HbA_{1c} and Coronary Heart Disease Risk Among Diabetic Patients

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OBJECTIVE

Clinical trials to date have not provided definitive evidence regarding the effects of glucose lowering with coronary heart disease (CHD) risk among diabetic patients.

RESEARCH DESIGN AND METHODS

We prospectively investigated the association of HbA_{1c} at baseline and during follow-up with CHD risk among 17,510 African American and 12,592 white patients with type 2 diabetes.

RESULTS

During a mean follow-up of 6.0 years, 7,258 incident CHD cases were identified. The multivariable-adjusted hazard ratios of CHD associated with different levels of HbA_{1c} at baseline (<6.0 [reference group], 6.0–6.9, 7.0–7.9, 8.0–8.9, 9.0–9.9, 10.0–10.9, and ≥11.0%) were 1.00, 1.07 (95% CI 0.97–1.18), 1.16 (1.04–1.31), 1.15 (1.01–1.32), 1.26 (1.09–1.45), 1.27 (1.09–1.48), and 1.24 (1.10–1.40) (*P* trend = 0.002) for African Americans and 1.00, 1.04 (0.94–1.14), 1.15 (1.03–1.28), 1.29 (1.13–1.46), 1.41 (1.22–1.62), 1.34 (1.14–1.57), and 1.44 (1.26–1.65) (*P* trend <0.001) for white patients, respectively. The graded association of HbA_{1c} during follow-up with CHD risk was observed among both African American and white diabetic patients (all *P* trend <0.001). Each one percentage increase of HbA_{1c} was associated with a greater increase in CHD risk in white versus African American diabetic patients. When stratified by sex, age, smoking status, use of glucose-lowering agents, and income, this graded association of HbA_{1c} with CHD was still present.

CONCLUSIONS

The current study in a low-income population suggests a graded positive association between HbA_{1c} at baseline and during follow-up with the risk of CHD among both African American and white diabetic patients with low socioeconomic status.

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Diabetes is one of the major public health problems worldwide, affecting ~24 million individuals in the U.S. alone (1). More than 70% of patients with type 2 diabetes die of cardiovascular causes (2). Although a consistent association between glycemic control and cardiovascular disease has been noted in epidemiological studies (3–5), randomized clinical trials (RCTs) did not show a benefit (6–9). In the UK Prospective Diabetes Study (UKPDS), there was a 16% reduction ($P = 0.052$) in cardiovascular events in the intensive glycemic control arm in the original RCT period (6). After an additional 10 years of follow-up for the UKPDS, those originally assigned randomly to intensive glycemic control had significant long-term reductions in incident myocardial infarction and in all-cause mortality despite a loss of glycemic differences with the control group (10). Several other RCTs, however, did not lead to a significant reduction in macrovascular complications in the intensive glycemic treatment among diabetic patients (7–9). RCTs may have insufficient sample sizes or follow-up periods to detect moderate differences in risk, as well as potential differences among ethnic groups.

Such inconsistent evidence has resulted in the American Heart Association (AHA), the American College of Cardiology (ACC), and the American Diabetes Association (ADA) providing a conservative class IIb (usefulness/efficacy is less well established by evidence/opinion) recommendation with level of evidence A for the benefit of glycemic control on cardiovascular disease compared with microvascular complications, which has a superior level recommendation of class I (abundant epidemiological studies and RCTs to confirm the benefit) (11). Thus, there is still an urgent need for more observational data to support the case for causality given the lack of conclusive evidence from RCTs. In addition, most epidemiological studies only use a single baseline measurement of HbA_{1c} to predict risk of future coronary heart disease (CHD), which may produce potential bias. Moreover, very few studies have assessed the race-specific association of HbA_{1c} with CHD risk. The aim of the current study is to examine the race-specific association between different levels of HbA_{1c} at baseline and during follow-up and the risk of incident CHD among African American and white diabetic patients in the Louisiana State University Hospital-Based Longitudinal Study (LSUHLS).

RESEARCH DESIGN AND METHODS

Study Population

The LSU Health Care Services Division (LSUHCSD) operates seven public hospitals and affiliated clinics in Louisiana, which provide quality medical care to the residents of Louisiana regardless of their income or insurance coverage (12–19). Overall, LSUHCSD facilities have served ~1.6 million patients (35% of the Louisiana population) since 1997. Administrative, anthropometric, laboratory (test code, test collection date, test result values, and abnormal flag), clinical diagnosis, and medication data collected at these facilities are available in electronic form for both inpatients and outpatients from 1997. Using these data, we have established the LSUHLS (12). A cohort of diabetic patients was established by using the ICD-9 (code 250) through the LSUHLS database between 1 January 1999 and 31 December 2009. Both inpatients and outpatients were included, and all patients were under primary care. LSUHCSD's internal diabetes disease management guidelines call for physician confirmation of diabetes diagnoses by applying the ADA criteria: a fasting plasma glucose level ≥126 mg/dL, 2-h glucose level ≥200 mg/dL after a 75-g 2-h oral glucose tolerance test, one or more classic symptoms, and a random plasma glucose level ≥200 mg/dL (20). The first record of diabetes diagnosis was used to establish the baseline for each patient in the present analyses due to the design of the cohort study. Before diagnosis with diabetes, these patients have used our system for an average of 5.0 years. We have validated the diabetes diagnosis in LSUHCSD hospitals. The agreement of diabetes diagnosis was 97%; 20,919 of a sample of 21,566 hospital discharge diagnoses based on ICD codes also had physician-confirmed diabetes using the ADA diabetes diagnosis criteria (20).

The current study included 30,102 diabetic patients (12,592 white and 17,510 African American) who were 30–94 years of age at baseline without a history of CHD or stroke and with complete repeated data on all risk factor variables. In these diabetic patients, ~79% of patients qualify for free care (by virtue of being low income and uninsured, any individual or family unit whose income is at or <200% of federal poverty level), ~5.1% of patients are self-pay (uninsured, but incomes not low enough to qualify for free care), ~5.1% of patients are covered by Medicaid, ~8.9% of patients have Medicare, and ~2.2% of patients are covered by commercial insurance. The study and analysis plan were approved by the Pennington Biomedical Research Center and LSU Health Sciences Center institutional review boards, LSU System. We did not obtain informed consent from the participants involved in our study because we used anonymized data compiled from electronic medical records.

Baseline and Follow-up Measurements

The patient characteristics, including age of diabetes diagnosis, sex, race/ethnicity, family income, smoking status, types of health insurance, body weight, height, BMI, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, HbA_{1c}, estimated glomerular filtration rate (eGFR), and medication (antihypertensive, cholesterol-lowering, and antidiabetic drugs), within a half year after the diabetes diagnosis (baseline) and during follow-up after the diabetes diagnosis (follow-up) were extracted from the computerized hospitalization records. The updated mean values of HbA_{1c}, LDL cholesterol, HDL cholesterol, triglycerides, BMI, blood pressure, and eGFR over time were measured first at baseline and second as an updated mean of annual measurements, calculated for each participant from baseline to each year of follow-up. For example, at 1 year, the updated mean is the average of the baseline and 1-year values, and at 3 years, it is the average of baseline, 1-year, 2-year, and 3-year values. In the case of an event during follow-up, the

period for estimating updated mean value was from baseline to the year before this event occurred (21). The average number of HbA_{1c} measurements during the follow-up period was 7.7.

Prospective Follow-up

Follow-up information was obtained from the LSUHLS inpatient and outpatient database by using the unique number assigned to every patient who visits the LSUHCSD hospitals. The diagnosis of CHD was the primary end point of interest of the study and was defined according to the ICD-9: CHD (ICD-9 codes 410–414). Since 1997, diagnoses of CHD were made by the treating physicians based on a clinical assessment and examinations as considered relevant by the clinician in charge of treatments. Follow-up of each cohort member continued until the date of the diagnosis of CHD, the date of the last visit if the subject stopped use of LSUHCSD hospitals, death, or 31 May 2012 (17).

Statistical Analyses

The association between HbA_{1c} and the risk of CHD was analyzed by using Cox proportional hazards models. HbA_{1c} was evaluated in the following two ways: *1*) as seven categories (HbA_{1c} <6.0% [42 mmol/mol] [reference group], 6.0–6.9% [42–52 mmol/mol], 7.0–7.9% [53–63 mmol/mol], 8.0–8.9% [64–74 mmol/mol], 9.0–9.9% [75–85 mmol/mol], 10.0–10.9% [86–96 mmol/mol], and ≥11.0% [97 mmol/mol]) and *2*) as a continuous variable. Different levels of HbA_{1c} were included in the models as dummy variables, and the significance of the trend over different categories of HbA_{1c} was tested in the same models by giving an ordinal numerical value for each dummy variable. All analyses were adjusted for age and sex and further for smoking, income, type of insurance, BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, eGFR, and use of antihypertensive drugs, diabetes medications, and cholesterol-lowering agents. When we analyzed the association between updated mean of HbA_{1c} and CHD risk, we adjusted for updated means of BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, and eGFR instead of the baselines of these variables. We stratified the samples by race because there was a significant interaction between race and HbA_{1c} on CHD risk. To avoid the potential bias due to severe diseases at baseline, additional analyses were performed excluding the subjects who were diagnosed with CHD during the first 2 years of follow-up. We used restricted cubic splines in Cox models to test whether there is a dose-response or nonlinear association of HbA_{1c} as a continuous variable with CHD risk. Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed with PASW for Windows, version 20.0 (IBM SPSS, Inc., Chicago, IL) and SAS for Windows, version 9.3 (SAS Institute, Cary, NC).

RESULTS

General characteristics of the study population are presented by race in Table 1. During a mean follow-up period of 6.0 years, 7,258 subjects (3,580 white and 3,678 African American) developed CHD. A significantly increased risk of CHD was observed among both African American and white diabetic patients with increasing baseline HbA_{1c} after adjustment for age and sex (Table 2). After further adjustment for other confounding factors (smoking, income,

Table 1—Baseline characteristics of African American and white patients with diabetes

	African American	White
No. of participants	17,510	12,592
Male, *n* (%)	6,098 (34.8)	4,760 (37.8)
Age, mean (SD), years	50.41 (10.0)	52.48 (10.2)
Income, median, $/family	11,208 (2,400–19,740)	13,440 (6,948–21,072)
BMI, mean (SD)	33.9 (8.5)	35.0 (8.9)
Baseline blood pressure, mean (SD), mmHg		
Systolic	147 (25)	142 (22)
Diastolic	82 (14)	78 (13)
Mean HbA_{1c}, % (mmol/mol)	8.1 (65)	7.4 (57)
Mean HbA_{1c} during follow-up, % (mmol/mol)	7.8 (62)	7.3 (56)
LDL cholesterol, mean (SD), mg/dL	114 (40)	112 (41)
HDL cholesterol, mean (SD), mg/dL	45 (14)	41 (12)
Triglycerides, mean (SD), mg/dL	134 (102)	195 (137)
Glomerular filtration rate, *n* (%) mL/min/1.73 m^2		
≥90	9,681 (55.4)	4,830 (38.4)
60–89	5,989 (34.3)	5,797 (46.2)
30–59	1,530 (8.8)	1,758 (14.0)
15–29	185 (1.1)	134 (1.1)
<15	100 (0.6)	46 (0.4)
Current smoker, *n* (%)	5,691 (32.5)	4,646 (36.9)
Type of insurance, *n* (%)		
Free	13,855 (79.1)	9,815 (78.0)
Self-pay	1,042 (5.9)	504 (4.0)
Medicaid	1,038 (5.9)	503 (4.0)
Medicare	1,277 (7.3)	1,398 (11.1)
Commercial	298 (1.7)	372 (3.0)
Uses of medications, *n* (%)		
Lipid-lowering medication	10,639 (60.8)	8,366 (66.4)
Antihypertensive medication	14,798 (84.5)	10,228 (81.2)
Glucose-lowering medication	13,347 (76.2)	9,321 (74.0)
Metformin	9,931 (56.7)	7,179 (57.0)
Sulfonylurea	6,152 (35.1)	4,911 (39.0)
Insulin	6,738 (38.5)	4,178 (33.2)
Others	3,229 (18.4)	30,222 (24.0)

BMI was calculated as the weight in kilograms divided by the square of the height in meters. SD of HbA_{1c} is 2.7 and 2.2% for baseline and 2.0 and 1.7% for follow-up, respectively.

Table 2—HR (95% CI) of CHD according to different levels of HbA_{1c} at baseline and during follow-up among African American and white patients with diabetes

	HbA_{1c} (%) (mmol/mol)							
	<6.0 (42)	6.0–6.9 (42–52)	7.0–7.9 (53–63)	8.0–8.9 (64–74)	9.0–9.9 (75–85)	10.0–10.9 (86–96)	≥11.0 (97)	*P* for trend
Baseline								
African American	4,219	4,308	2,337	1,588	1,221	1,033	2,804	
No. of cases	736	923	571	370	287	235	556	
Person-years	24,780	27,178	15,526	11,207	8,368	7,052	18,181	
Age adjustment	1.00	1.13 (1.02–1.24)	1.26 (1.13–1.41)	1.22 (1.07–1.38)	1.31 (1.14–1.50)	1.31 (1.13–1.52)	1.24 (1.11–1.39)	<0.001
Multivariable adjustment[a]	1.00	1.10 (1.00–1.21)	1.21 (1.08–1.35)	1.20 (1.06–1.37)	1.29 (1.13–1.48)	1.30 (1.11–1.51)	1.25 (1.12–1.40)	<0.001
Multivariable adjustment[b]	1.00	1.07 (0.97–1.18)	1.16 (1.04–1.31)	1.15 (1.01–1.32)	1.26 (1.09–1.45)	1.27 (1.09–1.48)	1.24 (1.10–1.40)	0.002
White	4,196	3,025	1,712	1,121	852	652	1,034	
No. of cases	1,027	871	548	361	270	196	307	
Person-years	21,334	16,633	9,910	6,401	4,723	3,747	5,381	
Age adjustment	1.00	1.09 (1.00–1.20)	1.23 (1.11–1.36)	1.37 (1.21–1.54)	1.48 (1.30–1.70)	1.36 (1.17–1.59)	1.47 (1.29–1.69)	<0.001
Multivariable adjustment[a]	1.00	1.07 (0.98–1.17)	1.20 (1.08–1.33)	1.34 (1.18–1.51)	1.47 (1.28–1.69)	1.37 (1.17–1.60)	1.49 (1.30–1.70)	<0.001
Multivariable adjustment[b]	1.00	1.04 (0.94–1.14)	1.15 (1.03–1.28)	1.29 (1.13–1.46)	1.41 (1.22–1.62)	1.34 (1.14–1.57)	1.44 (1.26–1.65)	<0.001
Follow-up								
African American	3,414	4,386	3,241	2,222	1,631	1,136	1,480	
No. of cases	547	902	766	562	393	256	254	
Person-years	18,905	26,717	21,746	15,460	11,598	8,089	9,781	
Age adjustment	1.00	1.15 (1.03–1.27)	1.26 (1.13–1.41)	1.42 (1.26–1.60)	1.42 (1.25–1.62)	1.40 (1.20–1.63)	1.21 (1.04–1.41)	<0.001
Multivariable adjustment[a]	1.00	1.09 (0.97–1.21)	1.21 (1.08–1.35)	1.37 (1.21–1.54)	1.42 (1.24–1.62)	1.44 (1.23–1.68)	1.31 (1.12–1.54)	<0.001
Multivariable adjustment[b]	1.00	1.05 (0.94–1.18)	1.16 (1.03–1.31)	1.32 (1.15–1.50)	1.37 (1.19–1.58)	1.42 (1.21–1.67)	1.33 (1.13–1.57)	<0.001
White	3,324	3,451	2,397	1,467	965	562	426	
No. of cases	756	975	774	474	302	179	120	
Person-years	15,696	18,762	13,937	8,548	5,760	3,239	2,185	
Age adjustment	1.00	1.09 (0.99–1.19)	1.30 (1.17–1.44)	1.44 (1.28–1.62)	1.45 (1.26–1.66)	1.65 (1.40–1.95)	1.66 (1.37–2.02)	<0.001
Multivariable adjustment[a]	1.00	1.03 (0.94–1.14)	1.25 (1.13–1.38)	1.45 (1.28–1.63)	1.47 (1.28–1.69)	1.72 (1.45–2.04)	1.75 (1.43–2.14)	<0.001
Multivariable adjustment[b]	1.00	0.98 (0.88–1.09)	1.17 (1.05–1.31)	1.37 (1.20–1.55)	1.40 (1.21–1.62)	1.64 (1.37–1.96)	1.76 (1.43–2.16)	<0.001

[a]Adjusted for age, sex, type of insurance, income, smoking, BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, and glomerular filtration rate at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses). [b]Adjusted for age, sex, type of insurance, income, smoking, BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, glomerular filtration rate at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), and use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents.

type of insurance, BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, eGFR, and use of antihypertensive drugs, diabetes medications, and cholesterol-lowering agents), this graded positive association remained significant among white (*P* trend <0.001) and African American (*P* = 0.002) diabetic patients (Table 2). When HbA_{1c} was considered as a continuous variable by using restricted cubic splines, a linear association of HbA_{1c} with CHD risk was observed (Supplementary Fig. 1). Each one percentage increase in baseline HbA_{1c} was associated with a 2% (95% CI 1.01–1.04) increased risk of CHD in African Americans and a 6% (1.05–1.08) increased risk of CHD in whites, and this association was significantly stronger among white diabetic patients than African American patients (*P* = 0.001).

When we stratified by sex, age, smoking status, and family income, the graded positive association of baseline HbA_{1c} with CHD risk did not change (almost all *P* trend <0.05) (Table 3). The graded positive association of HbA_{1c} with CHD risk was also confirmed among diabetic patients using glucose-lowering agents and those who were not using (all *P* trend <0.001) (Table 3).

After excluding the subjects who were diagnosed with CHD during the first 2 years of follow-up (*n* = 588), the multivariable-adjusted hazard ratios (HRs) of CHD associated with different levels of HbA_{1c} did not change (data not shown).

When we performed an additional analysis by using an updated mean of HbA_{1c} during follow-up, we found almost the same graded positive associations between baseline HbA_{1c} levels and updated mean levels of HbA_{1c} with CHD risk among both African American and white diabetic patients (Supplementary Table 1). During follow-up, each one percentage increase of HbA_{1c} was associated with a more obvious increase in CHD risk in white (HR 1.11 [95% CI 1.09–1.14]) than in African American (1.05 [1.03–1.08]) diabetic patients (*P* < 0.001). Moreover, we performed another analysis using age as the timescale and the results did not change (Supplementary Table 2).

Table 3—HR (95% CI) of CHD according to different levels of HbA_{1c} at baseline among various subpopulations

	HbA_{1c} (%) (mmol/mol)						*P* for trend	*P* for interaction
	<6.0 (42)	6.0–6.9 (42–52)	7.0–7.9 (53–63)	8.0–8.9 (64–74)	9.0–9.9 (75–85)	10.0–10.9 (86–96)	≥11.0 (97)		
Sex									<0.05
Male	1.00	1.07 (0.96–1.19)	1.13 (0.99–1.28)	1.25 (1.08–1.44)	1.40 (1.20–1.63)	1.22 (1.03–1.44)	1.33 (1.16–1.52)	<0.001	
Female	1.00	1.05 (0.96–1.14)	1.17 (1.06–1.30)	1.19 (1.06–1.34)	1.27 (1.12–1.45)	1.38 (1.19–1.60)	1.30 (1.16–1.46)	<0.001	
Age-groups, years									<0.001
<50	1.00	1.00 (0.88–1.13)	1.05 (0.91–1.21)	1.02 (0.88–1.19)	1.14 (0.98–1.34)	1.08 (0.92–1.28)	1.11 (0.97–1.28)	0.46	
50–59	1.00	1.06 (0.95–1.19)	1.21 (1.07–1.38)	1.30 (1.12–1.50)	1.27 (1.07–1.50)	1.47 (1.23–1.75)	1.36 (1.18–1.57)	<0.001	
60–94	1.00	1.09 (0.97–1.23)	1.14 (0.98–1.32)	1.25 (1.04–1.51)	1.67 (1.34–2.08)	1.14 (0.84–1.54)	1.19 (0.94–1.52)	0.001	
Smoking status									<0.025
Never	1.00	1.11 (1.02–1.21)	1.21 (1.11–1.33)	1.25 (1.12–1.39)	1.41 (1.25–1.59)	1.39 (1.22–1.59)	1.41 (1.27–1.57)	<0.001	
Ever or current	1.00	0.92 (0.80–1.04)	1.02 (0.88–1.19)	1.14 (0.97–1.35)	1.16 (0.97–1.38)	1.10 (0.91–1.34)	1.10 (0.94–1.29)	0.053	
Using glucose-lowering agents									<0.001
No	1.00	1.09 (0.98–1.23)	1.21 (1.05–1.41)	1.39 (1.17–1.64)	1.40 (1.14–1.72)	1.29 (1.03–1.60)	1.45 (1.22–1.72)	<0.001	
Yes	1.00	1.03 (0.94–1.12)	1.13 (1.02–1.24)	1.15 (1.03–1.28)	1.29 (1.15–1.45)	1.29 (1.14–1.47)	1.26 (1.13–1.39)	<0.001	
Income									<0.001
<Median of income	1.00	1.00 (0.91–1.10)	1.15 (1.02–1.28)	1.20 (1.06–1.36)	1.19 (1.03–1.37)	1.28 (1.09–1.49)	1.26 (1.12–1.43)	<0.001	
≥Median of income	1.00	1.11 (1.01–1.22)	1.17 (1.04–1.30)	1.22 (1.07–1.39)	1.48 (1.29–1.69)	1.32 (1.13–1.54)	1.34 (1.18–1.52)	<0.001	

Adjusted for age, sex, race, type of insurance, income, smoking, BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, glomerular filtration rate, and use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents at baseline, other than the variable for stratification.

CONCLUSIONS

Our study found a graded positive association between HbA_{1c} at baseline and during follow-up with the risk of CHD among both African American and white diabetic patients. This graded positive association was more significant in white than African American patients with diabetes.

Diabetic patients experience high mortality from cardiovascular causes (2). Observational studies have confirmed the continuous and positive association between glycemic control and the risk of cardiovascular disease among diabetic patients (4,5). But the findings from RCTs are sometimes uncertain. Three large RCTs (7–9) designed primarily to determine whether targeting different glucose levels can reduce the risk of cardiovascular events in patients with type 2 diabetes failed to confirm the benefit. Several reasons for the inconsistency of these studies can be considered. First, small sample sizes, short follow-up duration, and few CHD cases in some RCTs may limit the statistical power. Second, most epidemiological studies only assess a single baseline measurement of HbA_{1c} with CHD risk, which may produce potential bias. The recent analysis of 10 years of posttrial follow-up of the UKPDS showed continued reductions for myocardial infarction and death from all causes despite an early loss of glycemic differences (10). The scientific evidence from RCTs was not sufficient to generate strong recommendations for clinical practice. Thus, consensus groups (AHA, ACC, and ADA) have provided a conservative endorsement (class IIb recommendation, level of evidence A) for the cardiovascular benefits of glycemic control (11). In the absence of conclusive evidence from RCTs, observational epidemiological studies might provide useful information to clarify the relationship between glycemia and CHD risk. In the current study with 30,102 participants with diabetes and 7,258 incident CHD cases during a mean follow-up of 6.0 years, we found a graded positive association by various HbA_{1c} intervals of clinical relevance or by using HbA_{1c} as a continuous variable at baseline and during follow-up with CHD risk among both African American and white diabetic patients. Each one percentage increase in baseline and follow-up HbA_{1c} was associated with a 2 and 5% increased risk of CHD in African American and 6 and 11% in white diabetic patients. Each one percentage increase of HbA_{1c} was associated with a greater increase in CHD risk in white versus African American diabetic patients. This magnitude of CHD risk increase especially in African Americans is lower than that reported from the Atherosclerosis Risk in Communities (ARIC) Study (4) of a relative risk for CHD of 1.14 (95% CI 1.07–1.21) and a recent meta-analysis of cohort studies of a relative risk of 1.15 (1.0–1.20) (22) with 1% increase of HbA_{1c}. The hazard rates for CHD in African American patients were consistently lower than white patients for nearly all levels of HbA_{1c}. The higher mean values of HbA_{1c} at baseline and during follow-up among African American diabetic patients than white patients might result in the absolute lower hazard rates for CHD associated with each one percentage increase in HbA_{1c} among African American diabetic patients than white patients. In addition, the differences in hazard rates might be related to the recently recognized differences in HbA_{1c} levels between African American and white patients who have the same levels of blood glucose (23). The mechanism underlying this racial difference in HbA_{1c} level due to biological differences or to other sociobehavioral differences, including disparities in access to health and prevention care, has not been established. In addition, we found that this graded positive association was present in patients with diabetes with and without glucose-lowering agent treatment, and in patients in different age, sex, and smoking status groups.

Several plausible biological mechanisms have been proposed to explain a possible direct relationship between chronically elevated blood glucose levels and CHD (24). Glucose can react with many different proteins, creating advanced glycation end products, which contribute to long-term complications in diabetes as well as to endothelial dysfunction, changes in arterial distensibility, plaque formation, and atherosclerosis (25,26). But the pathophysiology may not only be linked directly to hyperglycemia but also to diabetic dyslipidemia, hypertension, and inflammation, which can accelerate vascular injury and cardiovascular disease risk. In the Steno-2 study, a multifactorial intervention showed an ~50% reduction in the risk of cardiovascular and microvascular events among diabetic patients (27).

There are several strengths to our study, including the large sample size, high proportion of African Americans, long follow-up time, and use of administrative databases to avoid differential recall bias. We have used both baseline HbA_{1c} levels and updated mean values of HbA_{1c} during follow-up in the analyses, which can avoid potential bias from a single baseline measurement. In addition, participants in this study use the same public health care system, which minimizes the influence from the accessibility of health care, particularly in comparing African Americans and whites. One limitation of our study is that our analysis was not performed on a representative sample of the population, which limits the generalizability of this study; however, LSUHCSD hospitals are public hospitals and cover >1.6 million patients, most of whom are low-income people in Louisiana. The results of the current study will have wide applicability for the population with low income and without health insurance in the U.S. Second, the validity of myocardial infarction diagnoses in our study has not been confirmed by specialists. But the method we used (hospital discharge register) to diagnose major nonfatal CHD has been widely used in American and European cohort studies, such as the Kaiser Permanente Medical Care Program (28,29), the ARIC Study (4), the Framingham Study (30,31), and the National FINRISK Survey (32). The validity of the diagnoses of myocardial infarction by using the hospital discharge register in these cohort studies is available (agreement 83–98%) (29,33). Third, even though our analyses adjusted for an extensive set of confounding factors, residual

confounding due to measurement error in the assessment of confounding factors, unmeasured factors such as heart rate, physical activity, education, dietary factors, and cognitive function for all patients, cannot be excluded. Based on the limitations above, our findings may need to be further confirmed by other studies.

In summary, our study demonstrates that there is a graded association between HbA_{1c} at baseline and during follow-up with the risk of CHD among both African American and white diabetic patients. Our study provides epidemiological support for glucose lowering as a strategy to reduce CHD in a large sample size of both white and African American diabetes patients with low socioeconomic status.

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