Published in final edited form as:
*Nutr Metab Cardiovasc Dis*. 2010 January ; 20(1): 15–21. doi:10.1016/j.numecd.2009.02.007.

# Glycosylated hemoglobin and the risk of death and cardiovascular mortality in the elderly

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## Abstract

**Background and aims—**Glycosylated hemoglobin ($HbA_{1c}$) has been associated with incident cardiovascular disease (CVD), but the findings are inconsistent. We tested the hypothesis that $HbA_{1c}$ may be associated with an increased risk of death and cardiovascular mortality in older adults.

**Methods and results—**We evaluated the association between $HbA_{1c}$ with all-cause and cardiovascular mortality in 810 participants without a history of diabetes in a sub-study of the Cardiovascular Health Study (CHS), a community cohort study of individuals ≥65 years of age. Glycosylated hemoglobin was measured at baseline and all-cause and cardiovascular mortality was assessed during the follow-up period. The relation between baseline $HbA_{1c}$ and death was evaluated with multivariate Cox proportional hazards regression models. After a median follow-up of 14.2 years, 416 deaths were observed. The crude incidence rates of all-cause mortality across $HbA_{1c}$ groups were: 4.4% per year, 4.3% per year and 4.6% per year for tertile 1 (≤5.6%), tertile 2 (5.61–6.20%) and tertile 3 (≥6.21%), respectively. In unadjusted and fully adjusted analyses, baseline $HbA_{1c}$ was not associated with all-cause mortality and cardiovascular mortality (hazard ratio: 1.16 [95% confidence interval 0.91–1.47] and hazard ratio: 1.31 [95% confidence interval 0.90–1.93], respectively for the highest $HbA_{1c}$ tertile compared with the lowest).

**Conclusion—**These results suggest that $HbA_{1c}$ does not significantly predict all-cause and cardiovascular mortality in non-diabetic community-dwelling older adults.



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### Keywords

Glycosylated hemoglobin; Hemoglobin A1c; Cardiovascular disease; Mortality; Elderly

## Introduction

Elevated non-diabetic glucose levels in the general population have been found to be associated with cardiovascular disease (CVD) [1]. This relationship is continuous and does not appear to have an obvious threshold [1,2]. However, the role of glycemia in causing CVD has been limited by several factors, above all by its measurement over time [3]. Glucose reacts non-enzymatically in the blood with amino groups of many plasma and tissue proteins to form glycated proteins, which represent an integrated measure of blood glucose over days to weeks [3,4].

Glycosylated hemoglobin ($HbA_{1c}$), a measure of total non-enzymatically glycated proteins in the blood, is an indicator of average blood glucose concentrations over the preceding 3 months and is a well established biomarker of long term glucose homeostasis in diabetic subjects [5, 6]. Furthermore, $HbA_{1c}$ is useful to characterize dysglycemia in population-based studies because it is simpler to perform than an oral glucose tolerance test [2,7–9]. In non-diabetics, elevated $HbA_{1c}$ has been shown to be associated with increased risk of diabetes [10], and incident cardiovascular events [11–13]. However, existing literature is scarce and inconclusive regarding whether $HbA_{1c}$ in non-diabetic individuals is associated with an increased risk of death and cardiovascular mortality, especially in the elderly. One population study suggested an association between higher $HbA_{1c}$ and all-cause mortality and cardiovascular events [2] while in another study, baseline $HbA_{1c}$ predicted cardiovascular mortality in women but not in men [14].

Using data from the Cardiovascular Health Study (CHS), the present analysis was undertaken to test the hypothesis that $HbA_{1c}$ is an independent predictor of all-cause and cardiovascular mortality in a community-based cohort of older non-diabetic adults among whom data pertaining to this issue is limited.

## Methods

### Study population and sample

The Cardiovascular Health Study is a prospective, community-based cohort study of cardiovascular disease among 5888 adults aged 65 years and older recruited from four different communities in the US (Forsyth County, NC; Sacramento County, CA; Allegheny County, PA; and Washington County, MD)[15]. The original CHS cohort of 5201 participants was recruited from 1989 to 1990, and a second cohort of 687 African American men and women was recruited during 1992 and 1993. The purpose of the study was to evaluate risk factors for the development or progression of CVD in the elderly. Details of the study design, sampling, and recruitment have been previously published [16,17].

One site (Forsyth County) measured $HbA_{1c}$ at baseline ($n$ = 1094). Of these, we excluded 284 for the following reasons: 168 patients had a diagnosis of diabetes defined as the use of insulin or oral hypoglycemic agents or a fasting glucose level $\geq$ 126 mg/dL; 86 subjects had a diagnosis of diabetes defined as a 2-h glucose after glucose load >200 mg/dL; and 30 had missing data on the 2-h glucose after oral glucose load. Thus, the final sample used in this study was 810 participants.

### Predictors and outcomes

The primary predictor was $HbA_{1c}$ level. Frozen whole blood samples stored at −70 °C from the baseline visit were available for measurement of $HbA_{1c}$. Glycosylated hemoglobin was measured using an affinity column method (normal values ranged 2.9–5.1%) using a standard kit. The method was standardized against high pressure liquid chromatography procedures. These determinations were conducted at the Wake Forest University Clinical Pathology Department with monitoring of internal and external quality assurance.

The outcomes of interest were all-cause death, CVD mortality and non-fatal cardiovascular events including myocardial infarction, congestive heart failure or stroke. Participants with a history of CVD were excluded from the analyses of incident non-fatal cardiovascular events. All events were adjudicated by a CHS outcome-assessment committee. The methods of ascertaining and adjudicating events have been described previously [17,18]. Mortality data were obtained through review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care utilization database for hospitalizations and from household contacts; 100% complete follow-up for ascertainment of mortality status was achieved. Cardiovascular mortality was defined as death caused by coronary heart disease, heart failure, peripheral vascular disease, or cerebrovascular disease.

### Other measurements

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Waist circumference was measured in a standing position at the level of the umbilicus. Participants were classified as current smokers if they reported smoking within the past 30 days or identified themselves as current smokers. Former and never smokers were classified on the basis of self-report of their smoking status and reporting no cigarette smoking in the past 30 days. Hypertension was diagnosed if the participant was taking antihypertensive medications, or the average of three blood pressure readings was a systolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg. Prescription data were ascertained from a review of prescription bottle labels by interviewers [19].

Laboratory tests were performed after an 8–12-h fast. Detailed methods for blood drawing, quality assurance, and assay performance were described previously [16]. Serum chemistry tests, including creatinine, were performed using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY). Serum creatinine was calibrated indirectly to the Cleveland Clinic "standard" assay used in the development of the Modified Diet Renal Disease (MDRD) Study glomerular filtration rate (GFR) prediction equation [20]. In this analysis, GFR was estimated from the abbreviated MDRD Study formula and chronic kidney disease (CKD) was defined as an estimated GFR level less than 60 mL/min per 1.73 $m^2$ [21]. The Olympus Demand System (Olympus, Lake Success, NY) was used for total and high-density lipoprotein cholesterol (HDL-C) and triglycerides, low-density lipoprotein cholesterol (LDL-C) was calculated by using the Friedewald formula, except when triglycerides exceeded 400 mg/dL (four participants) [22]. C-reactive protein (CRP) was measured by using an enzyme-linked immunosorbent assay [23]. Laboratory values used in these analyses were from the baseline visit.

### Analytical methods

Glycosylated hemoglobin was characterized by tertiles. Differences across groups were evaluated using Kruskal–Wallis test for continuous variables and chi-square for categorical variables, and *p*-values were calculated for linear trend across tertiles. Crude incidence rates for all-cause mortality, cardiovascular events and mortality were calculated by dividing the number of incident events by the cumulative time at risk for each $HbA_{1c}$ tertile. Time was calculated as the time to the first incident event for each type of event.

We used unadjusted and adjusted Cox proportional hazards regression models to examine the association between baseline $HbA_{1c}$ with time to all-cause mortality, cardiovascular events and death. Analyses of cardiovascular events were restricted to participants without any clinical cardiovascular disease at the baseline visit (for example participants with prevalent myocardial infarction at the baseline exam were excluded from the analysis for myocardial infarction as an outcome). Candidate covariates considered for insertion in the adjusted models included: age, gender, race, BMI, smoking status, history of hypertension, systolic and diastolic blood pressure, serum glucose, total cholesterol, HDL-C, LDL-C, CKD (i.e., estimated GFR < 60 mL/min per 1.73 $m^2$) and usage of hypertension medications.

In these multivariate models, candidate variables for adjustment were retained in the final models if they changed the beta coefficient of the primary predictor of interest ($HbA_{1c}$) by at least 5%. All models were adjusted for the following final covariates: age, gender, race, smoking status, BMI, hypertension, CKD and LDL-C. The proportional hazards assumption was not violated. Linearity between continuously measured $HbA_{1c}$ and all-cause mortality was explored by fitting restricted cubic splines. Statistical analyses were performed using SPSS 15.0.1.1 software for Windows (SPSS Inc, Chicago, IL). A *p*-value less than 0.05 was considered statistically significant. Confidence intervals (CIs) are expressed as 95% CIs.

## Results

### Population baseline characteristics

The study population had an average age of 72 ± 5 years, BMI of 25.3 ± 4.3 kg/$m^2$, and median follow-up of 14.2 years. Participants were predominantly white (94%), 41% were male, and 52% had a history of smoking. The median (IQR) of levels of $HbA_{1c}$ at study initiation were 5.9% [5.4, 6.4]. Participants who were African–Americans; and who had a larger waist circumference, higher BMI, impaired fasting glucose (110–125 mg/dL) and impaired glucose tolerance (141–199mg/dL) during oral glucose tolerance test were all more likely to have higher $HbA_{1c}$ levels. C-reactive protein levels, fasting serum glucose, and 2-h glucose after oral glucose load were higher in participants with higher $HbA_{1C}$. There were no significant differences in prevalence of hypertension, dyslipidemia, metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III and usage of antihypertensive medications including angiotensin converting enzyme inhibitors, β-blocker, calcium antagonist and thiazides across $HbA_{1c}$ tertiles (Table 1).

### Rates for all-cause mortality, cardiovascular events and mortality by category of glycosylated hemoglobin concentrations

There were a total of 416 deaths of which 139 were cardiovascular deaths. Tables 2 and 3 provide event rates according to $HbA_{1c}$ tertiles. During a median follow-up time of 14.2 years, the crude incidence rates for all-cause and cardiovascular mortality were: 4.4% per year and 1.5% per year, respectively (see Table 2). Subjects having high $HbA_{1c}$ (≥6.21%) at baseline had similar incidence rates for all-cause and cardiovascular mortality as those participants with a low $HbA_{1c}$ (<5.6%). Similarly, the incidence rates for all the different types of cardiovascular events did not vary significantly across $HbA_{1c}$ tertiles (see Table 3).

### Association between glycosylated hemoglobin concentrations and all-cause mortality, cardiovascular events and mortality

Table 4 shows the results of the Cox proportional hazard models for risk of all-cause mortality, cardiovascular events and death by tertile of $HbA_{1c}$. In unadjusted analyses, higher $HbA_{1c}$ concentration was not associated with an increased risk in all-cause mortality or cardiovascular event or death. In analyses adjusting for all covariates (including, age, gender, race, BMI, smoking history, hypertension, CKD and LDL-C) none of the tertiles was significantly

associated with an increased risk of death or cardiovascular events. Similarly, when $HbA_{1c}$ was modeled as a linear variable, there was no significant increase in risk for the pre-specified outcomes; these associations were adjusted HR: 1.01 (95% CI 0.92—1.10) and adjusted HR: 1.06 (95% CI 0.93–1.22), per 1% $HbA_{1c}$ difference respectively for all-cause and cardiovascular mortality risk. Fitting a cubic spline to $HbA_{1c}$, revealed no association with an increase risk of death and cardiovascular mortality (not shown). In addition, testing for a gender by $HbA_{1c}$ interaction for all-cause death, fatal and non-fatal cardiovascular events revealed none ($p > 0.15$ for all). Other covariates independently associated with all-cause and cardiovascular mortality were older age, smoking, hypertension and CKD.

Finally, the model was repeated with 2-h plasma glucose concentration instead of $HbA_{1c}$ as a dependent variable. After multivariate adjustment for age, gender, race, BMI, smoking history, hypertension, CKD and LDL-C, the 2-h glucose concentration was independently associated with cardiovascular mortality (HR: 1.19, 95% CI 1.00–1.42 per standard deviation increase). No significant association was observed between the 2-h glucose concentration and all-cause mortality (HR: 1.09, 95% CI 0.99–1.21) or non-fatal cardiovascular events including myocardial infarction (HR: 1.18, 95% CI 0.95–1.46), congestive heart failure (HR: 1.07, 95% CI 0.91–1.26) and stroke (HR: 0.90, 95% CI 0.73–1.10) per standard deviation increase.

Further analyses were performed including all 86 participants with diabetes during an oral glucose tolerance test ($n = 896$). Across increasing $HbA_{1c}$ tertiles 11 (13%), 24 (28%) and 51 (59%) had an abnormal 2-h oral glucose after a glucose load. In unadjusted and fully adjusted analyses, baseline $HbA_{1c}$ was significantly associated with all-cause mortality and cardiovascular mortality (adjusted HR: 1.32 [95% CI 1.00–1.75] and adjusted HR: 1.59 [95% CI 1.02–2.48], respectively for the highest $HbA_{1c}$ tertile compared with the lowest).

## Discussion

In this cohort of older, community-dwelling men and women, $HbA_{1c}$ does not significantly predict all-cause and cardiovascular mortality, suggesting that dysglycemia itself in non-diabetic elderly subjects might not be as important as other cardiovascular risk factors for development of vascular events. Other studies investigating the association between $HbA_{1c}$ and cardiovascular events have scrutinized non-diabetic participants [11–13] but few focused on $HbA_{1c}$ and its relationship with all-cause and cardiovascular mortality in older participants [2,14].

In contrast to our null findings, others have found an association between $HbA_{1c}$ and all-cause mortality. Our findings contradict those from the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) [2], a large observational study of 4662 men and 5570 women, where a 1% increment in $HbA_{1c}$ ($HbA_{1c} > 7\%$ excluded) was associated with a 26% increase in all-cause mortality (relative risk: 1.26 [95% CI 1.04–1.52]; $p = 0.02$) in men and women without cardiovascular disease or diabetes at baseline. In EPIC-Norfolk, the group of non-diabetic participants in the highest $HbA_{1c}$ group had a greater BMI than subjects with similar $HbA_{1c}$ in the CHS cohort ($28.6 \pm 3.4$ vs $26.1 \pm 4.5$). In addition, subjects with an abnormal oral glucose tolerance test were not excluded from the analysis. In another longitudinal study of 1239 older non-diabetic adults [14], baseline $HbA_{1c}$ was associated with cardiovascular mortality in women but not in men. The age-adjusted relative hazard for those women in the highest quintile of $HbA_{1c}$ ($\geq 6.7\%$) compared with women with lower levels was 2.37 for fatal CVD (95% CI 1.30–4.31, $p = 0.005$). Hence, this study suggested a relationship only in a selected population (i.e., elderly females).

With regard to incident cardiovascular disease, the Hoorn Study [24], Women's Health Study cohort [12] and the EPIC-Norfolk [2] reported significant associations between $HbA_{1c}$ and

incident cardiovascular disease in unadjusted analyses, though in all of these studies the relations were not independent after adjustment for traditional cardiovascular risk factors. Similarly, Pradhan and colleagues [10] found no significant association between $HbA_{1c}$ and incident cardiovascular events in a prospective cohort study of 26,563 US female health professionals aged 45 years or more without diagnosed diabetes or vascular disease after a median follow-up of 10.1 years. In contrast to these studies, the Framingham Offspring cohort [25] observed an increase in cardiovascular risk for a 1-percentage point increase in $HbA_{1c}$ level (2.36 [95% CI 1.43–3.90]) in persons without diabetes but with an $HbA_{1c}$ level greater than 4.6%. Thus, the association of $HbA_{1c}$ with an increase risk of death and cardiovascular disease in non-diabetic subjects remains uncertain.

Overall, it is conceivable that the apparent discrepant results among the published studies [2, 10–14,24,25] assessing the relationship between $HbA_{1c}$ and outcomes are likely due to differences in the study populations, study durations, and more importantly the predictive value of $HbA_{1c}$ level observed in some of these studies appears to be largely attributed to its association with other traditional cardiac risk factors. An alternative explanation is that that $HbA_{1c}$ is the wrong marker of dysglycemia with regards to prediction of CVD. Some studies have suggested that it is the 2-h glucose concentration after an oral glucose load that is a more important predictor of CVD events. In fact, in this cohort the 2-h glucose concentration was independently associated with cardiovascular mortality. Furthermore, the association between $HbA_{1c}$ and all-cause and cardiovascular mortality was significant after including those participants with diabetes during an oral glucose tolerance test. Hence, the relationship of $HbA_{1c}$ on allcause and cardiovascular mortality reported in previous population-based studies may be essentially driven by participants with glucose intolerance as shown in this study.

Our study has several limitations. First, because our cohort comprised predominantly elderly Caucasian subjects, our results may not be generalizable to other populations who may otherwise be at risk for dysglycemia. Second, because of our study design, values for $HbA_{1c}$ were measured on a single blood specimen. Therefore we cannot evaluate the effects of changes in this parameter over time. Third, the study population is limited by a relatively smaller sample size in comparison to other published reports, hence it is possible that this lack of significance reflects inadequate statistical power, rather than a true negative result. However, assuming a similar accrual and follow-up period to this study, a total of 694 participants will need to be in the study to detect the observed associations as significant. With a type I error rate of 5% and a power of 80% the minimum detectable hazard ratio is 1.3. The hazard of 1.3 has been reported by other published reports and in this analysis for the outcome of cardiovascular mortality. Finally, use of frozen samples may have theoretically affected our results, however, the exposure misclassification on this basis is likely to be small as the distribution, mean, and median values of $HbA_{1c}$ in our study are comparable to those of other referent populations with normal glucose tolerance [8–10].

Notwithstanding these limitations, the strengths of this study are the use of uniform methods to collect data on $HbA_{1c}$, and the extensive and complete data on other factors associated with CVD, which allowed us to give an unbiased estimate for the relationship between $HbA_{1c}$ and cardiovascular events and mortality. Furthermore, given that 2-h glucose after oral glucose loads were available in this cohort we were able to exclude lesser degrees of glucose intolerance making our findings applicable to those subjects with normoglycemia assessed by stringent metabolic criteria.

In conclusion, these results suggest that $HbA_{1c}$ does not significantly predict all-cause and cardiovascular mortality in a cohort of non-diabetic older subjects. Further studies may be important to determine whether dysglycemia is a modifiable risk factor for adverse cardiac outcomes in the general population.

## Acknowledgments

Drs Sarnak, Fried, Shlipak, Siscovick, and Newman are supported by R01 AG027002. The Cardiovascular Health Study (CHS) is supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-75150, N01-HC-45133, N01-HC-35129, and N01-HC-15103 from the National Heart, Lung, and Blood Institute (NHLBI). A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

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## Table 1

Characteristics of participants by tertiles of glycosylated hemoglobin.

| | Glycosylated hemoglobin (%) | | | |
|---|---|---|---|---|
| | **≤5.6 [5.00, 5.40] (*n* = 295)** | **5.61–6.20 [5.80, 6.10] (*n* = 253)** | **≥6.21 [6.50, 7.10] (*n* = 262)** | ***p*-value for trend** |
| *Characteristic* | | | | |
| Age (years) | 72 (5) | 72 (5) | 72 (5) | 0.939 |
| Gender (female, %) | 167 (57) | 151 (60) | 162 (62) | 0.209 |
| Race (black, %) | 12 (4) | 15 (6) | 24 (9) | 0.014 |
| Ever smoked (%) | 155 (53) | 133 (53) | 136 (52) | 0.885 |
| Hypertension (%) | 150 (51) | 117 (46) | 143 (55) | 0.410 |
| Chronic kidney disease (%) | 62 (21) | 54 (21) | 58 (22) | 0.750 |
| Metabolic syndrome (%) | 100 (34) | 81 (32) | 103 (39) | 0.205 |
| *Measurements* | | | | |
| Waist circumference (cm) | 90 (13) | 90 (12) | 92 (12) | 0.027 |
| Body mass index (kg/m$^2$) | 24.8 (4.5) | 25.1 (3.7) | 26.1 (4.5) | <0.001 |
| Glucose (mg/dL) | 96 (9) [90, 103] | 97 (8) [92, 102] | 100 (9) [94, 106] | <0.001 |
| Impaired fasting glucose (mg/dL) (%) | 104 (35) | 88 (35) | 135 (52) | <0.001 |
| 2-h glucose (mg/dL) | 123 (30) [99, 142] | 122 (32) [100, 145] | 132 (35) [104, 158] | <0.001 |
| Impaired glucose tolerance by oral glucose tolerance test (%) | 69 (23) | 73 (29) | 103 (39) | <0.001 |
| Total cholesterol (mg/dL) | 204 (35) | 207 (35) | 209 (39) | 0.143 |
| LDL-C (mg/dL) | 124 (32) | 127 (32) | 129 (34) | 0.060 |
| HDL-C (mg/dL) | 55 (16) | 55 (16) | 53 (15) | 0.231 |
| Triglycerides (mg/dL) | 131 (60) | 130 (65) | 134 (58) | 0.605 |
| C-reactive protein (mg/L)* | 2.21 [1.10, 3.68] | 2.11 [1.09, 4.07] | 2.51 [1.39, 4.77] | 0.007 |
| *Medication use* | | | | |
| Antihypertensive meds (%) | 115 (39) | 90 (36) | 106 (41) | 0.749 |
| ACE-I (%) | 17 (6) | 6 (2) | 14 (5) | 0.762 |
| β-Blockers (%) | 35 (12) | 26 (10) | 37 (14) | 0.436 |
| Calcium-channel blockers (%) | 27 (9) | 24(10) | 22 (8) | 0.764 |
| Diuretics (%) | 61 (21) | 58 (23) | 67 (26) | 0.171 |

Data are presented as mean (SD) or *N* (%) or *median [interquartile range]. ACEI, angiotensin converting enzyme inhibitors; HDL-C, highdensity lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Table 2**

All-cause mortality and cardiovascular mortality incidence rates.

| HbA1c tertiles (%) | *N* | All-cause mortality | | | CVD mortality | | |
|---|---|---|---|---|---|---|---|
| | | Person years at risk | Number of deaths observed | Rate (% per year) | Person years at risk | Number of deaths observed | Rate (% per year) |
| Total | 810 | 9,450 | 416 | 4.4 | 9,450 | 139 | 1.5 |
| ≤5.60 | 295 | 3502 | 153 | 4.4 | 3502 | 55 | 1.6 |
| 5.61–6.20 | 253 | 3003 | 128 | 4.3 | 3003 | 29 | 1.0 |
| ≥6.21 | 262 | 2945 | 135 | 4.6 | 2945 | 55 | 1.9 |

$HbA_{1C}$, glycosylated hemoglobin; CVD, cardiovascular disease.

**Table 3**

Cardiovascular events incidence rates.

| $HbA_{1c}$ tertiles | MI | | | | CHF | | | | Stroke | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (%) | *N* | Person year at risk | Number of events | Rate (% per year) | *N* | Person years at risk | Number of events | Rate (% per year) | *N* | Person years at risk | Number of events | Rate (% per year) |
| Total | 760 | 8,586 | 90 | 1.0 | 789 | 8,756 | 155 | 1.8 | 786 | 8,891 | 111 | 1.2 |
| ≤5.60 | 276 | 3150 | 27 | 0.9 | 287 | 3262 | 51 | 1.6 | 280 | 3254 | 41 | 1.3 |
| 5.61–6.20 | 239 | 2743 | 30 | 1.1 | 248 | 2790 | 51 | 1.8 | 249 | 2856 | 33 | 1.2 |
| ≥6.21 | 245 | 2693 | 33 | 1.2 | 254 | 2704 | 53 | 2.0 | 257 | 2780 | 37 | 1.3 |

$HbA_{1C}$, glycosylated hemoglobin; MI, myocardial infarction; CHF, congestive heart failure.

## Table 4

Hazard rates for all-cause mortality, cardiovascular events and death by glycosylated hemoglobin tertiles.

| | Glycosylated hemoglobin (%) | | |
|---|---|---|---|
| | **≤5.6** | **5.61–6.20** | **≥6.21** |
| *All-cause mortality (n = 416)*[b] | | | |
| Unadjusted HR (95% CI) | 1.00 (ref) | 0.97 (0.76, 1.23) | 1.09 (0.86, 1.38) |
| Adjusted HR (95% CI)[a] | 1.00 (ref) | 0.97 (0.77, 1.24) | 1.16 (0.91, 1.47) |
| *CV mortality (n = 139)*[c] | | | |
| Unadjusted HR (95% CI) | 1.00(ref) | 0.63 (0.40, 0.98) | 1.22 (0.84, 1.78) |
| Adjusted HR (95% CI)[a] | 1.00(ref) | 0.66 (0.42, 1.04) | 1.31 (0.90, 1.93) |
| *Myocardial infarction (n = 90)* | | | |
| Unadjusted HR (95% CI) | 1.00 (ref) | 1.28 (0.76, 2.15) | 1.42 (0.85, 2.36) |
| Adjusted HR (95% CI)[a] | 1.00 (ref) | 1.36 (0.81, 2.30) | 1.55 (0.93, 2.61) |
| *Congestive heart failure (n = 155)* | | | |
| Unadjusted HR (95% CI) | 1.00 (ref) | 1.17 (0.79, 1.72) | 1.27 (0.87, 1.87) |
| Adjusted HR (95% CI)[a] | 1.00 (ref) | 1.15 (0.78, 1.71) | 1.29 (0.88 1.91) |
| *Stroke (111)* | | | |
| Unadjusted HR (95% CI) | 1.00 (ref) | 0.87 (0.54, 1.38) | 1.06 (0.68, 1.66) |
| Adjusted HR (95% CI)[a] | 1.00 (ref) | 0.87 (0.54, 1.39) | 1.08 (0.69, 1.70) |

[a] Adjusted for age, gender, race, smoking, body mass index, hypertension, chronic kidney disease and low-density lipoprotein cholesterol. Abbreviations: see Table 3.

[b] *p*-value for quadratic trend: 0.69.

[c] *p*-value for quadratic trend: 0.50.