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Hemoglobin A_{1c} Levels and Risk of Sudden Cardiac Death – a Nested Case-Control Study

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Abstract

Background—Sudden cardiac death (SCD) is often the first manifestation of cardiovascular disease (CVD) and preventive strategies within this broad population are lacking. Patients with diabetes represent a high risk subgroup, but few data exist regarding whether measures of glycemia mediate risk and/or add to SCD risk stratification.

Objective—Examine the association between hemoglobin A_{1c} (HbA_{1c}) and SCD.

Methods—We performed a case-control analysis among individuals enrolled in 6 prospective cohort studies. HbA_{1c} levels were determined for 482 cases of SCD and 914 matched controls. Conditional logistic regression with fixed effects meta-analysis was used for analysis.

Results—In multivariable models, HbA_{1c} levels were linearly associated with SCD risk over a follow-up of 11.3 years ($P < 0.001$). Each 1% increment in HbA_{1c} was associated with a hazard ratio (HR) of 1.32 (95% CI 1.16–1.50). The magnitude of the association was greater in subjects without versus with known CVD [HR per 1% increment 1.64 (95% CI 1.31–2.06) versus 1.15 (95% CI 0.99–1.33); P interaction = 0.009]. In models simultaneously controlling for diabetes status and HbA_{1c}, the association between HbA_{1c} and SCD remained significant (HR 1.29; 95% CI 1.07–1.55, $P = 0.01$); whereas the association between diabetes and SCD was attenuated (RR 1.21, 95% CI 0.64–2.27, $P = 0.56$).

Conclusions—In these prospective cohorts, HbA_{1c} levels associated with SCD risk, particularly among those without known CVD, even after controlling for diabetes status. These data support the hypothesis that hyperglycemia mediates SCD risk among patients with diabetes.

Keywords

Sudden Cardiac Death; Hemoglobin A_{1c}; Diabetes; Risk Factor; Epidemiology

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Conflict of Interest Disclosures: None

Introduction

Sudden cardiac death (SCD) remains an important cause of death in the developed world, accounting for up to 450,000 deaths per year in the United States.^{1, 2} While cardiovascular disease (CVD) and specifically coronary heart disease (CHD) confer substantially elevated SCD risk,³ the majority of patients who suffer SCD do not have known structural heart disease at the time of the event⁴ and preventive strategies are lacking within this broad population.

Diabetes mellitus (DM) and elevated fasting plasma glucose levels have been associated with SCD,^{5–9} and patients with DM are a recognized high-risk subgroup within the general population. Hemoglobin A_{1c} (HbA_{1c}) is a time integrated marker of glucose concentration, which is increasingly utilized in clinical practice due to the test's convenience and reliability.¹⁰ It has been found to be more predictive of CVD complications than single, time sensitive glucose levels in patients with and without DM.¹⁰ Only one prospective study performed among patients with DM and end stage renal disease has examined the association between HbA_{1c} levels and SCD. This study found that the association between HbA_{1c} and SCD was stronger than that for nonfatal myocardial infarction (MI).⁶ Whether this association between HbA_{1c} and SCD translates to broader lower-risk populations with or without clinically apparent DM or CVD is unknown. Furthermore, it is unclear whether HbA_{1c} provides incremental information regarding SCD risk above and beyond the known association between DM and SCD. To address these questions, we examined the relationship between HbA_{1c} and SCD in individuals with and without known CVD in 6 large-scale, prospective cohort studies using a nested case-control design.

Methods

Study Populations

The study design is a nested case-control investigation sampled from prospective cohorts. The cohorts include the Physicians' Health Study (PHS I and II), the Nurses' Health Study (NHS), the Health Professionals Follow-Up Study (HPFS), the Women's Health Study (WHS), and the Women's Antioxidant Cardiovascular Study (WACS). NHS and HPFS are observational cohort investigations; PHS I, PHS II, WHS, and WACS were initially randomized trials in which treatment has ended.

Among all cohorts, medical history, lifestyle choices, and cardiac risk factors are assessed annually or biennially by self-administered questionnaires. In this analysis, we used information from the questionnaire closest in date to the blood draw for each cohort. Further details of study cohorts and baseline blood sample collection are outlined in Supplemental Table 1. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

End-Point Confirmation

The end points included incident cases of SCD defined as sudden and/or arrhythmic cardiac death that occurred after return of the blood sample and before July 1, 2014. All cohorts used similar methods to document the timing and mechanism of cardiovascular deaths,

which have been described previously. 482 SCDs occurred among participants who donated blood samples.

A definite SCD was defined as a death or fatal cardiac arrest which occurred within 1 hour of symptom onset as documented by medical records or next-of-kin reports (n=300) or had an autopsy consistent with SCD (i.e. acute coronary thrombosis or severe coronary artery disease without myocardial necrosis; n=25). Unwitnessed deaths or deaths during sleep in which the participant was documented to be symptom free when last observed within the preceding 24 hours were considered probable SCDs (n=117) and were also included in the study endpoint of SCD.^{3, 11, 12}

Since the primary interest was to identify predictors of deaths due to fatal arrhythmia, deaths were also classified as arrhythmic or nonarrhythmic on the basis of the definition by Hinkle and Thaler.¹³ An arrhythmic death was defined as an abrupt spontaneous loss of pulse without evidence of preceding circulatory impairment (shock or congestive heart failure) or neurological dysfunction (change in mental status, loss of consciousness, or seizure). Deaths before which the pulse gradually disappeared and/or those preceded by circulatory or neurological impairment were considered nonarrhythmic deaths, and were excluded from the SCD endpoint even if the death occurred within 1 hour of symptom onset. Deaths that fulfilled the criteria for arrhythmic death but were preceded by >1 hour of symptoms (n=40) were included in the combined SCD endpoint. A sensitivity analysis excluding these deaths was also performed.

Selection of Controls

Using risk-set sampling,¹⁴ we randomly selected up to 2 controls for each case from the same cohort. Controls were matched on age (+/-3 years), ethnicity, smoking status (current, never, past), time/date of blood sampling, follow up time, and CVD (myocardial infarction, angina, coronary artery bypass graft surgery, or stroke) diagnosed either at the time of blood draw or during the follow up period.

Measurement of HbA1c

Testing for HbA_{1c} was performed through a Roche P Modulator system and was based on Tina-Quant turbidimetric inhibition immunoassay (Roche Diagnostics, Indianapolis, IN). This method is approved by the Food and Drug Administration, and HbA_{1c} measurements from long-term storage samples are highly correlated to measurements obtained before storage.¹⁵ Laboratory personnel were unaware of the samples case-control status. Within-run coefficients of variation percent were assessed by analyzing quality control samples repeatedly. The coefficient of variation percent ranged from 0.9% to 1.5%.

Statistical Analyses

Means or proportions for baseline cardiac risk factors were calculated for cases and controls. The significance of associations between cases and controls was tested with the generalized estimating equations for categorical variables and with repeated measures analysis with an unstructured covariance matrix using Proc Mixed in SAS (SAS Institute Inc, Cary, NC) for continuous variables to account for the dependency among the controls matched to each

case. We analyzed the association between HbA_{1c} and the risk of SCD using conditional logistic regression analysis in the 6 cohorts,¹⁴ and then conducted fixed-effect meta-analyses on the basis of the summary conditional logistic regression results for each cohort.¹⁶ PROC MIXED of SAS was used to pool effect estimates over study cohorts using inverse variance weights. Tests for heterogeneity of the associations across cohorts were conducted using the Q-statistic.¹⁷ Statistically significant heterogeneity was not found for any analysis (data not shown) and results were similar with random effects meta-analysis.

HbA_{1c} levels were analyzed as both continuous and categorical variables in separate conditional regression models. The relationship between continuous levels of HbA_{1c} and SCD was tested for a linear and/or non-linear trend by fitting a restricted cubic spline transformation¹⁸ using five knots. Subjects were also divided into categories based on HbA_{1c} level (<5.7%, 5.7–<6.5%, ≥6.5%). In secondary analyses, we also explored the relationship between continuous HbA_{1c} and SCD using interaction terms in the following subgroups: (1) known DM, (2) known DM or HbA_{1c} level ≥6.5% (diagnosed and undiagnosed DM), and (3) known CVD at the time of the blood draw.

For all analyses, models adjusting for increasing levels of CVD risk factors were performed. Age and smoking were not perfectly matched, so these variables were entered into conditional logistic regression models to avoid potential for residual confounding. The multivariable model further adjusted for history of hypertension, high cholesterol, family history of MI, body mass index (<25, 25–<30, ≥30), physical activity (moderate to vigorous aerobic activity at least once per week), alcohol intake (less than weekly, weekly, daily, ≥2 drinks per day), aspirin use (≥15 d/mo), and fasting status. In order to explore the independent contribution of HbA_{1c} to SCD risk beyond that associated with known DM and to estimate the degree to which HbA_{1c} might mediate the association between DM and SCD, DM status and HbA_{1c} level were simultaneously included in a third multivariable conditional regression model. Statistical analysis was performed with SAS statistical software, version 9.1.

Results

Over a median follow up of 11.3 years from blood draw, 482 cases of SCD (254 men and 228 women) occurred within the 6 cohorts, and 914 matched controls were selected for a total study population of 1396. The mean age of the cases and matched-controls in this pooled population was 63.8 years, and 144 (10.3%) had been diagnosed with DM. A total of 169 individuals (12.1 %) had HbA_{1c} levels ≥6.5% and 54 (32%) of these did not report a history of diagnosed DM. The proportion of individuals with HbA_{1c} levels ≥6.5% who had not been diagnosed with DM was low, but slightly higher in cases versus controls [25 (5.2%) versus 29 (3.1%); P=0.038].

HbA_{1c} levels and clinical characteristics recorded closest to the time of baseline blood draw are displayed by case and control status in the pooled population in Table 1 and by cohort in Supplemental Table 2. HbA_{1c} levels were normally distributed and were higher among cases than controls (P<0.001). Cases were more likely to have reported a history of DM, a history

of hypertension, have a higher body mass index, drink less alcohol, and exercise less than once a week (Table 1).

Association of HbA_{1c} and SCD

When examined as a continuous variable, the direction of the association between HbA_{1c} and SCD was consistent across all cohorts, although the magnitudes of the associations varied across studies (Table 2; P-value for heterogeneity = 0.23). The association was strongest in the PHS I population and weakest in the WACS population. When these RRs were combined in the meta-analysis, a 1% increment in HbA_{1c} was significantly associated with risk of SCD after adjusting for imperfectly matched variables, age and smoking status (RR 1.32; 95% CI 1.18–1.48; P<0.001; Table 2). After adjustment for other cardiovascular and lifestyle risk factors (Table 2), the association was not altered (RR 1.32; 95% CI 1.16–1.50; P<0.001). Results were not appreciably altered in a sensitivity analysis excluding arrhythmic deaths preceded by more than 1 hour of symptoms (Multivariable model RR 1.29; 95% CI 1.12–1.49; P<0.001). In multivariable restricted cubic spline models, the association between HbA_{1c} and risk of SCD was confirmed to be linear (P<0.001, Figure 1).

When pre-specified clinical cut-points consistent with no diabetes (<5.7%), pre-diabetes (5.7–<6.5%) and diabetes (≥6.5%) were examined (Table 3), individuals with a HbA_{1c} level ≥6.5% had a two-fold greater relative risk of SCD compared to those with HbA_{1c} levels <5.7% after multivariable adjustment. Results were similar when HbA_{1c} levels <6.5% were used as the referent category (multivariable RR 2.18; 95% CI 1.43–3.33; P<0.001). Despite the linear relationship between HbA_{1c} and SCD in continuous analyses (Figure 1), mildly elevated HbA_{1c} levels consistent with pre-diabetes (HbA_{1c} 5.7–<6.5%) were not associated with an elevated risk of SCD. This may, in part, be explained by the modest increase in median HbA_{1c} levels between the pre-diabetics (5.89%) and the non-diabetics (5.47%) in our populations.

The presence of clinically diagnosed DM at the time of blood draw was associated with a similar elevation in the risk of SCD (RR 2.10, 95% CI 1.35–3.28, P=0.001) as that observed for HbA_{1c} ≥6.5% after multivariable adjustment. When DM status and continuous HbA_{1c} levels were included in the same multivariable model, the relationship between DM and SCD was attenuated and no longer significant (RR 1.21, 95% CI 0.64–2.27, P=0.56). In comparison, the association between HbA_{1c} and SCD remained significant after controlling for DM status (RR 1.29 per 1% increase, 95% CI 1.07–1.55).

Subgroup Analyses (Table 4)

In pre-specified sub-group analyses, the relationship between HbA_{1c} and SCD differed significantly according to whether clinically detected CVD was present prior to SCD (P for interaction = 0.009). The association was stronger in participants without known CVD (RR 1.64, 95% CI 1.31–2.06, P<0.001) as compared to those with known CVD prior to SCD (RR 1.15, 95% CI 0.99–1.33, P=0.06). When the population was stratified by whether clinically detected DM was present at the time of the blood draw, the association between HbA_{1c} and SCD appeared somewhat stronger in individuals with diagnosed DM at the time of blood

draw, although the test for interaction was not significant. These results were similar when the DM subgroup was expanded to include those with undiagnosed DM (HbA_{1c} ≥ 6.5%).

Discussion

In this nested case-control study performed in six prospective cohorts of men and women, baseline blood levels of HbA_{1c} were associated with SCD risk over 11 years of follow up. Individuals with HbA_{1c} ≥ 6.5% had a significant two-fold increase in SCD risk compared to those with lower levels, even after controlling for multiple CVD risk factors and CVD itself. This association was strongest among individuals without known CVD, where SCD was the first recognized clinical manifestation of CVD. Further, the degree of hyperglycemia as measured by HbA_{1c} appeared to mediate much of the SCD risk associated with DM.

DM has been associated with 2 to 4 fold elevations in SCD^{5, 7, 9}. However, few studies have examined whether HbA_{1c} levels, which are commonly used in the diagnosis and management of DM, would further associate with SCD risk among patients with or without DM. To our knowledge, the German Diabetes and Dialysis Study (4D Study)⁶ is the only study to report an association between HbA_{1c} and SCD. Among the 1255 patients with type II DM on hemodialysis in this study, each 1% increase in HbA_{1c} was associated with a HR for SCD of 1.21 (95% CI, 1.06–1.38) over a 4 year follow-up. In our broader population comprised of individuals with and without DM, we found a higher magnitude elevation in SCD risk (RR 1.32 per 1% increment of HbA_{1c}; 95% CI 1.16–1.50) over a longer duration of follow-up. Due to the inclusion of patients without DM, we were able to demonstrate that the association between HbA_{1c} and SCD was largely independent of a clinical diagnosis of DM, whereas the association between DM and SCD became non-significant after controlling for HbA_{1c}. These data support the hypothesis that hyperglycemia may mediate the excess SCD risk associated with DM; and collectively, both studies raise the possibility that improved glycemic control among patients with DM may have a role in SCD prevention.

Recent clinical trial data lend further support to the hypothesis that improved glycemic control may lower SCD risk in patients with DM. Two recent trials testing separate classes of hypoglycemic agents, empagliflozin [a sodium-glucose cotransporter 2 (SGLT2) inhibitor] and liraglutide [a glucagon-like peptide 1 (GLP-1) analogue], demonstrated significant reductions in cardiovascular mortality among patients with DM and established CVD or multiple CVD risk factors.^{19,20} Of note, the reduction in cardiovascular mortality in both trials was not accompanied by significant reductions in nonfatal MI or stroke, which raises the possibility that part of the benefit may have been through direct reductions in SCD. Although SGLT2 inhibitors and GLP-1 analogues have off-target effects, these clinical trial data in combination with our data raise the possibility that glycemic control among patients with DM may impact SCD and other causes of cardiovascular mortality through “non-atherosclerotic” mechanisms.

There are several potential “non-atherosclerotic” mechanisms which underlie an association between HbA_{1c} and SCD. These include hyperglycemia induced autonomic neuropathy and resultant cardiac autonomic dysfunction^{21, 22} and direct effects upon myocardial structure and function.²³ The autonomic dysfunction associated with hyperglycemia is characterized

by sympathetic over-activity, cardiac denervation, increased resting heart rate, and reduced heart rate variability,²¹ all markers of elevated SCD risk. DM also leads to increased myocardial fibrosis which may directly increase arrhythmia propensity by providing a substrate for scar induced reentry²⁴ as well as through the development of ventricular dysfunction, referred to as “diabetic cardiomyopathy.”²³ Finally, elevations and fluctuations in glucose levels in patients with DM have been correlated with dispersion of repolarization.^{25,26}

Our subgroup analyses suggest the association between HbA_{1c} and SCD is stronger among those without clinically evident CVD. This data raise the possibility that benefits of HbA_{1c} lowering on SCD risk may be greater among individuals who have yet to develop clinical CVD, a population where SCD preventive strategies are lacking. Potential explanations for this finding include a higher prevalence of silent ischemic events and/or a pro-arrhythmic milieu associated with uncontrolled hyperglycemia, resulting in a higher likelihood that SCD will be the first clinical manifestation of underlying CHD. Alternatively, patients with a diagnosis of CVD may be prescribed medications which counterbalance the adverse effects hyperglycemia may have on SCD risk. Current guidelines do not recommend screening for silent CHD in unselected patients with DM.¹⁰ It remains unknown if high risk diabetics as identified by elevated HbA_{1c} may benefit from routine evaluation for “silent” CHD in addition to aggressive glycemic control.

Although HbA_{1c} levels are associated with SCD, the low absolute risk of SCD combined with the infrequency of markedly elevated HbA_{1c} levels in the general population without diagnosed DM precludes its utility as a widespread screening tool for SCD prevention. However, HbA_{1c} levels may have a role in SCD risk stratification and prevention in DM patients and other recognized high risk subsets of the population in whom such testing is clinically indicated and often available.²⁷ Our subgroup analyses directly support the concept that HbA_{1c} levels may be utilized to identify DM patients at higher risk for SCD. Based upon recent developments, SCD risk stratification in DM patients has potential clinical significance. First, as outlined above, intensive glycemic control may mitigate the excess SCD risk in these patients. Knowledge regarding elevated SCD risk may motivate patients and physicians to more aggressively pursue lifestyle and pharmacologic efforts to control hyperglycemia. Second, the presence of DM in post-MI patients confers a similar elevation in SCD risk as an LVEF<35%,⁹ prompting a primary prevention trial of the subcutaneous implantable defibrillator in this population (MADIT S-ICD). If our findings translate to post-MI patients with DM, HbA_{1c} levels may enhance our ability to identify DM patients most likely to derive benefit from defibrillator therapy.

This study has several strengths and limitations. Strengths include the large number of strictly defined SCDs, the well-characterized cohorts, and the prospective nested case-control design. There are also several limitations that warrant consideration. Despite a large number of rigorously confirmed SCDs, there is the possibility of misclassification in population-based studies of SCD. However, the one-hour definition has been documented to have a reasonable sensitivity and specificity for arrhythmic death,^{13, 28} and a sensitivity analysis excluding probable cases did not alter results. The stringent criteria and the low frequency of SCD in relatively healthy populations required us to combine cases within

cohorts in order to achieve adequate power for the analysis. However, our power may have been limited to detect interactions and modest associations, such as those among individuals with pre-diabetes. Power may have also been limited by the availability of only a baseline level of HbA_{1c} and our inability to account for changes in HbA_{1c} level over time. Furthermore, we did not have information regarding glucose lowering medications in patients with DM and could not analyze confounding or effect modification by these medications. There were slightly more undiagnosed DM subjects among the cases than controls, which could have led to a minor imbalance in the aggressiveness of CVD risk factor modification. However, the latter is unlikely to have had a significant contribution to the overall result, as the association between HbA_{1c} and SCD was equally strong in the patients with diagnosed DM.

There are also limitations to the data available within the cohorts for inclusion in multivariable models. Most notably, echocardiograms, ECGs, and information on heart failure were not routinely collected. Therefore, we cannot determine whether the association between HbA_{1c} and SCD is independent of or mediated by alterations in heart failure, LV function, or the ECG. Finally, the cohorts were composed of predominantly Caucasian health professionals, and the results may not apply to other racial, ethnic or socioeconomic strata.

In summary, in this large combined population of men and women, increasing levels of HbA_{1c} were associated with SCD risk independent of established CVD and its known risk factors, and this association was stronger among individuals without clinically evident CVD. The association between HbA_{1c} and SCD was also independent of known DM status, and HbA_{1c} appeared to mediate the SCD risk among patients with DM. Therefore, efforts to improve glycemic control among patients with DM may favorably impact SCD rates, particularly among those without evident CVD. On a population level, lifestyle interventions that reduce hyperglycemia and DM would also be expected to beneficially impact SCD. Further research is required to determine if high risk populations with elevated levels of HbA_{1c} would benefit from additional therapies for SCD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Multivariate relative risk of SCD as related to Hemoglobin A_{1c}
Multivariate-adjusted linear model of the relationship between HbA_{1c} and relative risk of SCD. Dashed lines show 95% confidence interval

Table 1

Pooled Prevalence of Baseline Characteristics at the Time of the Blood Draw.

	Case (n=482)	Control (n=914)	P value
Age, mean $\pm$ SD (y)	63.8 $\pm$ 8.8	63.8 $\pm$ 8.9	Matching Factor
Female, n (%)	228 (47.3)	413 (45.2)	Matching Factor
White, n (%)	468 (97.1)	894 (97.8)	Matching Factor
Current Smoker, n (%)	78 (16.2)	137 (15.0)	Matching Factor
History of Prior CVD [†] , n (%)	195 (40.5)	354 (38.7)	Matching Factor
Family History of MI [‡] <60 y of age, n (%)	90 (18.7)	151 (16.5)	0.33
Hypertension [#] , n (%)	281 (58.3)	384 (42.0)	<0.001
High Cholesterol [¶] , n (%)	219 (45.7)	403 (44.1)	0.51
Body mass index, mean $\pm$ SD, kg/m ²	26.9 $\pm$ 4.9	26.0 $\pm$ 4.4	<0.001
Diabetes, n (%)	72 (15.0)	72 (7.9)	<0.001
Hemoglobin A _{1c} , median [IQR [§]], %	5.8 [5.5–6.2]	5.7 [5.5–6.0]	<0.001
Aspirin Use, n (%)	191 (39.7)	360 (39.8)	0.98
Alcohol Intake, median [IQR], gm/d	1.8 [0–11.2]	2.8 [0–13.7]	0.05
Weekly Exercise, n (%)	261 (54.6)	572 (62.9)	0.002
Fasting, n (%)	265 (55.0)	499 (54.6)	0.90

[†]CVD=cardiovascular disease (angina, myocardial infarction, coronary artery bypass surgery, or stroke)[‡]MI= myocardial infarction[§]IQR=interquartile range[#]Reported diagnosis of hypertension, systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or taking antihypertensive medication.[¶]Reported diagnosis of high cholesterol, cholesterol level $\geq$ 240 mg/dl, or taking cholesterol lowering medications.

Table 2Cohort Specific and Meta-Analytic Association of Hemoglobin A_{1c} and SCD.

Cohort	Case/Control	n	Age- and smoking- adjusted model RR per 1% increase in HbA _{1c} (95% CI)	P value	Multivariable Model RR per 1% increase in HbA _{1c} (95% CI)	P value
HPFS	Case	123				
HPFS	Control	245	1.21 (0.98–1.50)	0.08	1.27 (0.99–1.63)	0.06
PHS I	Case	91				
PHS I	Control	180	2.87 (1.40–5.89)	0.004	3.02 (1.31–6.98)	0.01
PHS II	Case	40				
PHS II	Control	76	1.35 (0.89–2.05)	0.16	1.65 (0.96–2.82)	0.07
NHS	Case	132				
NHS	Control	227	1.36 (1.10–1.68)	0.005	1.31 (1.04–1.65)	0.02
WACS	Case	46				
WACS	Control	89	1.21 (0.97–1.51)	0.09	1.14 (0.87–1.48)	0.34
WHS	Case	50				
WHS	Control	97	1.94 (1.14–3.31)	0.02	1.99 (0.96–4.14)	0.07
Meta-analysis	Case	482	1.32 (1.18–1.48)	<0.001	1.32 (1.16–1.50)	<0.001
Meta-analysis	Control	914				

Table 3Association of SCD with Hemoglobin A_{1c} according to Clinical Categories

	Category of HbA _{1c}			P-value trend
	<5.7%	5.7–<6.5%	6.5%	
HbA _{1c} , median, %	5.47	5.89	8.07	-
Cases/Controls, n	197/431	198/401	87/82	-
Age and Smoking Adjusted Model, RR (95% CI)	1	1.11 (0.86–1.43)	2.29 (1.56–3.37)	<0.001
Multivariable Model, RR (95% CI)	1	1.02 (0.76–1.37)	2.08 (1.31–3.31)	<0.001

Table 4

Subgroup Analysis of the Association of Hemoglobin A_{1c} and SCD.

	Cases, n	Controls, n	Multivariable Model,RR (95% CI)	P subgroup	P interaction
Diabetes					
Yes	72	72	1.31 (1.06–1.61)	0.01	0.59
No	409	842	1.19 (0.92–1.54)	0.18	-
Diabetes or HbA_{1c} 6.5%					
Yes	97	101	1.27 (1.05–1.53)	0.01	0.63
No	384	813	1.13 (0.74–1.73)	0.56	-
Cardiovascular Disease					
Yes	195	354	1.15 (0.99–1.33)	0.06	0.009
No	287	560	1.64 (1.31–2.06)	<0.001	-