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HbA_{1c} as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study

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Abstract

Aims/hypothesis—Heart failure (HF) incidence in diabetes in both the presence and absence of CHD is rising. Prospective population-based studies can help describe the relationship between HbA_{1c}, a measure of glycaemia control, and HF risk.

Methods—We studied the incidence of HF hospitalisation or death among 1,827 participants in the Atherosclerosis Risk in Communities (ARIC) study with diabetes and no evidence of HF at baseline. Cox proportional hazard models included age, sex, race, education, health insurance status, alcohol consumption, BMI and WHR, and major CHD risk factors (BP level and medications, LDL- and HDL-cholesterol levels, and smoking).

Results—In this population of persons with diabetes, crude HF incidence rates per 1,000 person-years were lower in the absence of CHD (incidence rate 15.5 for CHD-negative vs 56.4 for CHD-positive, $p<0.001$). The adjusted HR of HF for each 1% higher HbA_{1c} was 1.17 (95% CI 1.11–1.25) for the non-CHD group and 1.20 (95% CI 1.04–1.40) for the CHD group. When the analysis was limited to HF cases which occurred in the absence of prevalent or incident CHD (during follow-up) the adjusted HR remained 1.20 (95% CI 1.11–1.29).

Conclusions/interpretations—These data suggest HbA_{1c} is an independent risk factor for incident HF in persons with diabetes with and without CHD. Long-term clinical trials of tight glycaemic control should quantify the impact of different treatment regimens on HF risk reduction.

Keywords

Diabetes; HbA_{1c}; Heart Failure

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Introduction

Heart failure (HF) affects more than 5 million individuals in the US population and has a yearly incidence of more than 500,000 cases. The burden is magnified in individuals with diabetes, in whom incidence rates are two to five times higher [1]. Clinical trials of tight glycaemic control and cardiovascular events have had mixed results [2,3]. Diabetes-associated HF has been considered as a microvascular complication, but it is very difficult to exclude the confounding impact of associated CHD and its myocardial dysfunction sequelae.

HbA_{1c}, an important measure term of glycaemic control, reflects endogenous glucose levels over the previous 2–3 months [4]. In persons with diabetes, HbA_{1c} is related to the development of microvascular disease and is at the centre of the clinical management of hyperglycaemia [5]. A few previous epidemiological studies have looked at the relationship between HbA_{1c} and HF [3,6,7]. In the present study, we analysed data from the Atherosclerosis Risk in Communities (ARIC) study to investigate the relationship between HbA_{1c} and risk of HF in a community-based sample of persons with diabetes. We hypothesised that HbA_{1c} would be independently associated with HF incidence in persons with diabetes in the community. There is increasing evidence that diabetes results in cardiomyopathy independently of CHD [8]. Therefore, we looked separately at the relationship between glycaemic control and HF by the presence and absence of CHD at baseline and during follow-up.

Methods

Study population and design

The ARIC study is a community-based cohort study of 15,792 people aged 45–64 years at baseline sampled from four US communities [9]. The first clinical examination took place during 1987–1989, with three follow-up visits, one approximately every 3 years. A wealth of information on cardiovascular disease risk factors is available for all participants. Visit 2 (1990–1992) was the only visit for which stored whole blood samples were available for the measurement of HbA_{1c}, and was the baseline visit for the present study. We analysed prospective cohort data from persons with diabetes with follow-up for incident HF through to 1 January 2003. Considering that the incidence of HF could be strongly influenced by prevalent CHD, the study population was divided accordingly. The study was approved by the Institutional Review Boards or all participating institutions and all individuals gave informed consent.

Baseline variables and data collection

Exposure—*HbA1c* Frozen whole blood samples from ARIC Visit 2 were thawed and assayed for HbA_{1c} using HPLC (Tosoh Corporation, Tokyo, Japan). We have previously demonstrated the reliability of measurements from these stored samples [10].

Outcome—*HF* Study participants with evidence of prevalent HF were excluded from analyses. Prevalent HF was assumed if there was evidence of manifest HF stage 3, applying the Gothenburg criteria that require the presence of specific cardiac and pulmonary symptoms as well as medical treatment of HF [11,12].

Incident HF was defined either as death from HF in any position on the death certificate or as the first HF hospitalisation in any position of the hospital discharge list. Hospitalisations were coded as HF (428) using the International Classification of Diseases Code, Ninth Revision (ICD-9), and deaths were coded as HF (428 and I50) using the ICD-9 and ICD-10.

Other variables of interest

Demographics—Age, sex, race (white and African-American), level of education (basic [<12 years of education]; intermediate [12–16 years]; and advanced [>16 years]), health insurance status (present or absent), cigarette smoking status (current, former or never) and alcohol consumption status (current, former or never) information were obtained by a trained interviewer at the baseline visit.

Diabetes—Diabetes was defined as a fasting glucose level of ≥7.0 mmol/L (≥126 mg/dl; reported minimum of 8 h of fasting prior to visit), a non-fasting glucose level of ≥11 mmol/L (≥200 mg/dl), a self-reported physician diagnosis of diabetes, or medical treatment for diabetes at either the first or second ARIC examination.

Prevalent CHD—CHD was defined as a prior myocardial infarction by electrocardiogram, a history of physician-diagnosed myocardial infarction, or a prior coronary reperfusion procedure at either Visit 1 or Visit 2.

Physical measurements—Resting seated systolic BP (SBP) was recorded by certified technicians using a random-zero sphygmomanometer, and included in the analyses as the average of the second and the third of three readings. BMI was calculated as measured weight (kg)/height $(m)^2$. WHR was calculated according to a standardised protocol [9].

Medications—BP and diabetes medication use were verified by the inspection of medication bottles. Use of antihypertensive medication at baseline included the use of α-, β- and calcium channel blockers, ACE inhibitors, diuretics, or a combination thereof.

Laboratory measurements—Fasting blood samples were drawn, frozen, centrifuged and shipped to ARIC study laboratories for analysis. Kidney function was assessed by calculating the estimated GFR using the simplified Modification of Diet in Renal Disease equation [13].

Statistical analyses

Out of 2,099 participants with diabetes, analyses were limited to 1,827 participants after excluding prevalent HF (*n*=204), race other than African-American or white (*n*=4), and missing information on HbA_{1c} (*n*=31) and prevalent CHD (*n*=33).

Demographic and health characteristics by CHD, HF and HbA_{1c} status were compared using χ^2 tests, *t* tests and ANOVA as applicable. Crude HF incidence rates and 95% CIs were calculated using time-to-event methods. The proportion of individuals remaining free of incident HF at any time during follow-up was calculated using the Kaplan–Meier method. For all survival analyses, the follow-up time was defined as the period from entry into the study (Visit 2) to the first HF hospitalisation, death from HF, or up to the time an individual left the study; 1 January 2003 was considered the end of the follow-up if the individuals were free of HF. HbA_{1c} was divided into clinical cut-off points and risk of HF was compared across these categories using Cox proportional hazards models. We compared models with and without adjustment for major HF risk factor, comparing nested models using likelihood ratio tests. We also formally tested for interactions between HbA_{1c} and sex, ethnicity and prevalent CHD. The proportionality assumption of all Cox models was assessed by inspecting the complementary log[−log(survival function)] curves.

We also identified a subgroup of newly diagnosed diabetes patients with elevated blood glucose at baseline without a previous history or use of medications for diabetes, for whom the fully adjusted model was implemented for comparison with the original group.

We performed three sensitivity analyses. First, in the group without prevalent CHD at baseline, we assumed that CHD and HF could act as competing events and censored all participants who developed CHD prior to HF at the date of the CHD event. Essentially, this analysis has as the outcome HF occurring in individuals who have no clinical CHD at the time of first HF hospitalisation or death. Second, we considered the impact of excluding different lag-times (1–5 years) to increased HF risk, for the entire period of follow-up and when we censored all observations at 5 year follow-up. Finally, we ran our models on those participants who were not using any medication at baseline. All analyses were conducted using Stata version 9.2 software [14].

Results

The average follow-up (SD) for the 1,827 individuals with diabetes available for analysis was 9.9 years (3.0). Among our baseline diabetic study population, 48.4% were male, 39.4% were African-American, and the mean age (SD) was 58.0 (5.7) years. Over the course of follow-up, 384 study participants (21.1%) died.

Baseline characteristics

The baseline characteristics of participants by clinical categories of HbA_{1c} (<6%, 6–7%, 7–8% and >8%) are presented in Table 1. For participants without CHD at baseline, higher levels of HbA_{1c} were associated with female sex, African-American race, no health insurance, and higher WHR and LDL- and HDL-cholesterol levels. The proportion of never smokers, former or never drinkers, and the use of antihypertensive and glucose-lowering medications also increased with HbA_{1c} levels. In comparison, for participants with CHD at baseline, there were no clear differences in baseline characteristics, with the exception of race and use of glucose-lowering medications.

Incidence of HF

HF was documented in 328 (17.9%) of the 1,827 participants, with only 15 events (4.5%) being identified from death certificates. The incidence rates for the overall study population and for participants without CHD and with CHD at baseline were 18.1, 15.5 and 56.4 per 1,000 person-years, respectively. The incidence rates according to HbA_{1c} clinical cut-off points and CHD status at baseline are shown in Fig. 1. For participants without CHD at baseline, there was an increase in HF incidence with higher HbA_{1c} levels. The pattern was not as clear among the participants with pre-existing CHD at baseline.

Survival analysis

The cumulative incidence of HF by categories of HbA_{1c} according to clinical cut-points and stratified by status of CHD at baseline is shown in Fig. 2. For those participants without prevalent CHD at baseline, the difference among the cumulative incidence curves are clearly visible after the mean follow-up period of 9.9 years (log-rank test: $p<0.001$). For those participants with prevalent CHD at baseline, the HF risk was higher and the association with baseline HbA_{1c} not significant, with a possible threshold of increased risk at an HbA_{1c} level of 8% (Fig. 2).

Cox proportional hazards analysis with three different models was used to obtain HRs of HF incidence for HbA_{1c} as a continuous and categorical (HbA_{1c} clinical cut-points) variable (Table 2). The basic model including only HbA_{1c} as a continuous variable yielded crude HRs for HF of 1.20 (95% CI 1.13–1.26) for each 1% increase in HbA_{1c} for participants without CHD, and of 1.14 (95% CI 1.00–1.30) for those with CHD at baseline. The association between HbA_{1c} and incident HF was more consistent across CHD groups after adjustment for potential confounders, with HRs in the absence and presence of CHD of 1.17 (95% CI 1.11–1.25) and

1.20 (95% CI 1.04–1.40). HbA_{1c} was also modelled as a categorical variable (clinical cut-points) with similar findings (Table 2). No interaction for sex, ethnicity or CHD at baseline was significant. When the analysis using the fully adjusted model was restricted to the subgroup of new-onset diabetics without CHD where diabetes was diagnosed after the baseline visit, an association between HbA_{1c} and HF could no longer be demonstrated (HR 1.10 [95% CI 0.93–1.32]). This subgroup included 618 participants with 51 events and had a lower mean HbA_{1c} (6.1%, SD 1.5) when compared with those with diagnosed diabetes at baseline (7.0%, SD 2.2).

Incident CHD and HF were considered competing events and the follow-up time of individuals without prevalent CHD at baseline were censored at the time of the new CHD event if it ocurred. In this analysis, which only includes HF events which occur in the absence of CHD, the HR of incident HF per 1% increase in HbA_{1c} remained significant (1.20 [95% CI 1.11–1.29]) (Fig. 3).

Additional analyses showed that estimated GFR was associated with risk of HF [15] but did not confound the associations reported here with HbA_{1c}. There was no difference in the HR of HF associated with higher HbA_{1c} by sex (p=0.73) or prevalent CHD (p=0.47). A lag-time analysis was performed for all the different models. Lag-times from 0 to 5 years did not change the results, with the exception of the recently diagnosed diabetes sensitivity analysis group. In this group, the HRs increased with the increase in the lag-time (1.24 [95% CI 1.01–1.50] with a 4 year lag-time interval). HbA_{1c} was still related to HF risk when the analysis excluded diabetic patients treated with glucose-lowering medication at baseline (1.22 [95% CI 1.10–1.35]), even when limiting the outcome to HF in the absence of both prevalent and incident CHD (1.25 [95% CI 1.10–1.43]).

Discussion

Our findings suggest that HbA_{1c} is an independent risk factor for HF in adults with diabetes regardless of the presence of CHD at baseline or the development of CHD during follow-up. These findings are consistent with previous work by Iribarren et al. [6]. These data provide support for the theory that hyperglycaemia can cause damage to the myocardium.

Our findings are consistent with and extend previous prospective studies in patients with type 2 diabetes [4,6,16–19]. In the observational analysis of the UKPDS [3] study, the HR for HF in newly diagnosed diabetes patients was 1.16 (95% CI 1.03–1.26) per 1% higher updated HbA_{1c}, while baseline HbA_{1c} was not significant (1.00 [95% CI 0.88–1.11]). When we considered only participants with a recent diagnosis of diabetes, HbA_{1c} measured at baseline was also not significantly associated with HF 1.10 (95% CI 0.93–1.32). This could be caused also by the low HbA_{1c} levels seen in the overall study population, which included a large number of individuals with undiagnosed diabetes (two-thirds of those without CHD have HbA_{1c} <7% and >40% have HbA_{1c} <6%). Iribarren et al. [6] found an HR for HF of 1.08 (95% CI 1.05–1.12), using a very similar HF definition to ours. Nichols et al. [7] conducted a nested case–control study of 8,231 Kaiser Permanente Medical Care Program of Northern California Diabetes Registry which includes all members with type 2 diabetes and reported an HR of 1.32 (95% CI 1.23–1.41) per 1% higher updated mean HbA_{1c} for incident HF. The stronger association observed in the latter study may have resulted from the inclusion of outpatients and the use of average HbA_{1c} over a longer period of time (almost 5 years).

Overall, the HbA_{1c}–HF association observed in these previous studies is similar to our results. Other less-sensitive markers such as glycaemia have also been associated with increased risk of HF [20].

One possible problem for establishing a causal relationship between poor glycaemic control and HF could be the lag-time needed for myocardial damage. The amount of time from

exposure to elevated glucose levels to resulting myocardial damage is uncharacterised. We performed a lag-time analysis (from 0 to 5 years) for the non-prevalent CHD participants (total group and those with recently diagnosed diabetes) keeping the total amount of follow-up and limiting the follow-up to 5 years. Our findings showed that for all these analysis, HbA_{1c} remained a marker of increased HF incidence.

We did not adjust for the use of diabetes medications, as any medication use will directly influence HbA_{1c} levels and inclusion of medications in our multivariable analysis may have resulted in overadjustment. Newer oral glucose-lowering medications have been suggested to be a risk factor for incident HF [21], but the use of these medications was extremely low in the ARIC cohort, established more than 20 years ago. As such, this study population provided an opportunity to assess the HbA_{1c}–HF association in the absence of the possible confounding effect of these medications. Analyses limited to participants without CHD at baseline who were not taking diabetes medications did not change our results (1.22 [95% CI 1.10–1.35]). Nonetheless, we cannot rule out some effect of glucose-lowering medications over the entire follow-up.

Other limitations of our study include the lack of cardiac imaging data to detect subclinical myocardial dysfunction, no measures of CHD severity, and the small number of individuals with prevalent CHD (n=159). This study focused on HF hospitalisation or death, which excludes milder events and relies on hospital coding practices [22]. Duration and intensity of treatment of diabetes were not captured. Evaluation risk of clinical outcomes on the basis of a single baseline measurement has inherent limitations but does reflect the common clinical setting, in which the clinician is interested in the interpretation of a single HbA_{1c} value. Our ability to characterise the association of HbA_{1c} level with HF risk was limited by sample size among individuals with CHD.

Our study has a number of strengths. First, the ARIC study has rigorous measurements of cardiovascular risk factors. Second, we were able to exclude prevalent HF cases based on a wide range of criteria, using a highly sensitive definition. Finally, our study sample was from a multi-ethnic, community-based population, contributing to the generalisabilty of these results.

It is likely that higher HbA_{1c} reflects the deleterious effects of chronic hyperglycaemia on the heart muscle, the collective effects of which have been labelled ‘diabetic cardiomyopathy’ [23]. This information supports the recommendations of the American Heart Association/American College of Cardiology guidelines for HF, highlighting the need to identify persons at high risk of developing the syndrome for preventive measures [5].

Our finding that after adjustment for additional HF risk factors such as BP (model 3) the risk associated with HbA_{1c} between 6% and 7% was not significantly elevated over <6.0% is provocative; consistent UKPDS primary analyses did not show a definitive benefit for glycaemic control with respect to cardiovascular endpoints, including HF. The recently published Action to Control Cardiovascular Risk in Diabetes (ACCORD) study terminated the tight glycaemic control arm early because of a small but significant increase in all-cause mortality. No benefit for tight glycaemic control was observed for HF, a secondary endpoint in this trial [24]. Similarly, the ADVANCE trial did not demonstrate any benefit of intensive blood glucose control for HF risk [25]. In the UKPDS and ACCORD trials, it is not possible to separate the effects of tight glucose control from potential adverse effects (with respect to cardiovascular disease) of the drugs used, thus these results do not completely refute the hypothesis that lower HbA_{1c} is advantageous. However, the results may reflect a glycaemic threshold. In other words, it is only in the face of significant hyperglycaemia that diabetic cardiomyopathy predominates as an aetiology of clinical HF, over and above the effects of

hypertension and ischaemic heart disease. In the light of these findings, it seems that keeping the levels of HbA_{1c} according to those recommended by standard guidelines may be beneficial regarding HF incidence.

The American Diabetes Association Clinical Practice Guidelines do not specifically include HF as a complication of diabetes [26]. Diabetic cardiomyopathy remains a controversial issue, as a great part of the increased risk for HF in diabetic patients is attributed to incident CHD. Our data support reduction of HF risk as a potential benefit of improved glycaemic control, provided specific medications do not have harmful effects on myocardial function. Long-term clinical trials of specific glucose-lowering strategies on HF risk in persons with diabetes are needed.

In summary, a single measure of HbA_{1c} is an independent predictor of incident HF hospitalisation or death over the next decade in a community-based cohort of individuals with diabetes, regardless of the presence of CHD at baseline or the development of CHD during follow-up. Since the main results of the UKPDS trial did not show a reduction in macrovascular disease risk and no reduction in HF incidence was found in the ACCORD and ADVANCE trials, there is on-going debate regarding the role of hyperglycaemia in the development of cardiovascular complications [3,24,25]. Accumulating epidemiological evidence suggests that HbA_{1c} may be an important risk factor for cardiac disease. Our results add to this growing literature, supporting the hypothesis that improvements in glycaemic control may also reduce the risk of HF above and beyond any risk reduction for CHD, but optimal treatment strategies and targets remain controversial.

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Abbreviations

ARIC	Atherosclerosis Risk in Communities
HF	heart failure
SBP	systolic BP

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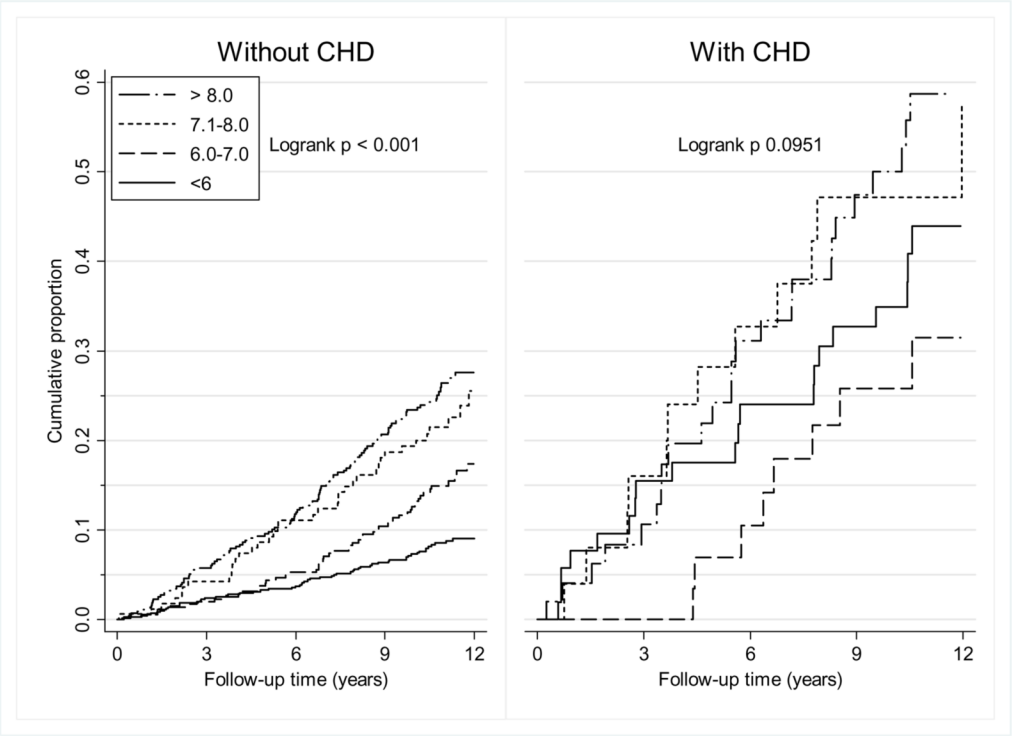

Fig. 1.

Crude incidence rates (95% CI) of HF in the ARIC cohort by baseline HbA_{1c} clinical categories and CHD status at baseline. Left-hand columns, without CHD; right-hand columns, with CHD

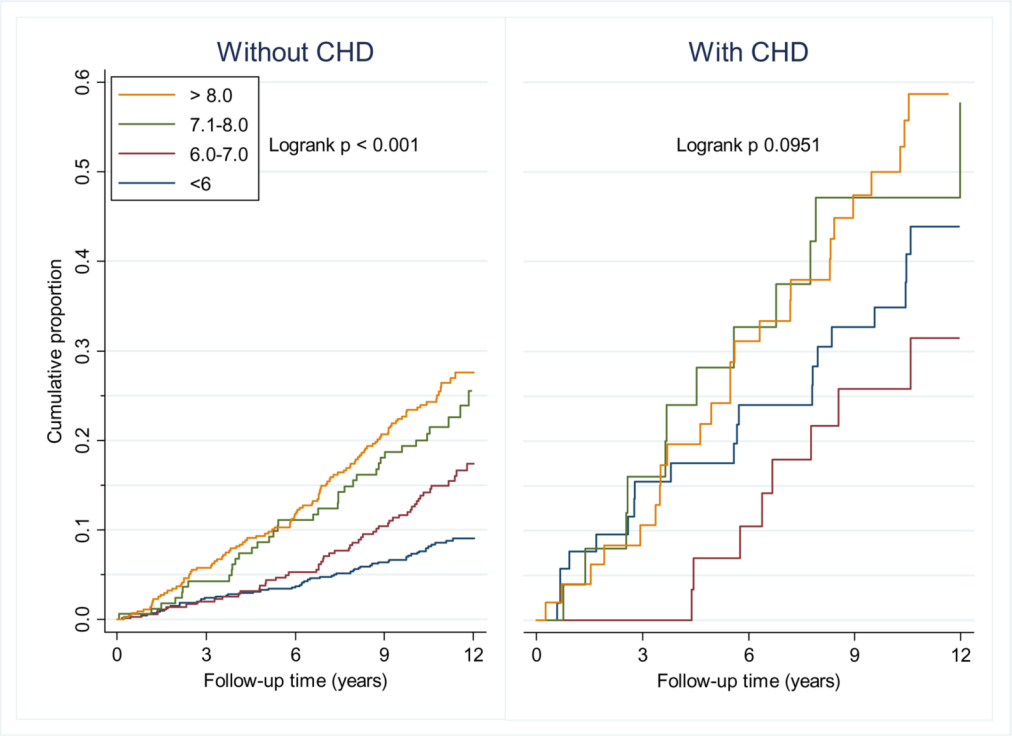

Fig. 2.

Cumulative incidence of HF stratified by HbA_{1c} clinical categories for those without CHD (left-hand graph, *n*=1,668, log-rank *p*<0.001) and with CHD (right-hand graph, *n*=159, log-rank *p*=0.0951) at baseline in our study sample of the ARIC population. Dash-dot lines, HbA_{1c} >8%; short-dashed lines, HbA_{1c} 7.1–8.0%; long-dashed lines, HbA_{1c} 6.0–7.0%; solid lines, HbA_{1c} <6%

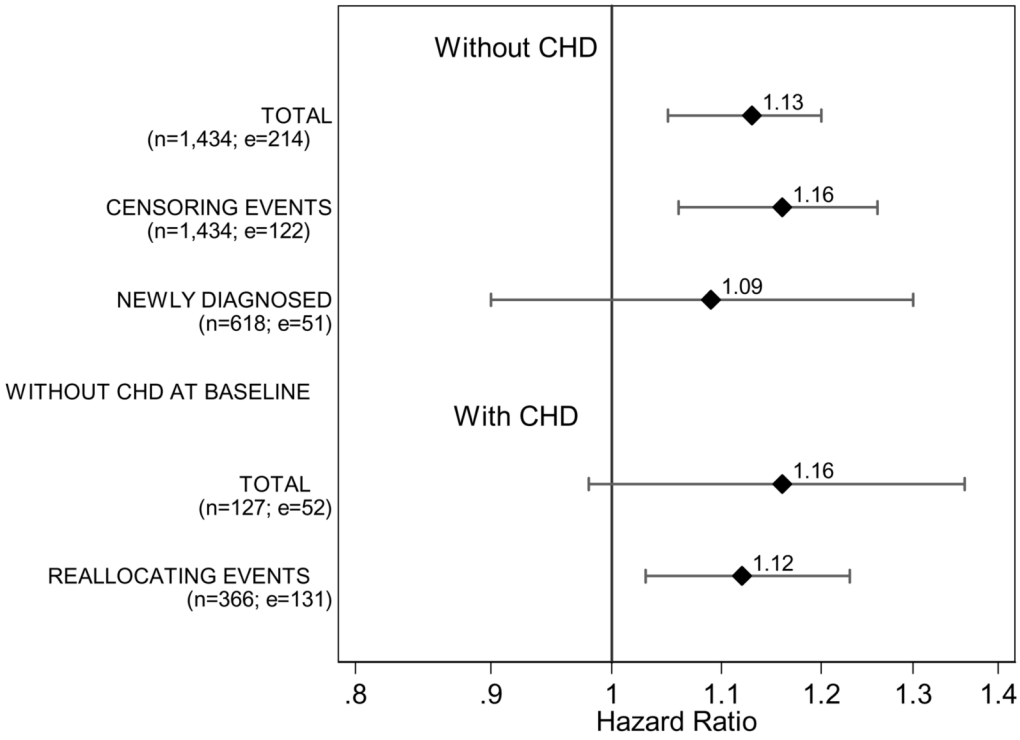

Fig. 3.

Adjusted HRs and 95% CIs (using the full model 3) according to baseline CHD status in participants with diabetes in the ARIC cohort. *n*, number of people; *e*, number of events. Censoring CHD events analysis shows the HR of HF events that occurred prior to any CHD at baseline or during follow-up. Newly diagnosed diabetes analysis limits the analysis to participants with elevated blood glucose without a history of diabetes diagnosis or treatment with diabetes medication. Lag-time analysis limits the events to those occurring only after 2 years of follow-up and limits the follow-up to 5 years of observation

Table 1

Baseline characteristics of the study population by CHD status and HbA_{1c} clinical categories

Characteristic	Without CHD					With CHD				
	HbA_{1c} (%)					HbA_{1c} (%)				
	≤6	6.1–7.0	7.1–08.0	≥8	*p* value for trend	≤6	6.1–7.0	7.1–8.0	≥8	*p* value for trend
n	709	354	166	439		52	32	25	50	
Age (years)	57.8 (5.8)	58.6 (5.8)	58.1 (5.6)	57.5 (5.7)	0.955	59.9 (5)	60.1 (5.5)	60.6 (4.8)	58.6 (5.4)	0.846
Sex (% male)	50.5	46.9	37.3	38.7	<0.001	80.7	90.6	80	74	0.328
Race (% African-American)	30.7	42.3	37.3	59.2	<0.001	19.2	9.4	16	38	0.012
Level of education (%)[a]					0.008					0.275
Basic (<12 years of study)	28.1	33.9	30.1	37.6		21.6	40.6	28.0	30.0	
Intermediate (12–16 years of study)	40.9	37.6	39.7	40.5		51.0	37.5	28.0	44.0	
Advanced (>16 years of study)	30.9	28.5	30.2	21.9		27.4	21.9	44.0	26.0	
Health insurance (%)	89.0	88.1	88.5	79.1	<0.001	96.1	90.6	92.0	92.0	0.753
Cigarette smoking (%)[a]					<0.001					0.101
Current	20.0	18.6	16.3	19.5		23.1	18.7	16.0	8.0	
Former	40.8	36.4	32.1	30.0		51.9	75.0	72.0	72.0	
Never	39.2	45.0	51.6	50.5		25.0	6.3	12.0	20.0	
Alcohol consumption (%)[a]					<0.001					0.622
Current	55.1	37.6	31.4	33.0		50.0	46.9	44.0	38.0	
Former	23.3	30.5	34.3	32.3		34.6	46.9	44.0	42.0	
Never	21.6	31.9	34.3	34.6		15.4	6.2	12.0	20.0	
SBP (mmHg)[a]	122.5 (18.8)	124 (18.9)	123.0 (19.4)	123.8 (19)	0.955	116.2 (16.5)	123.7 (18.7)	122.1 (16.4)	118.9 (18.1)	0.854
BMI (kg/m^2)[a]	30.1 (5.6)	32.6 (6.3)	31.1(6.1)	31.4 (5.8)	0.064	29.6 (4.4)	29.8 (3.3)	31.9 (4.6)	30.9 (4.9)	0.157
WHR[a]	0.95 (0.07)	0.97 (0.06)	0.96 (0.07)	0.97 (0.06)	<0.001	0.98 (0.05)	0.99 (0.04)	0.99 (0.06)	1.00 (0.04)	0.214
Hypertension medication (%)	43.7	53.4	47.6	51.0	0.012	75.0	75.0	72.0	78.0	0.951
Diabetes medication (%)					<0.001					
None	84.6	63.0	28.3	25.7		78.8	40.6	48.0	24.0	<0.001

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Characteristic	Without CHD					With CHD				
	HbA_{1c} (%)					HbA_{1c} (%)				
	≤6	6.1–7.0	7.1–08.0	≥8	*p* value for trend	≤6	6.1–7.0	7.1–8.0	≥8	*p* value for trend
Insulin	5.1	11.6	27.7	32.8		9.6	18.8	32.0	46.0	
Oral	10.3	25.4	44.0	41.5		11.6	40.6	20.0	30.0	
LDL-cholesterol (mmol/l)[a]	3.46 (1.01)	3.51 (0.96)	3.41 (1.15)	3.69 (1.09)	0.014	3.52 (1.06)	3.3 (0.98)	3.68 (0.63)	3.59 (1.02)	0.064
HDL-cholesterol (mmol/l)[a]	1.15 (0.36)	1.09 (0.33)	1.15 (0.41)	1.12 (0.36)	0.06	0.96 (0.31)	0.87 (0.24)	0.97 (0.28)	0.92 (0.23)	0.14

Data are presented as percentages for categorical variables and mean (SD) for continuous variables

[a]Missing variables: level of education (*n*=2); smoking status (*n*=5); alcohol consumption status (*n*=5); BMI (*n*=5); WHR (*n*=3); LDL-cholesterol (*n*= 84); HDL-cholesterol (*n*=57); SBP (*n*=180)

Table 2

Adjusted HRs of HF for HbA_{1c} modelled continuously and for HbA_{1c} clinical categories by CHD status at baseline

HbA_{1c} model	**CHD at baseline**	
	Absent	**Present**
HbA_{1c} (continuous)		
Model 1	1.20 (1.13–1.26)	1.14 (1.00–1.30)
Model 2	1.19 (1.13–1.37)	1.16 (1.01–1.32)
Model 3	1.17 (1.11–1.25)	1.20 (1.04–1.40)
HbA_{1c} by category		
Model 1		
≤6%	Reference	Reference
6.1–7.0%	1.85 (1.24–2.76)	0.67 (0.24–1.86)
7.1–8.0%	2.60 (1.64–4.11)	1.91 (0.86–4.22)
≥8%	3.39 (2.39–4.80)	1.70 (0.87–3.34)
p for trend[a]	<0.001	0.057
Model 2		
≤6%	Reference	Reference
6.1–7.0%	1.70 (1.14–2.54)	0.63 (0.22–1.80)
7.1–8.0%	2.54 (1.60–4.03)	1.88 (0.84–4.20)
≥8%	3.10 (2.16–4.45)	1.75 (0.87–3.51)
p for trend[a]	<0.001	0.042
Model 3		
≤6%	Reference	Reference
6.1–7.0%	1.40 (0.93–2.11)	0.69 (0.22–2.13)
7.1–8.0%	2.36 (1.47–3.77)	2.08 (0.82–5.27)
≥8%	2.65 (1.83–3.84)	2.14 (1.01–4.52)
p value for trend[a]	<0.001	0.018

Values are means (95% CI)

Model 1, unadjusted

Model 2, model 1+age, sex, race, level of education and insurance status

Model 3, model 2+SBP, hypertension medication status, smoking status, alcohol consumption status, BMI, WHR, and LDL- and HDL-cholesterol

[a] *p* value for linear trend across categories