), and at least 3 random plasma glucose values were available in 2002 to 2003 (Figure S1). Because the study involved only secondary analysis of data collected routinely in the course of clinical care, the requirement for informed consent from study participants was waived. The Institutional Review Boards of Emory University (Atlanta, GA) and VA Boston Healthcare System (Boston, MA) approved this study.

Exposures

The primary exposure was diabetes mellitus status, defined as ≥2 uses of *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis code 250.xx or ≥1 use of code 250.xx in conjunction with a primary care provider visit and use of a diabetes mellitus medication during 2002 to 2003. For analyses of HbA1c, values measured during the 2002 to 2003 enrollment period were included, and the value closest in time to measurements of covariates (eg, SBP) was used for individuals with multiple HbA1c measurements. Prior studies suggested that the association between HbA1c and mortality is nonlinear,[22] so we specified HbA1c in clinically relevant categories: <6.0%, 6% to 6.9%, 7% to 7.9%, 8% to 8.9%, and ≥9.0%.

Outcomes

The coprimary outcomes were all-cause mortality and CVD mortality. Deaths occurring during the first 2 years of follow-up were censored. Mortality data were based on the National Death Index[23] through 2014, classified into 10 cause-of-death categories: CVD, cancer, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, infection, mental illness, abnormal/accident, other chronic diseases,

and all other causes. CVD mortality was defined in the National Death Index as *ICD-10-CM* codes I00 to I02, I05 to I13, I20 to I22, I24 to I28, I30 to I38, I40, I42, I44 to I51, I60 to I63, I67 to I74, I77 to I78, I80 to I87, I89, I95, I97, I99, M30, M31, R58, G45, and R00 for the primary cause-of-death diagnosis.

Stratifying Variables

We performed analyses stratified by CVD status at baseline, defined as inpatient or outpatient diagnosis of stroke/cerebrovascular disease (*ICD-9-CM* diagnosis codes 430–438), coronary artery disease (*ICD-9-CM* diagnosis codes 410–414), peripheral vascular disease (*ICD-9-CM* diagnosis codes 440.2–440.4 or 443.9), or congestive heart failure (*ICD-9-CM* diagnosis code 428). We also performed analyses stratified at age 65 years, the mean for the study population.

Statistical Analysis

Patient-level demographics, CVD risk factors, and comorbidities were compared between individuals with and without diabetes mellitus using χ^2 tests for categorical data and 2-sample *t* tests for continuous or ordinal data. We used crude and adjusted incidence rates and multivariable Cox proportional hazards regression to examine mortality risk across diabetes mellitus and HbA1c categories. To standardize covariates across exposure categories, we estimated adjusted incidence rates using generalized linear models with the Poisson link, using inverse probability weighting by propensity for exposure category. Adjusted incidence rate and multivariable Cox proportional hazards models included demographic variables (baseline age, sex, race, and ethnicity) and baseline CVD risk factors (SBP, non–high-density lipoprotein cholesterol, BMI, and smoking status). Smoking status was determined using an algorithm developed for VA electronic health records that classifies individuals as ever or never smokers.[24] We performed Cox proportional hazards regression with 3 additional models: one including prior CVD; a second including baseline random plasma glucose; and a third including baseline diabetes mellitus treatment (classified as no medications, insulin-containing regimens, and regimens without insulin) and baseline blood pressure treatment (prescribed or not prescribed a diuretic, β blocker, angiotensin-converting inhibitor or angiotensin receptor blocker, or calcium channel blocker). For all Cox proportional hazards models with CVD mortality as the outcome, we used cumulative incidence function methods to account for competing risk from mortality attributable to noncardiovascular causes.[25] To determine if the association between baseline HbA1c and mortality differed over time, we repeated the multivariable Cox models with HbA1c as a time-dependent variable, evaluating the association of HbA1c with mortality in the first 2 to 5 years of follow-up and at >5 years of follow-up. Finally, to assess differential associations between HbA1c and outcomes for patients in different age strata, we included an interaction term between HbA1c and age, categorized as <65 or ≥65 years.

We used a significance threshold of $P<0.05$ for associations of diabetes mellitus status or HbA1c with mortality outcomes. All analyses were conducted in SAS Enterprise Guide 7.1 (SAS Inc, Cary, NC) or R, version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 963 648 total participants, 329 624 (34%) had diabetes mellitus. Mean follow-up time was 8 years. Participants with diabetes mellitus were more likely to be black (17.1% versus 14.5%), were more likely to have prior CVD (51.6% versus 40.3%), were more likely to have chronic kidney disease (3.1% versus 1.3%), and had a higher BMI (31.3 versus 28.8 kg/m^2). There were minor differences between patients with and without diabetes mellitus in most other variables examined (Table 1). Participants with diabetes mellitus had a mean HbA1c of 7.4% at baseline, and the distribution of covariates across HbA1c categories is shown in Table S1. CVD was the most common cause of mortality, with cancer ranking second, and diabetes mellitus ranking the third most common primary cause of death among individuals with diabetes mellitus (Table S2).

Diabetes Mellitus and Mortality

Individuals with diabetes mellitus had higher crude and adjusted incidence rates of all-cause and CVD mortality (all-cause mortality: adjusted incidence rate [95% CI], 50.6 [50.3–50.8] and 43.5 [43.4–43.7] deaths/1000 person-years in individuals with and without diabetes mellitus, respectively; CVD mortality: adjusted incidence rate [95% CI], 17.6 [17.5–17.8] and 14.2 [14.1–14.3] deaths/1000 person-years in individuals with and without diabetes mellitus, respectively; Figure 1A, Table S3, model A). Differential adjusted all-cause and cardiovascular mortality between those without and with diabetes mellitus was evident over the entire follow-up period (Figure 1B). Diabetes mellitus was associated with higher all-cause and CVD mortality in individuals with and without prior CVD, but a history of CVD had a larger effect on mortality than diabetes mellitus status (Figure 1C, Table S3, model A). In addition, the adjusted risk differences (95% CIs) in all-cause and CVD mortality between those with and without diabetes mellitus were greater in those with prior CVD (9.5 [9.0–10.0] and 4.0

Table 1. Study Participant Characteristics at Baseline

Characteristics	All Participants (N=963 648)	Those Without Diabetes Mellitus (N=634 024)	Those With Diabetes Mellitus (N=329 624)	*P* Value
Age, mean±SD, y	65.0±11.7	64.7±12.2	65.6±10.7	<0.001
Male sex, n (%)	936 379 (97.2)	612 583 (96.6)	323 796 (98.2)	<0.001
Race, n (%)				
American Indian or Alaska Native	4242 (0.4)	2559 (0.4)	1683 (0.5)	<0.001
Asian	3781 (0.4)	2245 (0.4)	1536 (0.5)	<0.001
Black or African American	148 507 (15.4)	91 998 (14.5)	56 509 (17.1)	<0.001
Native Hawaiian or other Pacific	7667 (0.8)	4782 (0.8)	2885 (0.9)	<0.001
Other	519 (0.1)	310 (0)	209 (0.1)	<0.001
Unknown or null	4417 (0.5)	3334 (0.5)	1083 (0.3)	<0.001
White	794 515 (82.4)	528 796 (83.4)	265 719 (80.6)	<0.001
Ethnicity, n (%)				
Hispanic or Latino	48 121 (5)	24 947 (3.9)	23 174 (7)	<0.001
Not Hispanic or Latino	912 171 (94.7)	606 538 (95.7)	305 633 (92.7)	<0.001
Unknown or null	3356 (0.3)	2539 (0.4)	817 (0.2)	<0.001
CVD at baseline, n (%)	425 577 (44.2)	255 613 (40.3)	169 964 (51.6)	<0.001
Cancer at baseline, n (%)	274 387 (28.5)	185 211 (29.2)	89 176 (27.1)	<0.001
Mental health disease at baseline, n (%)	138 384 (14.4)	92 994 (14.7)	45 390 (13.8)	<0.001
Kidney disease at baseline, n (%)*	18 441 (1.9)	8178 (1.3)	10 263 (3.1)	<0.001
Smoking status, n (%)				
Ever	785 010 (81.5)	519 509 (81.9)	265 501 (80.5)	<0.001
Never smoker	178 638 (18.5)	114 515 (18.1)	64 123 (19.5)	<0.001
Statin at baseline, n (%)	440 617 (45.7)	261 336 (41.2)	179 281 (54.4)	<0.001
Statin at follow-up, n (%)	792 749 (82.3)	495 221 (78.1)	297 528 (90.3)	<0.001
BMI, mean±SD, kg/m^2	29.67±5.7	28.8±5.3	31.3±5.9	<0.001
Glucose, mean±SD, mg/dL	123.44±51.5	104.1±24.3	160.6±67.2	<0.001
HbA1c, mean±SD, %	6.95±1.7	5.9±1.1	7.5±1.7	<0.001
Total cholesterol, mean±SD, mg/dL	189.56±42	192.6±41	183.7±43.2	<0.001
HDL-C, mean±SD, mg/dL	43.44±13.1	44.9±13.6	40.5±11.5	<0.001
Non–HDL-C, mean±SD, mg/dL	146.12±41.4	147.7±40.6	143.1±42.7	<0.001
Systolic blood pressure, mean±SD, mm Hg	138.72±19.9	137.9±19.7	140.3±20.2	<0.001
Follow-up time, mean±SD, y	8.5±3.3	8.2±3.5	9.0±2.9	<0.001

BMI indicates body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol.
*Kidney disease based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, v45.1, v56, and 996.73.

[3.7–4.4] all-cause and CVD deaths/1000 person-years, respectively) than in those without prior CVD (2.5 [2.1–2.8] and 1.4 [1.2–1.6] all-cause and CVD deaths/1000 person-years, respectively; Figure 1D, Table S3, model A). Finally, accounting for diabetes mellitus and blood pressure treatment at baseline attenuated diabetes mellitus–related all-cause and CVD mortality (adjusted risk difference [95% CI] of all-cause mortality comparing patients with versus without diabetes mellitus decreased from 7.0 [6.7–7.4] to 2.8 [−0.02 to 5.7] deaths/1000-person-years, and from 3.5 [3.3–3.7] to 1.8 [0.03–3.6] deaths/1000-person-years for CVD mortality; Table S3, model B).

In Cox proportional hazards regression models, the risk of all-cause and CVD mortality was higher in individuals with diabetes mellitus than in those without diabetes mellitus (Table 2). The association between diabetes mellitus and

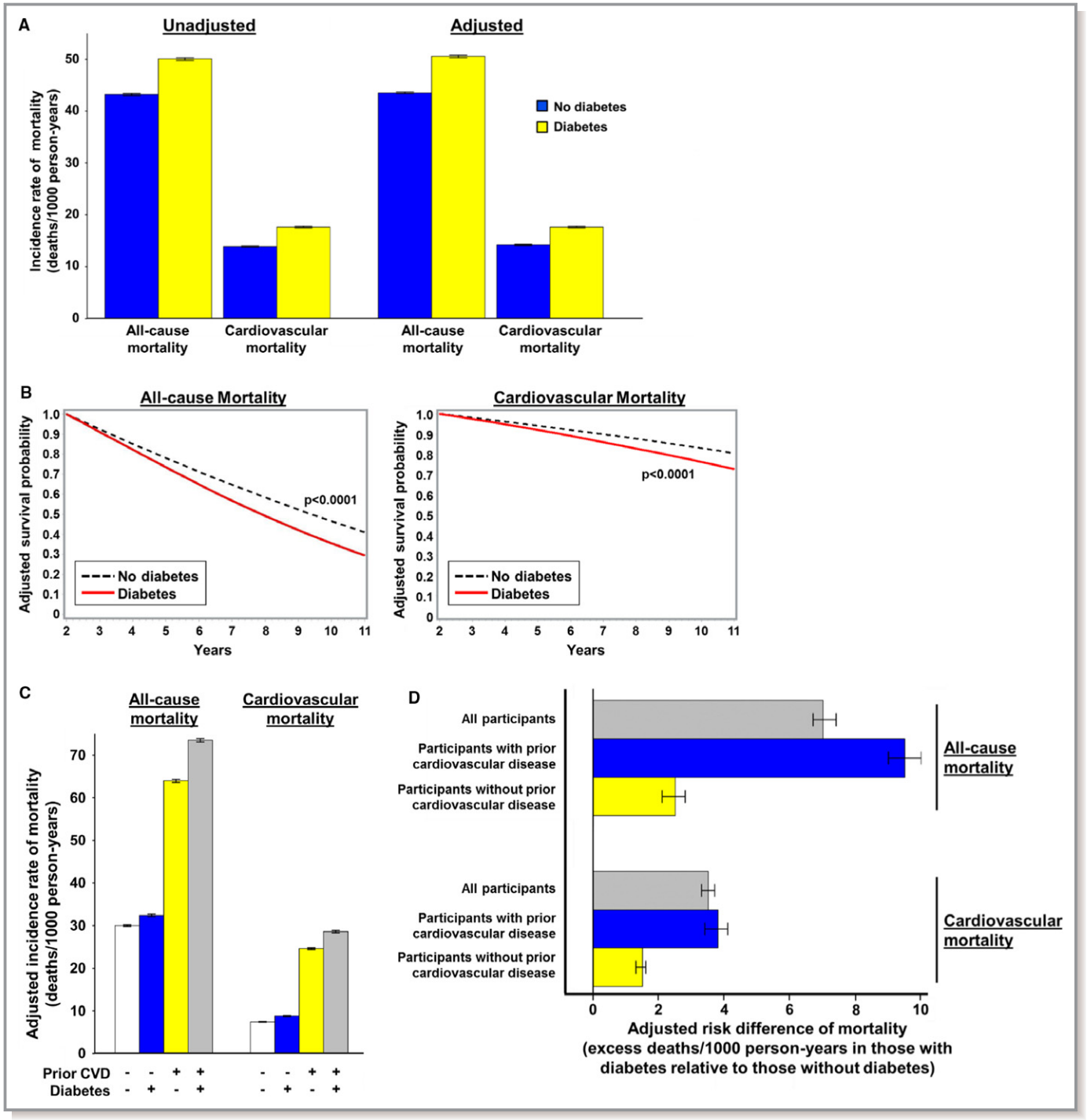

Figure 1. Association between diabetes mellitus and mortality. Diabetes mellitus is associated with higher all-cause and cardiovascular mortality. **A**, Incidence rate of mortality in unadjusted models and with adjustment for age, sex, race, ethnicity, body mass index (BMI), non–high-density lipoprotein (non-HDL) cholesterol, systolic blood pressure, and smoking status. **B**, Estimated survival probabilities of all-cause and cardiovascular mortality in individuals without and with diabetes mellitus in models adjusted for age, sex, race, ethnicity, BMI, non-HDL cholesterol, systolic blood pressure, and smoking status (outcomes occurring in the first 2 years of follow-up were censored). **C**, Diabetes mellitus is associated with increased incidence of all-cause and cardiovascular mortality in individuals without and with prior cardiovascular disease (CVD). **D**, Adjusted risk difference of mortality, relative to individuals without diabetes mellitus, in individuals with diabetes mellitus with and without prior CVD.

mortality strengthened in successive models that adjusted for age, sex, race, BMI, non–high-density lipoprotein cholesterol, SBP, and smoking status (Table 2). However, inclusion of prior CVD as a covariate reduced the association between diabetes mellitus and CVD mortality from hazard ratio (HR) (95% CI) of 1.26 (1.24–1.27) to 1.18 (1.16–1.19). Including baseline

Table 2. Association Between Diabetes Mellitus Status and Mortality in Successive Models Adjusting for Cardiovascular Risk Factors and Glycemia

	All-Cause Mortality		Cardiovascular Mortality*	
Model	HR (95% CI)†	*P* Value	HR (95% CI)†	*P* Value
1	1.15 (1.14–1.15)	<0.0001	1.25 (1.24–1.27)	<0.0001
2	1.18 (1.17–1.19)	<0.0001	1.29 (1.28–1.31)	<0.0001
3	1.20 (1.19–1.21)	<0.0001	1.26 (1.24–1.27)	<0.0001
4	1.16 (1.15–1.17)	<0.0001	1.18 (1.16–1.19)	<0.0001
5	0.99 (0.98–0.99)	0.0005	1.03 (1.02–1.05)	<0.0001
6	0.94 (0.93–0.95)	<0.0001	1.00 (0.98–1.02)	0.72

Model 1 is unadjusted. Model 2=model 1+age, sex, race, and ethnicity. Model 3=model 2+body mass index, non–high-density lipoprotein cholesterol, systolic blood pressure, and smoking status. Model 4=model 3+prior cardiovascular disease. Model 5=model 4+random plasma glucose. Model 6=model 4+diabetes mellitus medications and blood pressure medications. HR indicates hazard ratio.

*Cardiovascular mortality estimated in competing risk models that account for death attributable to noncardiovascular causes.

†HR of mortality in individuals with diabetes mellitus compared with those without diabetes mellitus.

random plasma glucose as a covariate fully attenuated the association between diabetes mellitus and all-cause mortality (HR, 0.99 [95% CI, 0.98–0.99]) and reduced the association with CVD mortality (HR, 1.03 [95% CI, 1.02–1.05]). Similarly, including baseline diabetes mellitus and blood pressure treatment fully attenuated the association between diabetes mellitus and both mortality end points (all-cause mortality HR, 0.96 [95% CI, 0.94–0.98]; CVD mortality HR, 1.00 [95% CI, 0.98–1.02]). In models adjusted for CVD risk factors and additionally for glycemia or for baseline diabetes mellitus and blood pressure treatment, a history of CVD was a stronger predictor of all-cause and CVD mortality than diabetes mellitus (Table S4).

HbA1c and Mortality

Among individuals with diabetes mellitus, individuals with HbA1c 6% to 6.9% had the lowest crude and adjusted incidence of all-cause and CVD mortality, and the incidence of all-cause and CVD mortality increased with successive HbA1c categories ≥7% (Figure 2A, Table S5). Incremental increases in all-cause and CVD mortality were greater with each increment in HbA1c ≥7% in individuals with prior CVD than in those without (Figure 2B, Table S5). HbA1c <6% was associated with higher all-cause mortality relative to HbA1c 6% to 6.9% irrespective of CVD history, and with higher CVD mortality only in individuals without prior CVD (Figure 2B, Table S5).

In Cox proportional hazards models adjusted for age, sex, race, ethnicity, BMI, non–high-density lipoprotein cholesterol, SBP, smoking status, CVD history, and baseline diabetes mellitus and blood pressure medications, we observed a J-shaped association between HbA1c and all-cause mortality over short-term (2–5 years) and long-term (>5 years) follow-up (Figure 2C). However, HbA1c was less strongly predictive of mortality at >5 years versus at 2 to 5 years for all HbA1c categories relative to HbA1c 6% to 6.9% (Figure 2C, Table S6). In competing risk models, short-term CVD mortality risk was 10%, 27%, and 48% higher in individuals with HbA1c 7% to 7.9%, 8% to 8.9%, and ≥9%, respectively, compared with those with HbA1c 6% to 6.9% (Figure 2C). The corresponding long-term CVD mortality risks were 6%, 14%, and 41% higher in individuals with HbA1c 7% to 7.9%, 8% to 8.9%, and ≥9%, respectively, compared with those with HbA1c 6% to 6.9% (Figure 2C, Table S6). HbA1c <6% was associated with higher all-cause mortality compared with HbA1c 6% to 6.9% over short- and long-term follow-up times but was associated only with higher short-term CVD mortality (Figure 2C, Table S6). We observed similar patterns of association between HbA1c ≥7% and all-cause and CVD mortality in individuals with and without prior CVD, although the HRs increased more steeply below and above a reference of HbA1c 6% to 6.9% in those without prior CVD, and HbA1c <6% was associated with higher CVD mortality only in individuals without prior CVD (Figure 2D, Table S6).

Subgroup Analyses

In age-stratified analyses, individuals ≥65 years of age at baseline had higher incidence of all-cause and CVD mortality. In both age groups, the lowest incidence rates of mortality were observed for those with HbA1c 6% to 6.9%, and mortality increased with increasing HbA1c (Figure 3A, Table S7). The adjusted risk differences associated with increasing HbA1c categories were greater in older than in younger individuals in crude and adjusted models (Figure 3B, Table S7). In Cox proportional hazards models, there was a significant interaction between age and HbA1c category and both all-cause and CVD mortality (interaction $P<0.0001$ for both outcomes). In contrast to the results on the risk difference scale, the relative hazard of CVD mortality increased more steeply with increasing HbA1c categories ≥7% in individuals <65 years of age than in those ≥65 years of age (Figure 3C, Table S8). HbA1c <6% was associated with higher all-cause mortality than HbA1c 6% to 6.9% in both age groups, and with higher short-term CVD mortality only in those ≥65 years (Figure 3C, Table S8). As in the unstratified analysis, baseline HbA1c was more strongly associated with short-term mortality than long-term mortality.

Discussion

In this study of individuals receiving care in an integrated national healthcare system, we found that diabetes mellitus

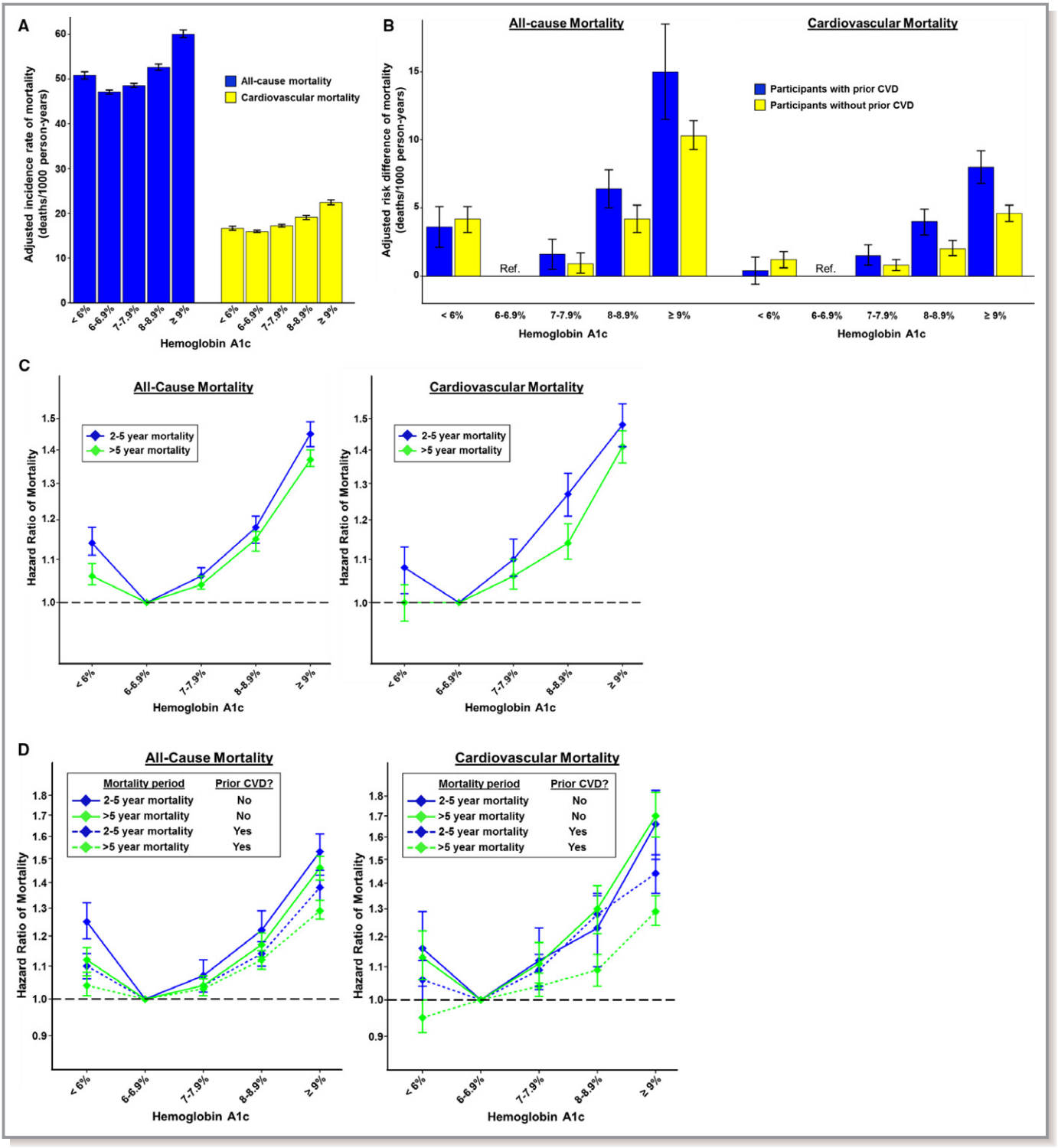

Figure 2. Association between hemoglobin A1c (HbA1c) and mortality. HbA1c is associated with all-cause and cardiovascular mortality after accounting for modifiable cardiovascular disease (CVD) risk factors. **A**, Incidence rate of all-cause and cardiovascular mortality across categories of baseline HbA1c in models adjusted for age, sex, race, ethnicity, body mass index (BMI), non–high-density lipoprotein (non-HDL) cholesterol, systolic blood pressure, smoking status, and diabetes mellitus and blood pressure treatment. **B**, Adjusted risk difference of all-cause and cardiovascular mortality, relative to individuals with HbA1c 6% to 6.9%, in individuals across categories of baseline HbA1c, stratified by baseline CVD history. Association between HbA1c category and short- and long-term all-cause and cardiovascular mortality in Cox proportional hazards models, adjusted for age, sex, race, ethnicity, BMI, non-HDL cholesterol, systolic blood pressure, smoking status, CVD history, and diabetes mellitus and blood pressure treatment (**C**), and stratified by CVD history (**D**).

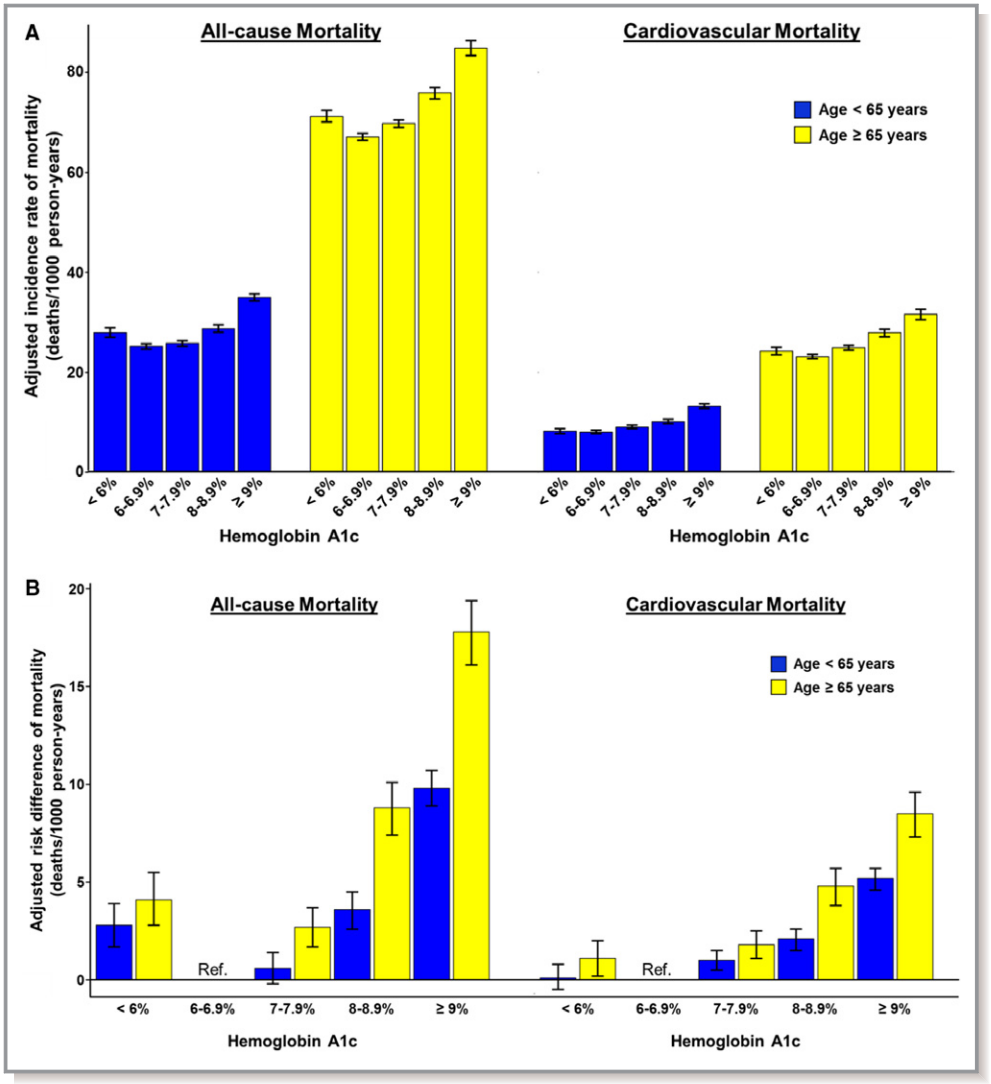

Figure 3. Age-stratified association between hemoglobin A1c (HbA1c) and mortality. Association between HbA1c and mortality accounting for modifiable cardiovascular disease risk factors and stratified by baseline age (<65 or ≥65 years). **A**, Incidence rate of all-cause and cardiovascular mortality across categories of baseline HbA1c in individuals <65 and ≥65 years of age, adjusting for age, sex, race, ethnicity, body mass index (BMI), non–high-density lipoprotein (non-HDL) cholesterol, systolic blood pressure, smoking status, and diabetes mellitus and blood pressure treatment. **B**, Adjusted risk difference of all-cause and cardiovascular mortality, relative to individuals with HbA1c 6% to 6.9%, in individuals across categories of baseline HbA1c, stratified by age at baseline. **C**, Association between HbA1c category and short- and long-term all-cause and cardiovascular mortality in Cox proportional hazards models, adjusted for age, sex, race, ethnicity, BMI, non-HDL cholesterol, systolic blood pressure, smoking status, cardiovascular disease history, and diabetes mellitus and blood pressure treatment, stratified by baseline age.

was independently associated with all-cause and CVD mortality even after adjusting for CVD risk factors. Relative to unadjusted models, the association between diabetes mellitus and mortality was modestly attenuated when accounting for prior CVD and nearly completely attenuated when adjusting for random plasma glucose levels or diabetes mellitus and blood pressure treatment. In contrast to older studies that described 3- to 4-fold excess mortality associated with diabetes mellitus,[13–16] in our contemporary US cohort, diabetes mellitus was associated with only an 18% increase in CVD mortality in models adjusted for other CVD risk factors. Among individuals with diabetes mellitus, we found all-cause and CVD mortality risk were lowest in individuals with HbA1c between 6% and 6.9%, all-cause mortality risk was higher in those with HbA1c <6%, and both all-cause and CVD mortality increased with HbA1c ≥7% in all participants and in analyses stratified by age or CVD history.

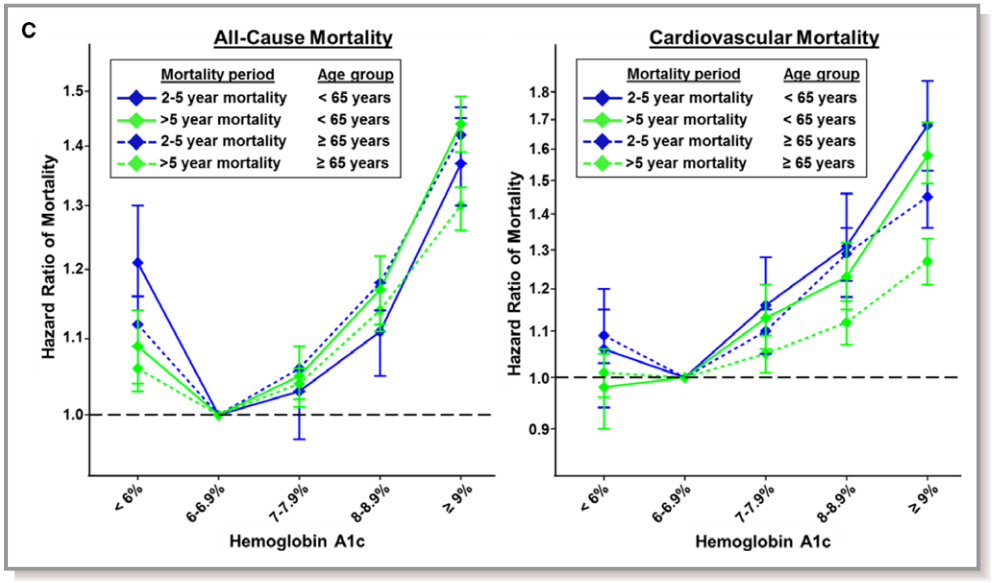

Figure 3. Continued.

Furthermore, this pattern of association was observed over both short (2–5 years) and long (>5 years) follow-up times. Finally, there was a significant interaction between HbA1c and age group, but similar qualitative patterns of association between HbA1c and mortality in individuals younger and older than 65 years of age.

This study, set in a national, clinically-derived cohort in the United States, supports prior work in European populations demonstrating that contemporary individuals with type 2 diabetes mellitus are at excess risk of mortality.[7,8,19–21,26] We extend the prior literature by demonstrating that accounting for CVD risk factors diminishes the association of diabetes mellitus with mortality, and that the association is nearly completely attenuated by further adjustment for glucose levels or treatment. Overall, diabetes mellitus had a smaller association with mortality in our study than in recent cohort studies based in Europe and elsewhere[7,13–16,19,21] and studies before the broad adoption of CVD risk factor reduction.[14,16] In contrast to a recent study set in Denmark,[27] we found that diabetes mellitus was a significant predictor of mortality, even in individuals without prior CVD. Among those with diabetes mellitus, glycemia appears to be a risk factor for all-cause and CVD mortality independent of other modifiable CVD risk factors, a finding in this US clinical cohort that mirrors data from a Swedish national registry.[8] Taken together, our results suggest that improvements in diabetes mellitus care in the United States[17,18] are reflected in improvements in diabetes mellitus–related mortality, supported by the attenuation of the association between diabetes mellitus and mortality after accounting for risk factor levels and treatment.

There has been recent attention to potential diabetes mellitus overtreatment, particularly among older patients.[28–33] However, we found that HbA1c <6% was associated with higher all-cause mortality irrespective of age and that optimal outcomes occurred among those with HbA1c between 6% and 6.9%. A greater absolute benefit but diminishing relative benefit was accrued with better baseline glycemia by those ≥65 years of age than in younger individuals. The analyses stratified by CVD history mirrored the age-stratified results. Individuals in the higher-risk subgroup (those with prior CVD) had greater absolute mortality risk reductions but smaller relative risk reductions, comparing HbA1c 6% to 6.9% with higher HbA1c categories. The stratified analyses suggest that achieving HbA1c 6% to 6.9% is associated with lower short- and long-term mortality in those for whom glucose lowering is safe.

Our study has several limitations. First, causal inferences are limited by our observational design, and we cannot estimate the influence of unmeasured confounders, including social factors, such as socioeconomic status or family history of CVD. However, our analysis included many covariates and clinical risk factors, and the findings were consistent over short- and long-term follow-up, suggesting that the associations between HbA1c and mortality are unlikely to be attributable solely to time-varying confounding events. Second, this study focused on associations of a single baseline measurement of exposures and covariates with mortality. Because we did not examine changes in risk factors or treatment over time, we were unable to draw conclusions about the effects of longitudinal risk factor control and clinical outcomes. Similarly, because our study aimed to estimate associations of baseline diabetes mellitus status and glycemic control with mortality, our study design did not permit evaluation of associations between specific treatments and clinical outcomes. Third, we included >27 000 women, but

the study population was predominantly male. Finally, external validity to the general US population may be limited given that our study was limited to patients receiving primary care through the VA, who are older, who are more likely to be men, and who have more comorbidities than counterparts receiving care outside the VA.

Our study has several clinically relevant implications. First, diabetes mellitus prevention could impact long-term mortality in individuals at risk for CVD, especially in those with a history of CVD, and should continue to be included along with smoking cessation, blood pressure control, and lipid management as the basis for CVD prevention. Second, diabetes mellitus–related mortality appears to be substantially reduced now that CVD risk factor control is the standard of care, and diabetes mellitus and prior CVD should no longer be considered equivalent risk factors for CVD mortality. In fact, the attenuation of the association between diabetes mellitus and mortality after accounting for prior CVD, CVD risk factors, and diabetes mellitus control or treatment suggests that excess diabetes mellitus–related mortality may be largely preventable with improved treatment and risk factor management. Third, the association of HbA1c <6% with higher mortality in our national cohort mirrors that observed in other clinical settings[22,33] and supports the notion that overly intensive glycemic control could be associated with adverse outcomes. Finally, each 1% increment in HbA1c ≥7% was associated with higher short- and long-term all-cause and CVD mortality, irrespective of age category or CVD history. Although the results of our observational study might suggest that HbA1c 6% to 6.9% or, alternatively, the lowest safely achievable HbA1c level >7% could be considered as a target for management of patients with diabetes mellitus, this conclusion has not been supported by randomized trials failing to demonstrate a macrovascular benefit of intensive glycemic control compared with standard glycemic targets.[34–36] Rather, even in the absence of a causal association between lower HbA1c and mortality, HbA1c may be an informative marker of important clinical outcomes in individuals with diabetes mellitus and may serve to identify individuals at higher or lower risk of mortality, even after accounting for other CVD risk factors.

Author Contributions

Study design was conceived by Raghavan, Vassy, Cho, Gagnon, Wilson, Phillips. Data collection and organization were performed by Ho, Cho, Wilson, Phillips. Analyses were performed by Ho, Song, Cho, Gagnon. Results were interpreted by Raghavan, Vassy, Ho, Cho, Gagnon, Wilson, Phillips. All authors participated in manuscript writing and critical revision, and all authors approve of the manuscript submission in its current form.

Sources of Funding

Ho, Song, Gagnon, Cho, Wilson, and Phillips are supported by Veterans Health Administration Merit Grant I01-CX001025. Raghavan is supported by a University of Colorado General Internal Medicine Small Grant and American Heart Association Award 17MCPRP33670728. Vassy is supported by Veterans Health Administration Career Development Award IK2-CX001262. Phillips is also supported by Food and Drug Administration award RO1FD003527, Veterans Health Administration Health Services Research & Development Award IIR 07-138, National Institutes of Health awards R21DK099716, DK066204, U01 DK091958, U01 DK098246, and P30DK111024, and a Cystic Fibrosis Foundation award PHILLI12A0. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. All authors are also supported in part by the Veterans Health Administration. This work is not intended to reflect the official opinion of the Veterans Health Administration or the US government.

Disclosures

Phillips has served on Scientific Advisory Boards for Janssen and the Profil Institute for Clinical Research; and has or had research support from Merck, Amylin, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, Abbvie, Vascular Pharmaceuticals, Janssen, Glaxo SmithKline, Pfizer, and the Cystic Fibrosis Foundation. In the past, he was a speaker for Novartis and Merck, but not for the past 5 years. Phillips is also a cofounder, officer, board member, and stockholder of a company, DIASYST, Inc, which is developing software aimed to help improve diabetes mellitus management. The remaining authors have no disclosures to report.

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Supplemental Material

Figure S1. CONSORT diagram of study cohort development from VA electronic health records.

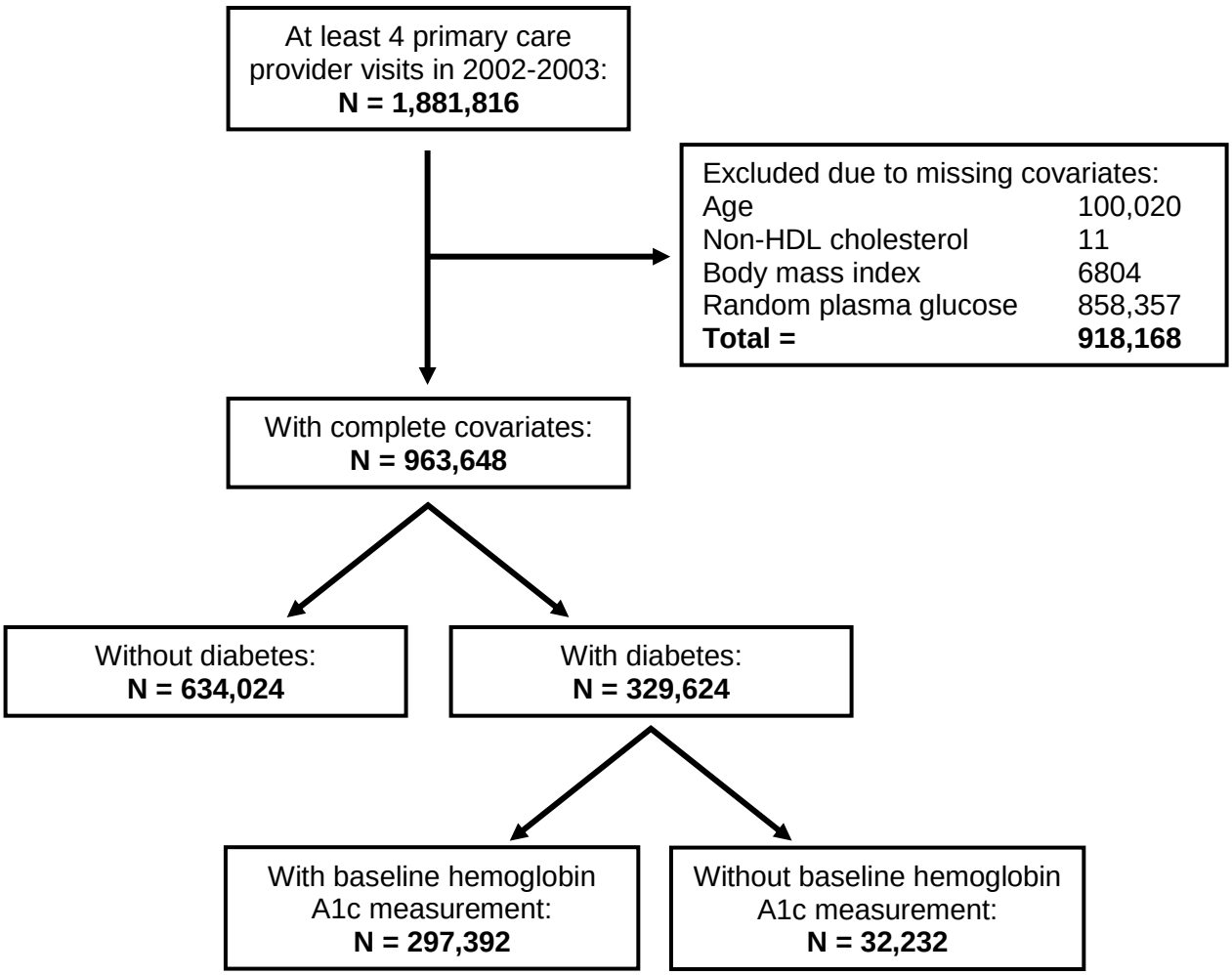

Table S1. Characteristics of participants with diabetes at baseline, stratified by baseline HbA1c.

		HbA1 < 6% N=40439	HbA1c 6-6.9% N=90609	HbA1c 7-7.9% N=73805	HbA1c 8-8.9% N=42497	HbA1c ≥ 9% N=50042	p-value
Age, mean ± SD (years)		65.94 ± 10.8	67.4 ± 10.3	66.77 ± 10.2	64.87 ± 10.5	60.75 ± 10.6	<0.001
Male, n (%)		39643 (98%)	89039 (98.3%)	72532 (98.3%)	41833 (98.4%)	49039 (98%)	<0.001
Race, n (%)	*American Indian or Alaska Native*	219 (0.5%)	402 (0.4%)	374 (0.5%)	214 (0.5%)	345 (0.7%)	<0.001
	Asian	156 (0.4%)	417 (0.5%)	410 (0.6%)	217 (0.5%)	260 (0.5%)	<0.001
	Black or African American	6401 (15.8%)	13654 (15.1%)	11651 (15.8%)	7588 (17.9%)	13082 (26.1%)	<0.001
	Native Hawaiian or Other Pacific	330 (0.8%)	740 (0.8%)	657 (0.9%)	390 (0.9%)	485 (1%)	<0.001
	Other	18 (0%)	58 (0.1%)	55 (0.1%)	32 (0.1%)	35 (0.1%)	<0.001
	Unknown or Null	117 (0.3%)	222 (0.2%)	193 (0.3%)	151 (0.4%)	287 (0.6%)	<0.001
	White	33198 (82.1%)	75116 (82.9%)	60465 (81.9%)	33905 (79.8%)	35548 (71%)	<0.001
Ethnicity, n (%)	*Hispanic or Latino*	2638 (6.5%)	5808 (6.4%)	5155 (7%)	3291 (7.7%)	4717 (9.4%)	<0.001
	Not Hispanic or Latino	37720 (93.3%)	84642 (93.4%)	68505 (92.8%)	39085 (92%)	45106 (90.1%)	<0.001
	Unknown or Null	81 (0.2%)	159 (0.2%)	145 (0.2%)	121 (0.3%)	219 (0.4%)	<0.001
CVD at baseline, n (%)		20403 (50.5%)	47835 (52.8%)	39243 (53.2%)	22139 (52.1%)	22981 (45.9%)	<0.001
Cancer at baseline, n (%)		12394 (30.6%)	27146 (30%)	20363 (27.6%)	10555 (24.8%)	9496 (19%)	<0.001
Mental Health Disease at baseline, n (%)		7260 (18%)	12065 (13.3%)	8952 (12.1%)	5589 (13.2%)	7495 (15%)	<0.001
Kidney Disease at baseline, n (%)		1606 (4%)	2869 (3.2%)	2272 (3.1%)	1337 (3.1%)	1177 (2.4%)	<0.001
Smoking Status, n (%)	*Ever*	32788 (81.1%)	73435 (81%)	59209 (80.2%)	34047 (80.1%)	39935 (79.8%)	<0.001
	Never Smoker	7651 (18.9%)	17174 (19%)	14596 (19.8%)	8450 (19.9%)	10107 (20.2%)	<0.001
Statin at baseline, n (%)		19489 (48.2%)	49605 (54.7%)	41703 (56.5%)	24178 (56.9%)	26185 (52.3%)	<0.001
Statin during follow-up, n (%)		34629 (85.6%)	81462 (89.9%)	67339 (91.2%)	39024 (91.8%)	46154 (92.2%)	<0.001
BMI, mean ± SD (kg/m^2)		30.84 ± 5.9	31.13 ± 5.8	31.32 ± 5.9	31.56 ± 6	31.6 ± 6.2	<0.001
Glucose, mean ± SD (mg/dL)		119.78 ± 35.7	135.31 ± 40.5	156.94 ± 49.5	181.77 ± 62.3	234.25 ± 89.8	<0.001
Total Cholesterol, mean ± SD (mg/dL)		176.01 ± 39.4	179.01 ± 39.3	181.53 ± 40.1	186.11 ± 43.2	199.48 ± 52.5	<0.001
HDLC, mean ± SD (mg/dL)		40.93 ± 12.3	40.6 ± 11.2	40.38 ± 11.1	40.27 ± 11.3	40.85 ± 12.1	<0.001
Non-HDL Cholesterol, mean ± SD (mg/dL)		135.08 ± 38.7	138.4 ± 38.8	141.15 ± 39.7	145.84 ± 42.8	158.63 ± 52.2	<0.001
Systolic Blood Pressure, mean ± SD (mmHg)		139.09 ± 20.1	140.15 ± 20	140.89 ± 20	141.16 ± 20.4	140.4 ± 20.6	<0.001
Count of comorbidities, median (IQR)		11 (7, 16)	11 (7, 16)	11 (7, 15)	11 (7, 16)	11 (7, 16)	<0.001
Follow-up time, mean ± SD (years)		9.0 ± 2.9	9.0 ± 2.8	8.9 ± 2.9	8.9 ± 2.9	9.0 ± 2.9	<0.001

Table S2. Causes of death since 2002 of US veterans with and without diabetes.

Causes of death	All participants n (%)	Non-diabetic n (%)	Diabetic n (%)	p-value
Cardiovascular diseases	139756 (32.8)	81616 (31.6)	58140 (34.5)	<0.001
Cancer	100788 (23.6)	68332 (26.5)	32456 (19.3)	<0.001
COPD*	28860 (6.8)	20518 (8.0)	8342 (5.0)	<0.001
Diabetes	20093 (4.7)	2477 (1)	17616 (10.5)	<0.001
Chronic kidney disease	14027 (3.3)	7035 (2.7)	6992 (4.2)	<0.001
Infection	11822 (2.8)	6765 (2.6)	5057 (3.0)	<0.001
Mental Illness	11594 (2.7)	8125 (3.1)	3469 (2.1)	<0.001
Abnormal/Accident	6603 (1.5)	4418 (1.7)	2185 (1.3)	<0.001
Other chronic diseases	312 (0.1)	242 (0.1)	70 (0)	<0.001
All other	92589 (21.7)	58485 (22.7)	34104 (20.2)	<0.001

* COPD = chronic obstructive pulmonary disease

Table S3. Crude and adjusted mortality in participants with and without diabetes, stratified by baseline cardiovascular disease.

		All-cause Mortality			CVD Mortality		
		Crude	Model A*	Model B†	Crude	Model A*	Model B†
		Incidence Rate‡	Incidence Rate‡	Incidence Rate‡	Incidence Rate‡	Incidence Rate‡	Incidence Rate‡
All participants	Non-diabetic	43.2 (43.0, 43.4)	43.5 (43.4, 43.7)	41.8 (39.2, 44.6)	13.9 (13.8, 14.0)	14.2 (14.1, 14.3)	13.5 (12.0, 15.2)
	Diabetic	50.1 (49.8, 50.3)	50.6 (50.3, 50.8)	44.6 (44.2, 45.0)	17.6 (17.5, 17.8)	17.6 (17.5, 17.8)	15.3 (15.1, 15.5)
	Risk Difference	6.9 (6.6, 7.2)	7.0 (6.7, 7.4)	2.8 (-0.02, 5.7)	3.7 (3.5, 3.9)	3.5 (3.3, 3.7)	1.8 (0.03, 3.6)
Prior CVD	Non-diabetic	65.6 (65.3, 66.0)	64.0 (63.6, 64.3)	68.3 (60.8, 76.7)	25.0 (24.8, 25.3)	24.6 (24.4, 24.8)	23.9 (20.4, 28.0)
	Diabetic	70.0 (69.5, 70.4)	73.5 (73.1, 73.9)	65.5 (64.9, 66.1)	27.3 (27.1, 27.6)	28.6 (28.3, 28.9)	25.3 (24.9, 25.8)
	Risk Difference	4.4 (3.8, 4.9)	9.5 (9.0, 10.0)	-2.8 (-11.2, 5.7)	2.3 (1.9, 2.7)	4.0 (3.7, 4.4)	1.5 (-2.7, 5.6)
No Prior CVD	Non-diabetic	29.8 (29.6, 30.0)	30.0 (29.8, 30.2)	29.7 (27.4, 32.2)	7.2 (7.1, 7.3)	7.4 (7.3, 7.5)	7.9 (6.5, 9.5)
	Diabetic	32.0 (31.7, 32.3)	32.4 (32.1, 32.7)	28.7 (28.3, 29.2)	8.8 (8.6, 8.9)	8.8 (8.6, 8.9)	7.6 (7.3, 7.8)
	Risk Difference	2.3 (1.9, 2.6)	2.5 (2.1, 2.8)	-1.0 (-3.5, 1.6)	1.6 (1.4, 1.7)	1.4 (1.2, 1.6)	-0.3 (-2.0, 0.4)

* Model A = Adjusted for age, sex, race, ethnicity, body mass index, non-HDL cholesterol, systolic blood pressure, and smoking status
† Model B = Model A + diabetes medications and blood pressure medications
‡ deaths/1000-person-years

Table S4. Comparison of associations of diabetes status and history of cardiovascular disease with all-cause and cardiovascular mortality.

Risk Factor	All-cause Mortality						Cardiovascular Mortality*					
	Model 4†		Model 5‡		Model 6§		Model 4†		Model 5‡		Model 6§	
	HR‖ (95% CI)	p-value	HR‖ (95% CI)	p-value	HR‖ (95% CI)	p-value	HR‖ (95% CI)	p-value	HR‖ (95% CI)	p-value	HR‖ (95% CI)	p-value
Diabetes	1.16 (1.15, 1.17)	<0.0001	0.99 (0.98, 0.99)	0.0005	0.94 (0.93, 0.95)	<0.0001	1.18 (1.16, 1.19)	<0.0001	1.03 (1.02, 1.05)	<0.0001	1.00 (0.98, 1.02)	0.72
Prior CVD	1.60 (1.59, 1.62)	<0.0001	1.60 (1.59, 1.61)	<0.0001	1.50 (1.49, 1.51)	<0.0001	2.27 (2.24, 2.30)	<0.0001	2.26 (2.23, 2.29)	<0.0001	2.02 (1.99, 2.04)	<0.0001

* Cardiovascular mortality estimated in competing risk models that account for death due to non-cardiovascular causes.
† Model 4 = adjusted for age, sex, race, ethnicity, body mass index, non-HDL cholesterol, systolic blood pressure, and smoking status.
‡ Model 5 = Model 4 + random plasma glucose.
§ Model 6 = Model 4 + diabetes medications and blood pressure medications
‖ Hazard ratio of mortality in individuals with versus without diabetes or with versus without a history of cardiovascular disease (CVD).

Table S5. Crude and adjusted mortality in patients with diabetes across levels of HbA1c, stratified by baseline cardiovascular disease.

		All-cause Mortality					CVD Mortality				
		Crude	Model A*		Model B†		Crude	Model A*		Model B†	
		Incidence Rate‡	Incidence Rate‡	Risk Difference	Incidence Rate‡	Risk Difference	Incidence Rate[a]	Incidence Rate‡	Risk Difference	Incidence Rate‡	Risk Difference
All participants	**HbA1c**										
	< 6.0	49.2 (48.5, 49.9)	47.3 (46.7, 48.0)	2.2 (1.4, 3.0)	50.8 (50.0, 51.6)	3.7 (2.8, 4.6)	16.1 (15.7, 16.6)	15.6 (15.2, 16.0)	0.4 (-0.1, 0.9)	16.6 (16.2, 17.1)	0.7 (0.2, 1.3)
	6.0-6.9	49.3 (48.8, 49.8)	45.1 (44.7, 45.5)	Reference	47.1 (46.6, 47.5)	Reference	16.8 (16.5, 17.1)	15.2 (15.0, 15.5)	Reference	15.9 (15.7, 16.2)	Reference
	7.0-7.9	51.3 (50.8, 51.9)	48.8 (48.3, 49.3)	3.7 (3.1, 4.3)	48.5 (48.1, 49.0)	1.5 (0.8, 2.2)	18.2 (17.9, 18.5)	17.3 (17.0, 17.6)	2.1 (1.7, 2.5)	17.2 (16.9, 17.5)	1.3 (0.9, 1.7)
	8.0-8.9	52.2 (51.5, 52.9)	54.2 (53.6, 54.9)	9.1 (8.3, 9.9)	52.6 (51.9, 53.3)	5.5 (4.7, 6.4)	19.0 (18.5, 19.4)	19.7 (19.3, 20.2)	4.5 (3.9, 5.1)	19.1 (18.6, 19.5)	3.1 (2.6, 3.7)
	≥ 9.0	49.6 (48.9, 50.2)	61.7 (60.9, 62.5)	16.6 (15.7, 17.5)	60.0 (59.2, 60.9)	13.0 (12.0, 13.9)	18.5 (18.1, 18.9)	23.1 (22.5, 23.6)	7.9 (7.3, 8.5)	22.4 (21.9, 23.0)	6.5 (5.8, 7.1)
Participants with prior CVD	**HbA1c**										
	< 6.0	68.4 (67.2, 69.7)	65.7 (64.6, 66.8)	1.4 (0.1, 2.7)	70.7 (69.4, 72.0)	3.6 (2.1, 5.1)	25.0 (24.3, 25.8)	24.1 (23.4, 24.8)	-0.4 (-1.2, 0.4)	26.0 (25.1, 26.8)	0.4 (-0.6, 1.4)
	6.0-6.9	68.1 (67.3, 69.0)	64.3 (63.6, 65.0)	Reference	67.1 (66.3, 67.8)	Reference	26.0 (25.5, 26.5)	24.5 (24.0, 24.9)	Reference	25.6 (25.1, 26.1)	Reference
	7.0-7.9	71.1 (70.2, 72.0)	69.1 (68.3, 69.9)	4.8 (3.7, 5.9)	68.7 (67.9, 69.5)	1.6 (0.5, 2.7)	27.9 (27.3, 28.5)	27.1 (26.6, 27.7)	2.6 (1.9, 3.3)	27.1 (26.5, 27.6)	1.5 (0.8, 2.3)
	8.0-8.9	72.9 (71.7, 74.2)	75.3 (74.2, 76.5)	11.0 (9.6, 12.4)	73.5 (72.3, 74.7)	6.4 (5.0, 7.8)	29.3 (28.5, 30.1)	30.2 (29.4, 31.0)	5.7 (4.8, 6.6)	29.5 (28.7, 30.3)	4.0 (3.0, 4.9)
	≥ 9.0	73.0 (71.8, 74.3)	84.3 (83.0, 85.6)	20.0 (18.5, 21.5)	82.1 (80.7, 83.5)	15.0 (11.5, 18.5)	30.4 (29.6, 31.2)	34.7 (33.7, 35.6)	10.2 (9.2, 11.2)	33.6 (32.5, 34.6)	8.0 (6.8, 9.2)
Participants without prior CVD	**HbA1c**										
	< 6.0	32.4 (31.6, 33.2)	31.5 (30.7, 32.3)	3.2 (2.3, 4.1)	33.6 (32.7, 34.5)	4.2 (3.2, 5.1)	8.4 (8.0, 8.8)	8.3 (7.9, 8.7)	1.1 (0.6, 1.6)	8.7 (8.2, 9.2)	1.2 (0.6, 1.8)
	6.0-6.9	31.2 (30.7, 31.7)	28.3 (27.8, 28.8)	Reference	29.4 (28.9, 29.9)	Reference	8.0 (7.7, 8.3)	7.2 (7.0, 7.5)	Reference	7.5 (7.2, 7.8)	Reference
	7.0-7.9	32.3 (31.7, 32.9)	30.4 (29.9, 31.0)	2.1 (1.3, 2.9)	30.3 (29.8, 30.9)	0.9 (0.2, 1.7)	8.8 (8.5, 9.2)	8.3 (8.0, 8.6)	1.1 (0.7, 1.5)	8.3 (8.0, 8.6)	0.8 (0.4, 1.2)
	8.0-8.9	33.1 (32.3, 33.9)	34.4 (33.6, 35.2)	6.1 (5.2, 7.0)	33.6 (32.8, 34.4)	4.2 (3.2, 5.2)	9.4 (9.0, 9.8)	9.8 (9.3, 10.2)	2.6 (2.1, 3.1)	9.5 (9.1, 10.0)	2.0 (1.5, 2.6)
	≥ 9.0	32.8 (32.1, 33.5)	40.5 (39.6, 41.4)	12.2 (11.2, 13.2)	39.7 (38.8, 40.7)	10.3 (9.3, 11.4)	10.0 (9.6, 10.4)	12.1 (11.6, 12.7)	4.9 (4.2, 5.6)	12.1 (11.5, 12.7)	4.6 (4.0, 5.2)

* Model A = Adjusted for age, sex, race, ethnicity, body mass index, non-HDL cholesterol, systolic blood pressure, and smoking status

† Model B = Model A + diabetes medications and blood pressure medications

‡ deaths/1000-person-year

Table S6. Hazard ratios for all-cause and cardiovascular mortality across levels of HbA1c over short- and long-term follow-up times, stratified by baseline cardiovascular disease.

		All-cause Mortality				CVD Mortality			
		2-5 year mortality		>5 year mortality		2-5 year mortality		>5 year mortality	
		Hazard Ratio (95% CI	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
All participants	**HbA1c**								
	< 6.0	1.14 (1.11, 1.18)	<0.0001	1.06 (1.04, 1.09)	<0.0001	1.08 (1.02, 1.13)	0.004	1.00 (0.96, 1.04)	0.9
	6.0-6.9	Reference	-	Reference	-	Reference	-	Reference	-
	7.0-7.9	1.06 (1.03, 1.08)	<0.0001	1.04 (1.03, 1.06)	<0.0001	1.10 (1.06, 1.15)	<0.0001	1.06 (1.03, 1.10)	0.0001
	8.0-8.9	1.18 (1.14, 1.21)	<0.0001	1.15 (1.12, 1.17)	<0.0001	1.27 (1.21, 1.33)	<0.0001	1.14 (1.10, 1.19)	<0.0001
	≥ 9.0	1.45 (1.41, 1.49)	<0.0001	1.37 (1.35, 1.40)	<0.0001	1.48 (1.41, 1.55)	<0.0001	1.41 (1.36, 1.46)	<0.0001
Participants with prior CVD	**HbA1c**								
	< 6.0	1.10 (1.06, 1.14)	<0.0001	1.04 (1.01, 1.07)	0.004	1.06 (1.00, 1.12)	0.05	0.95 (0.91, 1.00)	0.04
	6.0-6.9	Reference	-	Reference	-	Reference	-	Reference	-
	7.0-7.9	1.04 (1.01, 1.07)	0.005	1.03 (1.01 ,1.06)	0.002	1.09 (1.04, 1.14)	0.0003	1.04 (1.01, 1.08)	0.02
	8.0-8.9	1.14 (1.10, 1.18)	<0.0001	1.12 (1.09, 1.15)	<0.0001	1.28 (1.21, 1.35)	<0.0001	1.09 (1.04, 1.14)	0.0001
	≥ 9.0	1.38 (1.33, 1.43)	<0.0001	1.29 (1.26, 1.33)	<0.0001	1.44 (1.36, 1.52)	<0.0001	1.29 (1.24, 1.35)	<0.0001
Participants without prior CVD	**HbA1c**								
	< 6.0	1.25 (1.19, 1.32)	<0.0001	1.12 (1.08, 1.16)	<0.0001	1.16 (1.04, 1.29)	0.008	1.13 (1.06, 1.22)	0.0005
	6.0-6.9	Reference	-	Reference	-	Reference	-	Reference	-
	7.0-7.9	1.07 (1.02, 1.12)	0.007	1.04 (1.01, 1.07)	0.01	1.12 (1.03, 1.23)	0.01	1.11 (1.05, 1.18)	0.0004
	8.0-8.9	1.22 (1.15, 1.29)	<0.0001	1.17 (1.13, 1.21)	<0.0001	1.23 (1.10, 1.36)	0.0002	1.3 (1.21, 1.39)	<0.0001
	≥ 9.0	1.53 (1.45, 1.61)	<0.0001	1.46 (1.41, 1.51)	<0.0001	1.66 (1.50, 1.83)	<0.0001	1.71 (1.6, 1.82)	<0.0001

Table S7. Crude and adjusted mortality in participants with diabetes across levels of HbA1c, stratified by age.

		All-cause Mortality					CVD Mortality				
		Crude	Model A*		Model B†		Crude	Model A*		Model B†	
		Incidence Rate‡	Incidence Rate‡	Risk Difference	Incidence Rate‡	Risk Difference	Incidence Rate‡	Incidence Rate‡	Risk Difference	Incidence Rate‡	Risk Difference
< 65 years	**HbA1c**										
	< 6.0	25.6 (24.9, 26.4)	25.3 (24.5, 26.0)	1.7 (0.4, 3.0)	27.9 (27.0, 28.9)	2.8 (1.7, 3.9)	7.3 (6.9, 7.7)	7.4 (7.0, 7.8)	-0.1 (-0.6, 0.4)	8.2 (7.7, 8.7)	0.1 (-0.5, 0.8)
	6.0-6.9	24.0 (23.5, 24.5)	23.6 (23.1, 24.1)	Reference	25.2 (24.6, 25.7)	Reference	7.7 (7.4, 8.0)	7.5 (7.2, 7.8)	Reference	8.0 (7.7, 8.4)	Reference
	7.0-7.9	26.3 (25.7, 26.9)	25.8 (25.2, 26.3)	2.2 (1.5, 2.9)	25.8 (25.2, 26.3)	0.6 (-0.2, 1.4)	9.2 (8.8, 9.6)	9.0 (8.7, 9.3)	1.5 (1.1, 1.9)	9.0 (8.7, 9.4)	1.0 (0.5, 1.5)
	8.0-8.9	29.9 (29.2, 30.7)	29.8 (29.1, 30.5)	6.2 (5.3, 7.1)	28.7 (28.0, 29.5)	3.6 (2.6, 4.5)	10.6 (10.1, 11.1)	10.5 (10.1, 11.0)	3.0 (2.4, 3.6)	10.1 (9.7, 10.6)	2.1 (1.5, 2.6)
	≥ 9.0	34.5 (33.9, 35.2)	36.1 (35.4, 36.8)	12.5 (11.6, 13.4)	35.0 (34.3, 35.7)	9.8 (8.9, 10.7)	12.9 (12.5, 13.3)	13.6 (13.1, 14.0)	5.9 (5.2, 6.6)	13.2 (12.8, 13.7)	5.2 (4.6, 5.7)
≥ 65 years	**HbA1c**										
	< 6.0	70.0 (68.8, 71.2)	67.9 (66.8, 68.9)	2.9 (1.7, 4.1)	71.2 (70.1, 72.4)	4.1 (2.8, 5.5)	23.9 (23.3, 24.6)	23.2 (22.5, 23.8)	0.8 (0.1, 1.5)	24.2 (23.5, 25.0)	1.1 (0.2, 2.0)
	6.0-6.9	66.4 (65.7, 67.2)	65.0 (64.4, 65.6)	Reference	67.1 (66.4, 67.8)	Reference	23.0 (22.6, 23.4)	22.4 (22.0, 22.8)	Reference	23.1 (22.7, 23.6)	Reference
	7.0-7.9	70.3 (69.5, 71.2)	70.3 (69.5, 71.0)	5.3 (4.4, 6.2)	69.8 (69.0, 70.5)	2.7 (1.7, 3.7)	25.0 (24.5, 25.6)	25.0 (24.5, 25.5)	2.6 (2.0, 3.2)	24.9 (24.4, 25.4)	1.8 (1.1, 2.5)
	8.0-8.9	75.9 (74.7, 77.2)	77.7 (76.6, 78.8)	12.7 (11.4, 14.0)	75.9 (74.7, 77.0)	8.8 (7.4, 10.1)	27.9 (27.1, 28.6)	28.5 (27.8, 29.3)	6.1 (5.2, 7.0)	27.9 (27.1, 28.6)	4.8 (3.8, 5.7)
	≥ 9.0	82.1 (80.7, 83.6)	87.4 (86.0, 88.8)	22.4 (20.9, 23.9)	84.9 (83.4, 86.4)	17.8 (16.1, 19.4)	30.5 (29.6, 31.5)	32.7 (31.7, 33.7)	10.3 (9.2, 11.4)	31.6 (30.5, 32.6)	8.5 (7.3, 9.6)

* Model A = Adjusted for age, sex, race, ethnicity, body mass index, non-HDL cholesterol, systolic blood pressure, and smoking status
† Model B = Model A + diabetes medications and blood pressure medications
‡ deaths/1000-person-year

Table S8. Hazard ratios for all-cause and cardiovascular mortality across levels of HbA1c over short- and long-term follow-up times, stratified by age.

		All-cause Mortality				CVD Mortality			
		2-5 year mortality		>5 year mortality		2-5 year mortality		>5 year mortality	
		Hazard Ratio (95% CI	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
< 65 years	**HbA1c**								
	< 6.0	1.21 (1.14, 1.30)	<0.0001	1.09 (1.04, 1.14)	0.0002	1.06 (0.94, 1.20)	0.3	0.98 (0.90, 1.06)	0.6
	6.0-6.9	Reference	-	Reference	-	Reference	-	Reference	-
	7.0-7.9	1.03 (0.97, 1.09)	0.4	1.05 (1.01 ,1.09)	0.02	1.16 (1.05, 1.28)	0.003	1.13 (1.06, 1.21)	0.0003
	8.0-8.9	1.11 (1.05, 1.18)	0.0007	1.17 (1.12, 1.22)	<0.0001	1.31 (1.18, 1.46)	<0.0001	1.23 (1.15, 1.32)	<0.0001
	≥ 9.0	1.37 (1.30, 1.45)	<0.0001	1.44 (1.39, 1.49)	<0.0001	1.68 (1.53, 1.84)	<0.0001	1.58 (1.49, 1.69)	<0.0001
≥ 65 years	**HbA1c**								
	< 6.0	1.12 (1.09, 1.16)	<0.0001	1.06 (1.03, 1.09)	<0.0001	1.09 (1.03, 1.15)	0.003	1.01 (0.96, 1.05)	0.8
	6.0-6.9	Reference	-	Reference	-	Reference	-	Reference	-
	7.0-7.9	1.06 (1.03, 1.09)	<0.0001	1.04 (1.02, 1.06)	<0.0001	1.10 (1.05, 1.15)	<0.0001	1.05 (1.01, 1.09)	0.007
	8.0-8.9	1.18 (1.14, 1.22)	<0.0001	1.14 (1.11, 1.17)	<0.0001	1.29 (1.22, 1.36)	<0.0001	1.12 (1.07, 1.17)	<0.0001
	≥ 9.0	1.42 (1.37, 1.47)	<0.0001	1.30 (1.26, 1.33)	<0.0001	1.45 (1.36, 1.53)	<0.0001	1.27 (1.21, 1.33)	<0.0001