The Association of Hemoglobin A1c With Incident Heart Failure Among People Without Diabetes: The Atherosclerosis Risk in Communities Study

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OBJECTIVE—This study sought to investigate an association of HbA1c (A1C) with incident heart failure among individuals without diabetes and compare it to fasting glucose.

RESEARCH DESIGN AND METHODS—We studied 11,057 participants of the Atherosclerosis Risk in Communities (ARIC) Study without heart failure or diabetes at baseline and estimated hazard ratios of incident heart failure by categories of A1C (<5.0, 5.0–5.4 [reference], 5.5–5.9, and 6.0–6.4%) and fasting glucose (<90, 90–99 [reference], 100–109, and 110–125 mg/dl) using Cox proportional hazards models.

RESULTS—A total of 841 cases of incident heart failure hospitalization or deaths (*International Classification of Disease*, 9th/10th Revision, 428/I50) occurred during a median follow-up of 14.1 years (incidence rate 5.7 per 1,000 person-years). After the adjustment for covariates including fasting glucose, the hazard ratio of incident heart failure was higher in individuals with A1C 6.0–6.4% (1.40 [95% CI, 1.09–1.79]) and 5.5–6.0% (1.16 [0.98–1.37]) as compared with the reference group. Similar results were observed when adjusting for insulin level or limiting to heart failure cases without preceding coronary events or developed diabetes during follow-up. In contrast, elevated fasting glucose was not associated with heart failure after adjustment for covariates and A1C. Similar findings were observed when the top quartile (A1C, 5.7–6.4%, and fasting glucose, 108–125 mg/dl) was compared with the lowest quartile (<5.2% and <95 mg/dl, respectively).

CONCLUSIONS—Elevated A1C (≥5.5–6.0%) was associated with incident heart failure in a middle-aged population without diabetes, suggesting that chronic hyperglycemia prior to the development of diabetes contributes to development of heart failure. ***Diabetes*** **59:2020–2026, 2010**

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Diabetes is one of the most important risk factors for heart failure (1). Among people with diabetes, a dose relationship between glycemia measured by HbA1c (A1C) and heart failure risk has been reported in observational studies (1–6). The risk of hospitalization for heart failure increases 8–32% per 1% unit increase in A1C (3–6).

In contrast, to our knowledge, no previous study has investigated the association between A1C and the risk of heart failure in a population without diabetes. In this population, fasting glucose is only marginally or not associated with heart failure risk (7,8). This may be partially attributable to relatively high variability in glucose measurements (9) and to the fact that fasting glucose levels do not necessarily reflect postprandial hyperglycemia, a condition potentially contributing to development of cardiovascular disease (10,11).

In January 2010, the American Diabetes Association published new clinical guidelines recommending the use of A1C as a diagnostic test for diabetes (12), with cutpoints based largely on the documented association of A1C with microvascular disease. Little is known, however, regarding the risk relationship of A1C levels with heart failure incidence in nondiabetic adults. The objective of this study was to investigate a possible relationship between A1C and the incidence of heart failure in a community-based study of people without diabetes. We also compared the associations of A1C and fasting glucose levels with risk of incident heart failure in this middle-aged nondiabetic population.

RESEARCH DESIGN AND METHODS

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based cohort study of 15,792 people aged 45–64 years at baseline sampled from four U.S. communities: Forsyth County, North Carolina; suburban Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi (13). The first examination was conducted during 1987–1989, with three triennial follow-up visits (visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998)). Visit 2 was the only visit at which A1C was measured and was the baseline for the present study. There were 14,348 participants (91.4%) who attended visit 2. Of these, we excluded participants reporting race other than Caucasian or African American (n = 42); missing values of A1C (n = 278); with prevalent heart failure defined as self-reported treatment for heart failure, hospitalization for heart failure between visit 1 and 2, or the Gothenburg stage 3, a status with dyspnea due to cardiac causes and under treatment with digitalis or loop diuretics (n = 455) (14,15); or missing information about incident heart failure during follow-up (n = 245). We also excluded participants with diabetes defined by a fasting glucose of ≥7.0 mmol/l (≥126 mg/dl), nonfasting glucose of ≥11.1 mmol/l (≥200 mg/dl), A1C ≥6.5% (12), self-reported physician diagnosis of diabetes, or use of glucose-lowering medication (n = 2,174) or missing information for diabetes (n = 97) at either of visit 1 or visit 2, for a final study population size of 11,057 participants. The study

TABLE 1
Characteristics of participants according to categories of A1C

	Categories of A1C (%)			
	3.5–4.9	5.0–5.4	5.5–5.9	6.0–6.4
n	1,012	5,263	3,883	899
Age (years)	55.4 ± 5.5	56.3 ± 5.6	57.4 ± 5.7	58.0 ± 5.6
Male sex (%)	46.8	42.6	44.9	46.1
African American race (%)	15.9	11.8	26.7	50.7
Educational level (%)*				
<12 years completed	13.4	14.5	23.4	31.9
12–16 years completed	40.4	44.5	40.8	36.6
>16 years completed	46.2	41.0	35.8	31.5
Current smokers (%)*	13.0	18.4	29.1	31.3
Current alcohol drinkers (%)	64.3	64.5	56.0	46.1
BMI (kg/m^2)*	26.4 ± 4.7	26.6 ± 4.5	27.8 ± 5.2	29.7 ± 5.9
Fasting glucose (mg/dl)*	97.9 ± 8.4	99.4 ± 8.6	103.4 ± 9.1	108.1 ± 9.7
Antihypertensive medication (%)	23.7	23.5	29.2	42.2
Systolic blood pressure (mmHg)*	118.6 ± 17.4	118.4 ± 18.0	121.6 ± 18.0	125.4 ± 19.5
Diastolic blood pressure (mmHg)*	72.1 ± 10.0	71.5 ± 10.1	72.4 ± 10.3	73.9 ± 10.3
LDL-C (mmol/l)*	3.18 ± 0.91	3.37 ± 0.91	3.54 ± 0.95	3.62 ± 0.96
HDL-C (mmol/l)*	1.37 ± 0.48	1.35 ± 0.45	1.29 ± 0.42	1.22 ± 0.38
Triglycerides (mmol/l)*	1.33 ± 0.77	1.42 ± 0.87	1.46 ± 0.85	1.53 ± 0.87
History of CHD (%)	2.5	3.7	5.0	5.0
Carotid atherosclerosis (%)*	4.4	4.7	6.9	10.1
eGFR (ml/min/1.73 m^2)	86.5 ± 17.6	84.9 ± 16.6	85.7 ± 18.3	87.9 ± 19.6

Data are mean ± SD or percentage. All comparisons were significant at $P < 0.001$, except for sex ($P = 0.017$). eGFR = estimated glomerular filtration rate. *Missing values (number missing): educational level, 13; current smokers, 1; BMI 9, fasting glucose 191; blood pressure, 1; LDL-C, 136: HDL-C, 37; triglycerides, 7; history of CHD, 98; carotid atherosclerosis, 211.

was approved by the Institutional Review Boards of all participating institutions, and all participants gave informed consent.

Data collection. ARIC study participants provided information on demographic and behavioral variables and medical history to a trained interviewer at each visit. In this study, we used information obtained at visit 2, unless otherwise noted. Smoking status and alcohol intake were determined by self-report. Participants were asked to bring all medications, which were coded by trained personnel. Information about completed years of education was obtained at visit 1. Certified technicians measured three systolic and diastolic blood pressures with participants in the sitting position after 5 min of rest using a random-zero sphygmomanometer. The average of the second and third readings was recorded. A1C was measured using a high-performance liquid chromatography instrument (Tosoh 2.2 Plus in 2003–2004 and the Tosoh G7 in 2007–2008, Tosoh Corporation, Tokyo, Japan) on all participants with available stored whole blood (16). We have previously demonstrated the reliability of measurements from these stored samples (17). Fasting serum glucose was measured by the optimized DART GLUCOSE reagent method and cholesterol, triglycerides, and HDL cholesterol were determined using enzymatic methods. LDL cholesterol was calculated using the Friedewald equation (18). Insulin was measured by radioimmunoassay (125Insulin kit; Cambridge Medical Diagnosis, Bilerica, MA) at visit 1 (19). Serum creatinine concentration was measured using a modified kinetic Jaffe method. Estimated glomerular filtration rate was computed by the Modification of Diet in Renal Disease Study equation (20). Evidence of atherosclerosis of the common carotid arteries (shadowing/plaque on either side or none) was determined by ultrasound examination (13,21).

Outcome. ARIC investigators conduct continuous, comprehensive surveillance for all cardiovascular disease-related hospitalizations and deaths in the four communities. Incident heart failure was defined as death from heart failure in any position on the death certificate or as the first heart failure hospitalization with the International Classification of Diseases Code, Ninth Revision (ICD-9) 428 or Tenth Revision (ICD-10) I50 in any position of the hospital discharge list (6). Incident heart failure from visit 2 to January 1, 2006, was analyzed in the present study.

Statistical analyses. We categorized A1C using the following cut-points: <5.0, 5.0–5.4, 5.5–5.9, and 6.0–6.4%. Baseline characteristics of the population were compared across these A1C categories. We evaluated the continuous association between A1C and the incidence rates of heart failure using a Poisson regression model incorporating linear spline terms for A1C (knots at 5.0, 5.5, and 6.0%) with adjustment for age, sex, and race. Cox proportional hazards models were used to quantify the association between the above categories of A1C and incident heart failure. We tested for interactions using the likelihood-ratio test. For 10,866 participants (98.3%) who provided fasting (≥8 h) blood samples, we also evaluated the association of fasting glucose levels and incident heart failure by using clinical categories of glucose concentration as follows: <5.0, 5.0–5.5, 5.6–6.0, 6.1–6.9 mmol/l (<90, 90–99, 100–109, and 110–125 mg/dl). We used the most prevalent category within a normal range as a reference group for both A1C (5.0–5.4%) and fasting glucose (5.0–5.5 mmol/l) levels.

We implemented three models for the adjustment for covariates. Model 1 was adjusted for age, sex, and race. Model 2 was further adjusted for level of education, carotid atherosclerosis, systolic blood pressure, antihypertensive medication, smoking, alcohol intake, BMI, LDL cholesterol, HDL cholesterol, a self-reported history of coronary heart disease (CHD) by visit 2, clinical examination, or hospital records and estimated glomerular filtration rate. Model 3 was adjusted for all variables in model 2 plus either baseline fasting glucose or A1C, as appropriate. We also investigated the association of quartiles of A1C or fasting glucose with heart failure risk.

We conducted several sensitivity analyses to assess the robustness of our results. First, we examined heart failure occurring in the absence of clinical CHD. To accomplish this, we conducted our analysis censoring incident CHD cases that occurred prior to the date of heart failure ($n = 1,088$). Second, we repeated our analyses after excluding participants who had incident diabetes in the first 6 years of follow-up (between visit 2 and visit 4) defined by a fasting glucose of ≥7.0 mmol/l, nonfasting glucose of ≥11.1 mmol/l, self-reported physician diagnosis of diabetes, or use of glucose-lowering medication at visit 3 or visit 4 ($n = 600$). After visit 4, the ARIC Study obtained self-reported information on diabetes diagnosis and medication use by annual telephone calls, for a maximum of 15 years of follow-up. Using this information, we investigated heart failure occurring in the absence of diagnosed diabetes by censoring incident diabetes cases occurring before the heart failure event ($n = 1,497$).

We also examined the association of 1% unit increase in A1C with heart failure risk. To evaluate whether this association was consistent in groups with low-/high-risk profile, we evaluated this association in the subgroup of participants according to the absence/presence of cardiovascular risk factors. All analyses were conducted using Stata 10.1 software (Stata Corp, College Station, TX) and a P value of <0.05 was considered statistically significant.

RESULTS

Demographic characteristics of participants by categories of A1C are shown in Table 1. Participants with A1C ≥5.5% were more likely to be older, African American, and smokers but less likely to be current drinkers as compared with the reference group (A1C 5.0–5.4%). Individuals with

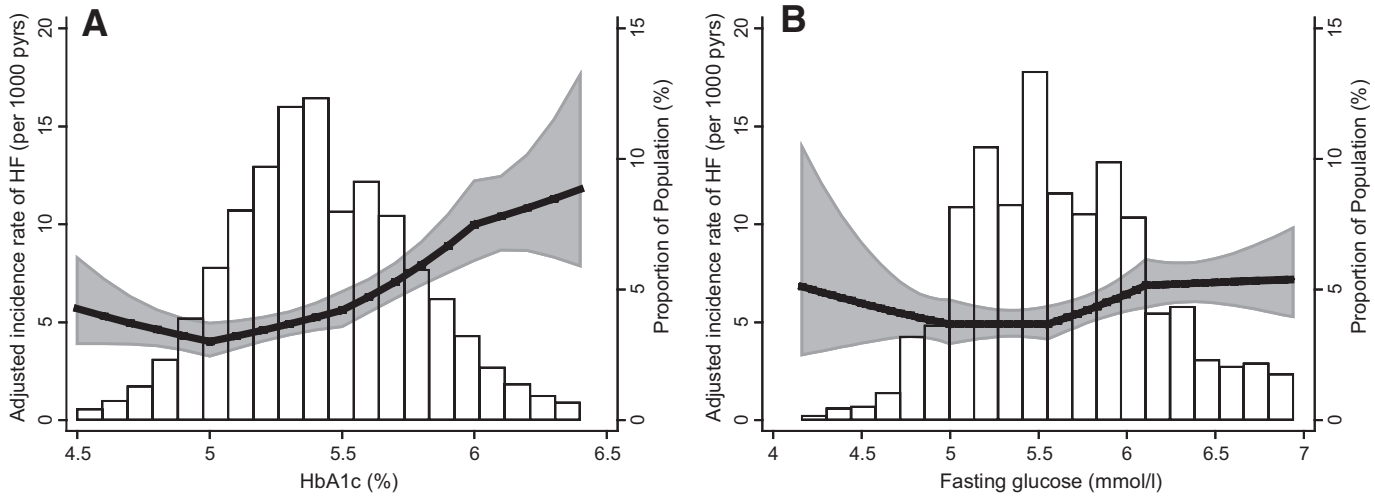

FIG. 1. Incident rates of heart failure (HF) according to A1C and fasting glucose. The graph shows incidence rates (per 1,000 person-years) and 95% CIs (shaded area) of heart failure with spline terms of A1C (knots at 5.0, 5.5, and 6.0%) (*A*) and fasting glucose (knots at 5.0, 5.6, and 6.1 mmol/l [90, 100, and 110 mg/dl]) (*B*) adjusted for age, sex, and race. The histograms represent the frequency distribution of A1C (4.5–6.5%) and fasting glucose (4.2–6.9 mmol/l [75–125 mg/dl]) in the study sample.

A1C 6.0–6.4% at baseline were also more likely to have higher BMI, higher blood pressure, adverse lipid profile, and higher prevalence of CHD and carotid atherosclerosis. A1C and fasting glucose were weakly, but significantly, correlated ($r = 0.32$, $P < 0.001$).

During a median follow-up time of 14.1 years, there were 841cases of incident heart failure. The overall incidence rate of heart failure was 5.7 per 1,000 person-years. The continuous associations of A1C and fasting glucose levels with incidence rate of heart failure with the adjustment for age, sex, and race are shown in Fig. 1. The incidence rate of heart failure increased linearly above A1C 5.0% (tests for differences in slopes above A1C 5.0% were not statistically significant; data not shown) and was ~2-fold or higher in a range of A1C ≥6.0% as compared with that of A1C 5.0%. Although the incidence rate of heart failure increased at a fasting glucose level of 5.6 mmol/l, the slope was much shallower than that for A1C and was flat at the range of 5.0–5.5 mmol/l. Increased risk of heart failure was observed at the low ranges of A1C (<5.0%) and fasting glucose (<5.0 mmol/l), although 95% CIs were wide, reflecting imprecision of the estimate.

We estimated the hazard ratios and corresponding 95% CIs for incident heart failure by categories of A1C using Cox proportional hazards models adjusting for multiple covariates (Table 2). As compared with participants with A1C 5.0–5.4, the hazard ratios of heart failure rose progressively from 1.44 (95% CI, 1.24–1.68) to 2.04 (95% CI, 1.63–2.54) across categories of A1C ≥5.5% in the model adjusted for age, sex, and race (model 1). The association among individuals with A1C 6.0–6.4% remained significant even after adjustment for all traditional cardiovascular risk factors (model 2, hazard ratio 1.38 [95% CI, 1.09–1.75]), although the association among participants with A1C 5.5–5.9% was attenuated to borderline significance (hazard ratio 1.16 [0.98–1.36], $P = 0.08$). The adjustment for fasting glucose did not alter the results (model 3). These associations did not change appreciably after further adjustment for use of antihypertensive drugs (i.e., β-blockers, ACE inhibitors, or diuretics), which might potentially affect both glucose metabolism and risk of heart failure (data not shown).

There was no evidence of effect modification by a history of CHD at baseline (P for interaction = 0.83), and similar, but slightly attenuated, associations were observed when we censored participants without prevalent CHD at baseline who developed CHD prior to heart failure (hazard ratio 1.27 [95% CI, 0.95–1.70] for A1C 6.0–6.4% and trend $P = 0.095$). We obtained similar results even after further adjusting for insulin levels. The exclusion of par-

TABLE 2
Adjusted hazard ratios (HRs; 95% CI) for incident heart failure (HF) according to A1C categories

	Categories of A1C, range (%)				
Models*	<5.0	5.0–5.4	5.5–5.9	6.0–6.4	trend *P*
Model 1					
No. of cases/subjects	50/1,012	307/5,263	361/3,883	123/899	
HR (95% CI)	0.92 (0.68–1.24)	Reference	1.44 (1.24–1.68)	2.04 (1.63–2.54)	<0.001
Model 2					
No. of cases/subjects†	45/970	289/5,078	338/3,707	111/840	
HR (95% CI)	0.96 (0.70–1.31)	Reference	1.16 (0.98–1.36)	1.38 (1.09–1.75)	0.006
Model 3					
No. of cases/subjects‡	45/955	285/5,002	329/3,642	110/824	
HR (95% CI)	0.96 (0.70–1.32)	Reference	1.16 (0.98–1.37)	1.40 (1.09–1.79)	0.008

*Model 1: adjusted for age, race, and sex. Model 2: model 1 + level of education, carotid atherosclerosis, systolic blood pressure, antihypertensive medication, smoking, alcohol intake, BMI, LDL-C, HDL-C, a history of CHD at baseline, and eGFR. Model 3: model 2 + fasting glucose. †Participants with all variables used in model 2. ‡Participants with all variables used in model 2 and fasting glucose.

TABLE 3
Adjusted HRs (95% CI) for incident HF according to fasting glucose categories

Models*	Categories of fasting glucose, range (mmol/l)				trend *P*
	<5.0	5.0–5.5	5.6–6.0	6.1–6.9	
Model 1					
No. of cases/subjects	67/977	238/3,864	301/3,949	219/2,076	
HR (95% CI)	1.27 (0.97–1.66)	Reference	1.13 (0.95–1.34)	1.49 (1.23–1.79)	0.001
Model 2					
No. of cases/subjects†	64/942	221/3,728	280/3,789	204/1,964	
HR (95% CI)	1.51 (1.14–2.00)	Reference	1.04 (0.87–1.24)	1.19 (0.98–1.45)	0.743
Model 3					
No. of cases/subjects†	64/942	221/3,728	280/3,789	204/1,964	
HR (95% CI)	1.54 (1.16–2.04)	Reference	1.00 (0.84–1.20)	1.11 (0.90–1.35)	0.609

*Model 1: adjusted for age, race, and sex. Model 2: model 1 + level of education, carotid atherosclerosis, systolic blood pressure, antihypertensive medication, smoking, alcohol intake, BMI, LDL-C, HDL-C, a history of CHD at baseline, and eGFR. Model 3: model 2 + A1C. †Participants with all variables used in model 2.

ticipants who developed diabetes during the first 6 years or censoring participants who self-reported diagnosed diabetes before heart failure during follow-up did not alter the results (data not shown).

Participants with fasting glucose levels of 6.1–6.9 mmol/l but not 5.6–6.0 mmol/l had an increased risk of heart failure as compared with those with glucose levels of 5.0–5.5 mmol/l in model 1 (Table 3). However, the association was greatly attenuated after adjustment for multiple covariates (model 2) and no longer significant when A1C was included in the model (model 3, hazard ratio 1.11 [95% CI, 0.90–1.35]). By contrast, fasting glucose <5.0 mmol/l was associated with higher risk of heart failure as compared with the reference group, even after adjusted for multiple covariates (model 2, hazard ratio 1.51 [1.14–2.00]). This association remained significant even after adjusting for A1C (model 3) or restricting the sample to participants who contribute more than 5 years follow-up time (hazard ratio 1.55 [1.13–2.13]). We repeated the analyses using an average fasting glucose level at visit 1 and visit 2 and obtained similar results (data not shown).

When we compared the quartiles of A1C and fasting glucose in model 2, the highest quartile of A1C (5.7–6.4%) but not fasting glucose (6.0–6.9 mmol/l [108–125 mg/dl]) was associated with heart failure risk as compared with the lowest quartile of A1C (<5.2%) and fasting glucose (<5.3 mmol/l [<95 mg/dl]) (hazard ratio 1.42 [1.13–1.78] and 1.03 [0.84–1.27], respectively). Similar results were observed when we used the second quartile of fasting glucose (5.3–5.6 mmol/l [95–100 mg/dl]) as the reference group (data not shown).

We also examined the joint association of A1C and fasting glucose with heart failure risk (Table 4). A1C 6.0–6.4% compared with 5.0–5.4% was significantly associated with increased risk for heart failure at fasting glucose levels of 5.0–5.5 mmol/l with similar association at other fasting glucose levels. In contrast, the association of elevated fasting glucose with heart failure was not significant at A1C 5.0–5.4%. Similarly, there was no consistent increase in heart failure risk associated with higher fasting glucose at other A1C categories. Although the relative risk associated with higher A1C tended to be larger among participants with low/normal fasting glucose levels as compared with those with elevated fasting glucose levels, the interaction of A1C and fasting glucose categories on heart failure risk was not significant ($P = 0.257$).

Finally, we modeled the association of heart failure risk per 1% unit increase in A1C and examined this association in different subgroups (Fig. 2). Overall, each 1% unit increase in A1C was associated with 39% (95% CI, 13–70%) increased risk of heart failure after adjusted for multiple covariates. These results were largely consistent across the different subpopulations (all *P*s for interaction >0.05).

TABLE 4
Adjusted* HRs (95% CI) for incident HF according to the combination of A1C and fasting glucose categories

Categories of fasting glucose, mmol/l	Categories of A1C, %			
	<5.0	5.0–5.4	5.5–5.9	6.0–6.4
<5.0				
No. of cases/subjects	10/151	29/576	22/212	5/26
HR (95% CI)	1.99 (1.04–3.81)	1.42 (0.94–2.15)	1.75 (1.10–2.79)	3.57 (1.45–8.79)
5.0–5.5				
No. of cases/subjects	15/444	104/2,151	83/1,075	25/131
HR (95% CI)	0.83 (0.49–1.44)	Reference	1.18 (0.88–1.58)	2.19 (1.40–3.43)
5.6–6.0				
No. of cases/subjects	17/288	108/1,736	126/1,499	32/312
HR (95% CI)	1.15 (0.68–1.92)	1.11 (0.85–1.45)	1.16 (0.89–1.51)	1.29 (0.86–1.94)
6.1–6.9				
No. of cases/subjects	3/87	48/615	107/921	49/371
HR (95% CI)	0.62 (0.20–1.96)	1.20 (0.85–1.70)	1.44 (1.09–1.90)	1.38 (0.97–1.96)

*Adjusted for age, race, and sex, level of education, carotid atherosclerosis, systolic blood pressure, antihypertensive medication, smoking, alcohol intake, BMI, LDL-C, HDL-C, a history of CHD at baseline, and eGFR.

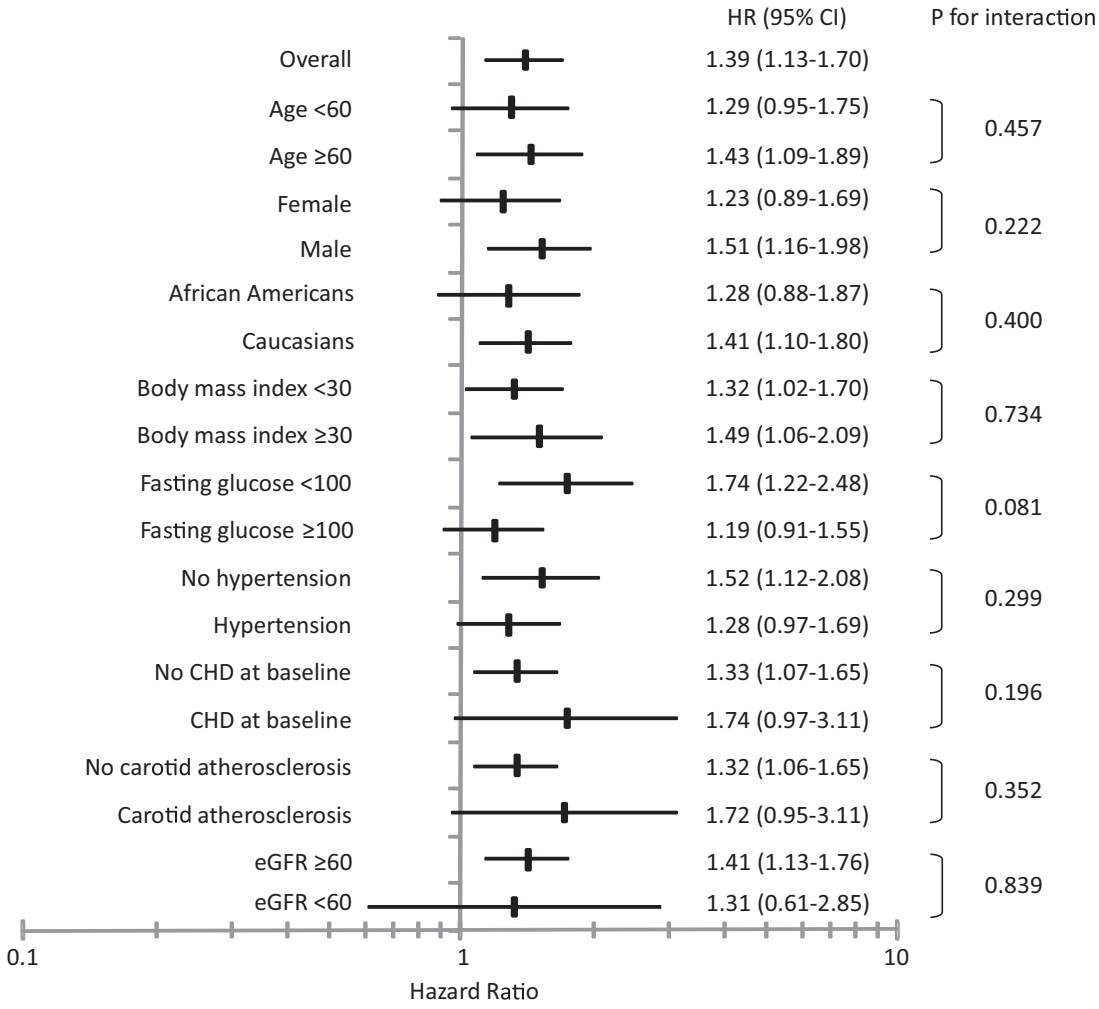

FIG. 2. Hazard ratios (HRs) of heart failure per 1% unit increase in A1C. Hazard ratios overall and within subgroups adjusted for the same covariates as model 2 in Table 2 are shown. Error bars represent 95% CIs. eGFR = estimated glomerular filtration rate.

DISCUSSION

In this community-based population, we found that elevated A1C even in the range under 6.5% was associated with heart failure risk independently of traditional cardiovascular risk factors in middle-aged individuals during a median of 14 years of follow-up. The risk conferred by 1% unit increase in A1C in our study was 39% and was slightly higher than what has been reported in populations of people with diabetes (3–6). This association remained significant even after censoring participants who developed diabetes during median follow-up of 14 years before incident heart failure, suggesting that impaired glucose metabolism even before the development of diabetes is an independent risk factor of heart failure.

Given that the association between A1C and heart failure risk was somewhat attenuated by limiting to heart failure cases without preceding CHD, elevated A1C apparently confers heart failure risk partially through its association with increased CHD risk (22). Several other mechanisms might explain the positive association between A1C and risk of heart failure. People with glucose intolerance may have other comorbidities like hypertension or obesity predisposing to the development of heart failure (23). Hyperinsulinemia may also play a role by stimulating sodium retention and/or activating the sympathetic nervous system (8). Insulin is a known growth factor and may contribute to myocardial dysfunction via increases in cardiac mass (8). However, the association of A1C with risk of heart failure in our study was independent of hypertension, obesity, other traditional cardiovascular risk factors, and insulin concentration, suggesting direct effects of hyperglycemia on the development of heart failure. Indeed, hyperglycemia may harm the heart via oxidative stress (7,24). Increased oxidative stress is associated with cell injury or apoptosis, resulting in decreased cardiac contractile (24). Glucose may also interact with collagen and stimulate the production of advanced glycation end products (25). Advanced glycation end products are hypothesized to induce fibrosis in the heart, leading to myocardial stiffness and diastolic dysfunction (25,26).

Whether lowering A1C via lifestyle modification or medication can reduce the risk of heart failure in nondiabetic populations is an important question. To our knowledge, no study has specifically investigated this issue. Some clinical trials (27,28), but not all (29), demonstrated that interventions with lifestyle modification or glucose-lowering medications may reduce cardiovascular risk in individuals with impaired glucose tolerance. The STOP-NIDDM Trial showed reduced risk of cardiovascular events by an α-glucosidase inhibitor, acarbose, but had few heart failure cases (27). Although an increased risk of

heart failure with rosiglitazone treatment was reported in the DREAM Trial (29), the elevated risk of heart failure may be specific to this pharmacologic agent (30). Further studies are needed to evaluate whether early interventions to prevent glucose intolerance and lower A1C levels might reduce subsequent heart failure risk.

In contrast to the robust independent association of A1C with increased risk of heart failure, fasting glucose was only weakly associated and no longer significant after adjusting for A1C in our study population. This weak association between fasting glucose and incident heart failure in a nondiabetic population is consistent with the previous literature (7,8) and may result from relatively high variability in glucose measurements (9). Superiority of A1C to fasting glucose for disease prediction has also been observed for CHD, stroke, and total mortality (31). Nevertheless, our results suggest that A1C is a better risk marker of heart failure as compared with fasting glucose in a nondiabetic population.

Participants with a fasting glucose <5.0 mmol/l had an increased risk of heart failure compared with individuals with fasting glucose 5.0–5.5 mmol/l in our study. Such a J-shaped association has been observed for all-cause or cardiovascular mortality in some studies (32–34) but not for heart failure (7,8,35). Given that excluding heart failure cases within 5 years of follow-up did not alter our findings, reverse causation is unlikely. There remains the possibility that comorbid conditions associated with both lower glucose concentration and risk of heart failure, e.g., liver dysfunction (36), might account for the observed higher heart failure risk at low serum glucose concentrations.

Several limitations of the present study should be mentioned. First, we evaluated the association of a single measurement of A1C and heart failure. A previous study showed that updated average A1C may predict future heart failure better than a single baseline A1C in patients with diabetes (4). However, in nondiabetic populations, a single A1C measurement is highly reliable (37,38). Second, as with any observational study, we cannot rule out the possibility of residual confounding despite adjustment for all major cardiovascular risk factors. Third, identification of heart failure cases relied entirely on ICD codes abstracted from hospital records and death certificates (6,39). Reliance on hospital discharge codes may underestimate heart failure incidence (40). Finally, because the ARIC Study consists of a middle-aged, bi-ethnic community-based population of the U.S., additional studies are needed in younger populations, the elderly, or other ethnicities.

In conclusion, elevated A1C (≥5.5–6.0%) was more strongly associated with increased risk of heart failure as compared with fasting glucose in a middle-aged bi-ethnic population without diabetes. Our findings suggest that chronic hyperglycemia even before the development of diabetes is an independent risk factor of heart failure and may contribute to the development of heart failure beyond its effect on CHD risk.

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REFERENCES

1. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, Narula J, Shor ES, Young JB, Hong Y, American Heart Association Council on Epidemiology and Prevention, American Heart Association Council on Clinical Cardiology, American Heart Association Council on Cardiovascular Nursing, American Heart Association Council on High Blood Pressure Research, Quality of Care and Outcomes Research Interdisciplinary Working Group, Functional Genomics and Translational Biology Interdisciplinary Working Group. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008; 117:2544–2565
2. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480–486
3. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001;103:2668–2673
4. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
5. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care 2004;27:1879–1884
6. Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, Coresh J. HbA 1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia 2008;51:2197–2204
7. Held C, Gerstein HC, Yusuf S, Zhao F, Hilbrich L, Anderson C, Sleight P, Teo K, ONTARGET/TRANSCEND Investigators: Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation 2007;115:1371–1375
8. Ingelsson E, Sundström J, Arnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005;294:334–341
9. Selvin E, Crainiceanu CM, Brancati FL, Coresh J. Short-term variability in measures of glycemia and implications for the classification of diabetes. Arch Intern Med 2007;167:1545–1551
10. Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, Anfossi G, Costa G, Trovati M. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab 2006;91:813–819
11. Hanefeld M, Koehler C, Schaper F, Fuecker K, Henkel E, Temelkova-Kurktschiev T. Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. Atherosclerosis 1999;144:229–235
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
13. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687–702
14. Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L,

Svärdsudd K. Cardiac and pulmonary causes of dyspnoea–validation of a scoring test for clinical-epidemiological use: the Study of Men Born in 1913. Eur Heart J. 1987;8:1007–1014
15. Wilhelmsen L, Eriksson H, Svardsudd K, Caidahl K. Improving the detection and diagnosis of congestive heart failure. Eur Heart J 1989;10(Suppl. C):13–18
16. Selvin E, Coresh J, Zhu H, Folsom AR, Steffes MW. Measurement of HbA1c from stored whole blood samples in the Atherosclerosis Risk in Communities Study. J Diabetes 2010;2:118–124
17. Selvin E, Coresh J, Jordahl J, Boland L, Steffes MW. Stability of haemoglobin A1c (HbA1c) measurements from frozen whole blood samples stored for over a decade. Diabet Med 2005;22:1726–1730
18. Loganathan R, Bilgen M, Al-Hafez B, Alenezy MD, Smirnova IV. Cardiac dysfunction in the diabetic rat: quantitative evaluation using high resolution magnetic resonance imaging. Cardiovasc Diabetol 2006;5:7
19. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, Heiss G. Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2005; 28:668–674
20. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470
21. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Nephrol 2007;18:1307–1315
22. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med 2005;165:1910–1916
23. Kannel WB, Belanger AJ: Epidemiology of heart failure. Am Heart J. 1991;121:951–957
24. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007; 115:3213–3223
25. Asbun J, Villarreal FJ. The pathogenesis of myocardial fibrosis in the setting of diabetic cardiomyopathy. Journal of the American College of Cardiology 2006;47:693–700
26. Avendano GF, Agarwal RK, Bashey RI, Lyons MM, Soni BJ, Jyothirmayi GN, Regan TJ. Effects of glucose intolerance on myocardial function and collagen-linked glycation. Diabetes 1999;48:1443–1447
27. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003;290:486–494
28. Goldberg RB, Temprosa M, Haffner S, Orchard TJ, Ratner RE, Fowler SE, Mather K, Marcovina S, Saudek C, Matulik MJ, Price D, Diabetes Prevention Program Research Group. Effect of progression from impaired glucose tolerance to diabetes on cardiovascular risk factors and its amelioration by lifestyle and metformin intervention: the Diabetes Prevention Program randomized trial by the Diabetes Prevention Program Research Group. Diabetes Care 2009;32:726–732
29. DREAM Trial Investigators, Dagenais GR, Gerstein HC, Holman R, Budaj A, Escalante A, Hedner T, Keltai M, Lonn E, McFarlane S, McQueen M, Teo K, Sheridan P, Bosch J, Pogue J, Yusuf S. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care 2008;31:1007–1014
30. Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, Feldman L, Vassy J, Wilson R, Bass EB, Brancati FL. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med 2008;168:2070–2080
31. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811
32. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Stern MP, Blair SN. Low fasting plasma glucose level as a predictor of cardiovascular disease and all-cause mortality. Circulation 2000;101:2047–2052
33. DECODE Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care 2003; 26:688–696
34. Wen CP, Cheng TY, Tsai SP, Hsu HL, Wang SL. Increased mortality risks of pre-diabetes (impaired fasting glucose) in Taiwan. Diabetes Care 2005;28: 2756–2761
35. Thrainsdottir IS, Aspelund T, Gudnason V, Malmberg K, Sigurdsson G, Thorgeirsson G, Hardarson T, Rydén L. Increasing glucose levels and BMI predict future heart failure experience from the Reykjavík Study. Eur J Heart Fail 2007;9:1051–1057
36. Møller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut 2008;57:268–278
37. Meigs JB, Nathan DM, Cupples LA, Wilson PW, Singer DE. Tracking of glycated hemoglobin in the original cohort of the Framingham Heart Study. J Clin Epidemiol 1996;49:411–417
38. Lacher DA, Hughes JP, Carroll MD. Estimate of biological variation of laboratory analytes based on the third national health and nutrition examination survey. Clin Chem 2005;51:450–452
39. Manual 3A: Surveillance of Heart Failure Manual of Operations, 2009.v2. The Atherosclerosis Risk in Communities (ARIC), University of North Carolina, Chapel Hill, North Carolina; Available from http://www.cscc.unc.edu/aric/visit/Surveillance_Procedures_-_Heart_Failure.6_3a.pdf
40. Khand AU, Shaw M, Gemmel I, Cleland JG. Do discharge codes underestimate hospitalisation due to heart failure? Validation study of hospital discharge coding for heart failure. Eur J Heart Fail 2005;7:792–797