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Dysglycemia and Incident Heart Failure among Blacks: The Jackson Heart Study

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Abstract

Background: We aimed to investigate the associations of glycemic markers (hemoglobin A_{1C} [HbA_{1C}], fasting plasma glucose [FPG] and glycemic status [normoglycemia, prediabetes and diabetes]) with incident heart failure (HF) and its subtypes, among Blacks.

Methods: We included 2,290 community-dwelling Blacks(64% women, mean age 58 years) without prevalent HF from the Jackson Heart Study who attended the second exam (2005–2008). The associations between glycemic markers and incident HF (and subtypes including HF with preserved ejection fraction [HFpEF] and reduced ejection fraction [HFrEF]) were evaluated using Cox proportional hazards regression models, adjusting for risk factors and coronary heart disease.

Results: There were 119 incident HF events (48 HFpEF, 58 HFrEF, and 13 unclassified HF events) over a median follow-up of 10.5 years. Higher levels of HbA_{1C} (HR per SD increment, 1.30; 95% CI 1.12, 1.51) and FPG (HR per SD increment FPG: 1.32; 95% CI: 1.17, 1.48) were associated with a higher risk of incident HF. Compared to normal glycemia, diabetes status

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was associated with a higher risk of incident HF (HR: 1.24; 95%CI: 1.02, 2.05). HbA_{1C} was significantly associated with higher risks of HFpEF (HR per SD increment: 1.41, 95% CI: 1.18, 1.69) and HFrEF (HR per SD increment: 1.32; 95% CI: 1.12, 1.56). FPG was significantly associated with higher risk of HFpEF (HR per SD increment: 1.35, 95% CI: 1.14, 1.62) but not HFrEF (HR per SD increment: 1.12; 95% CI: 0.53, 2.35).

Conclusions: Among community-dwelling Blacks, higher levels of glycemic markers were associated with higher risk of HF subtypes.

Clinical Trials. gov Identifier: NCT00005485) of the Jackson Heart Study.

Keywords

Diabetes; Fasting glucose; Glycosylated hemoglobin; Heart Failure subtypes

INTRODUCTION

Heart failure (HF) and type 2 diabetes are highly prevalent and commonly co-occurring conditions (1,2). Individuals with diabetes are at increased risk of HF compared to those without diabetes (3). One in three HF patients has diabetes (4), and HF is a common complication of diabetes (5). In the US, Blacks are disproportionately affected by both HF and diabetes (1,2). An exploration of the relation of various hyperglycemic markers and HF can be useful to improve our understanding of HF pathogenesis, as well as its control and prevention strategies among Blacks. However, a limited number of studies have comprehensively assessed the relation between glycemic markers and incident HF among Blacks (6,7). These studies have included a limited number of Blacks, and have not examined the whole spectrum of measures of glucose homeostasis, which would capture different aspects of the pathophysiology of diabetes-related cardiac dysfunction. Indeed, several biological mechanisms have been proposed to explain the independent link of hyperglycemia to cardiac dysfunction (8). The variety of mechanisms suggest that the different markers of hyperglycemia (fasting blood glucose [FPG] and glycosylated hemoglobin [HbA_{1C}]) could capture different aspects of the hyperglycemia and HF relation (8). This may be particularly important, given the glucose independent differences in HbA_{1C} observed across ethnicities; with higher levels of HbA_{1C} at similar levels of glycemia in Blacks compared to other ethnic groups (9).

Using the community-based Jackson Heart Study (JHS) cohort, we evaluated the associations of several glycemic markers (FPG, HbA_{1C}, and overall glycemic status) with incident HF hospitalizations, among Blacks.

METHODS

Study sample

The JHS recruited Blacks aged 21 to 94 years, from the Jackson, Mississippi, metropolitan area (10). The JHS study design and methods have been described elsewhere (10). After completing a baseline clinic visit (examination 1 [2000–2004]), participants returned for two additional clinic visits, examination 2 (2005–2008) and examination 3 (2009–2013).

The present study included participants who underwent the examination 2 (n=4,205) because the ascertainment of HF only started at examination 2 (Figure 1). We excluded participants with missing data on HbA_{1C} and FPG (n=1370), prevalent HF (n=50), missing outcome (n=420), and missing data on the covariates to be used in the analyses (n=125).

The study protocol was approved by the institutional review boards of the University of Mississippi Medical Center, Jackson State University and Tugaloo College, all located in Jackson, Mississippi, USA. All the participants provided informed consent.

Markers of Glucose Metabolism

FPG and HbA_{1C} were assessed at examination 2. HbA_{1C} was measured using high-performance liquid chromatography (Tosoh G7, Tosoh Corporation, Tokyo, Japan). The coefficient of variation for HbA_{1C} assay ranged from 1.4% to 1.9%. A National Glycohemoglobin Standardization Program (NGSP)-certified assay was used to measure HbA_{1C}. Fasting plasma glucose was measured using the glucose oxidase method. Glucose assays were run in duplicate; the intra-assay coefficient of variation was <3%.

Diabetes was defined according to the American Diabetes Association (ADA) criteria as a FPG ≥ (126 mg/dL) or HbA_{1C} ≥ 6.5% (11), self-reported of physician-diagnosed diabetes or confirmed use diabetes medications. Prediabetes was defined as a FPG of 100 to 125 mg/dL or HbA_{1C} of 5.7 to 6.4% (11).

Incident Heart Failure Assessment

The primary outcome of interest was incident HF hospitalization. The process of adjudication of HF events in the JHS has been described previously (12). Briefly, HF hospitalizations were identified through annual follow-up telephone interviews and confirmed with HF hospitalization records. The hospital discharge lists with relevant International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes were obtained from Jackson, Mississippi tri-county area hospitals and out of catchment area hospitals. The formal physician-adjudicated diagnosis of HF hospitalization begun in January 2005 and included probable or definite HF hospitalization. The medical records that include ICD-9-CM codes for primary diagnoses of HF were reviewed, and an adjudication through examination of clinical documentation including presenting signs and symptoms, laboratory tests and imaging (echocardiography and magnetic resonance imaging). The adjudication of HFpEF versus HFrEF was conducted in the subset of subset of individuals with available hospitalization data on cardiac imaging (echocardiogram or other cardiac imaging such as cardiac magnetic resonance imaging). HFpEF was defined as a HF event with an ejection fraction ≥50% (12).. The evaluation of adjudicated incident HF events was performed through December 31, 2015.

Covariates

The covariates, including demographic and behavioral characteristics, as well as medical history and medication use, were assessed at examination 2. The methods of risk factor ascertainment in JHS have been reported elsewhere (10).

Information on personal medical and family history, medication use, income, physical activity, alcohol use (within the past 12 months), and current smoking was obtained using standardized questionnaires.

Height, and weight were measured and body mass index (BMI) was calculated (kg/m^2). Blood pressure (BP) was measured twice in the left arm of the seated subject with a mercury column sphygmomanometer. The average of the two readings was used as the examination BP, and hypertension was defined as systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg, or self-reported antihypertensive medication use. Serum creatinine was measured using the rate Jaffe reaction, and the kidney function was assessed using the estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI study equation (13). Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides concentrations were measured using standard enzymatic methods, on a Vitros 950 or 250, Ortho-Clinical Diagnostics analyzer (Raritan, NJ) in accordance with the College of American Pathologists Proficiency Testing Program.(14) Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation (which was not used for individuals with triglycerides levels ≥400 mg/dL) (15).

Statistical Analysis

We classified participants into clinically relevant categories of HbA_{1C} (<5.7%; 5.7 % to 6.4% and ≥ 6.5%) and compared differences in baseline characteristics of participants' variables across HbA_{1C} groups, using ANOVA (for continuous variables) or the Chi square test (for categorical variables). We also assessed the baseline characteristics of participants by glycemic categories (defined by FPG alone, or FPG and HbA_{1C} concomitantly).

Crude HF incidence rates and 95% confidence intervals were calculated by exposure levels (clinically relevant categories of FPG and $HbA_{1C}$and diabetes status). The person-time of follow up from baseline (examination 2) until the first occurrence of a) HF outcomes b) death or c) censoring (date of the last available follow-up). Heart failure-free survivor curves were plotted using the Kaplan–Meier method, and differences between event-free survivor probabilities between the different categories of HbA_{1C} were compared using the log-rank test. For the multivariable analyses, we fitted Cox proportional hazards regression models to relate each glycemic marker to incident HF, after verification of the assumption of proportionality of hazards tested using Schoenfeld residuals and the plots of these residuals over time. We modelled each glycemic marker both as a continuous and categorical variable using the relevant categories.

For each glycemic marker, identical covariates in models. These variables included age, sex, smoking, alcohol use, physical activity, body mass index, ratio of total to HDL-cholesterol, systolic blood pressure, use of antihypertensive medications, use of statins, eGFR, and CHD (time-varying covariate).

For the HFpEF and HFrEF separate analyses, we used cause-specific Cox proportional hazards models, treating the other type of HF as a censoring event.

Two-sided *P* values of <0.05 were considered statistically significant, including for interaction terms. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Source of funding

The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Minority Health and Health Disparities (NIMHD). The funding agencies had no role in the formulation, editing, or decision to submit this manuscript. Justin Echouffo Tcheugui was supported by NIH/NHLBI grant K23 HL153774. Robert J. Mentz was supported by the National Institutes of Health (U01HL125511–01A1 and R01AG045551–01A1). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

RESULTS

Study Sample

The final study population included 2,290 participants (63.7 % women, mean age 58 years). Table 1 summarizes the baseline characteristics of participants by categories of HbA_{1C}. Compared to the lowest HbA_{1C} category, individuals with higher HbA_{1C} were older, had higher FPG levels, systolic blood pressure, and body mass index, but had worse renal function, and were more likely to have an atherogenic lipid profile and less likely to be active. In additional analysis, the distributions of the characteristics of participants were examined by categories of FPG alone, FPG and HbA_{1C} (Supplementary Tables 2, 3, **4** &**5**). The distributions of the characteristics of participants were roughly similar across levels of worsening glycemia using samples defined by categories of FPG alone, FPG and HbA_{1C}.

The comparison of the characteristics of the included and excluded participants is detailed in Supplementary Table 1. Given the difference between the included and excluded participants, we performed sensitivity analyses to test for potential bias. We estimated propensity scores using logistic regression and the distribution are summarized in Supplementary Figure 1. In addition, to account for missingness and thus minimize bias, we converted the scores into inverse probability weighting and included it in the Cox proportional hazard regression models, using previously described approaches. (16) We observed that the including of weights to account for missingness had no effect on our effect estimates, suggesting that our inclusion-exclusion criteria did not introduce bias.

Associations of Glycemic Markers and Incident Heart Failure

Over a median follow-up of 10.5 years, there were 119 incident HF events observed (48 HFpEF events, 58 HFrEF events, and 13 unclassified HF events). The overall incidence rate of HF was 5.17 (4.32, 6.19) per 1,000 person-years.

The incidence rate of HF increased across levels of HbA_{1C}, FPG, glycemic categories (as defined by both FPG and HbA_{1C}) (Table 2). Indeed, the incidence rate for HF among individuals with diabetes was at least a 3-fold higher than that of individuals without diabetes (Table 2).

Compared to the lowest clinically relevant category, individuals in the highest levels of HbA_{1C} or FPG exhibited at least a three-time higher incidence rates of HF events (Table 2&Figure 2, *P*-log rank <0.001 for both HbA_{1C} and FPG).

In multivariable adjusted Cox proportional hazards (Table 3), compared to the referent HbA_{1C} category (<5.7%), higher levels of HbA1c (≥ 6.5%) were associated with incident HF (hazard ratio [HR] 1.65; 95% confidence interval [CI]: 1.03, 2.62). When modeled as a continuous predictor, HbA_{1C} was also associated with greater risk of heart failure (HR per SD increment in HbA_{1C}: 1.30; 95% CI 1.12, 1.51) (Table 3).

Higher levels of FPG (>125 mg/dL) as compared to lower levels (<100 mg/dL), were associated with an increased risk of incident HF (HR, 1.92; 95% CI: 1.20, 3.08). When fitted as a continuous variable, FPG was associated with a higher risk of incident HF (HR per SD increment in FPG: 1.32; 95% CI: 1.17, 1.48, Table 3).

Having diabetes (as defined by both HbA_{1C} and FPG) was associated with incident HF (HR: 1.24; 95% CI: 1.02, 2.05), compared to no-diabetes (Table 3). Prediabetes as not associated with incident HF.

Additionally accounting for the use of medications such angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers did not affect our results in terms of overall HF (Supplementary Table 6).

The incidence rates of HFpEF and HFrEF were higher with increasing glycemia (Supplementary Tables 7 & 9). Higher levels of HbA_{1C} were associated with higher relative risks of HFpEF (HR for each SD change in HbA_{1C}: 1.41, 95%CI: 1.18, 1.69) and HFrEF (HR for each SD change in HbA_{1C}: 1.32, 95% CI: 1.12, 1.56]) (Supplementary Tables 8 & 10). FPG was significantly associated with higher risk of HFpEF (HR per SD increment: 1.35, 95% CI: 1.14, 1.62) but not significantly HFrEF (HR per SD increment: 1.12; 95% CI: 0.53, 2.35). Diabetes status was not significantly associated with higher relative risks of HFpEF and HFrEF (Supplementary Tables 8 & 10).

DISCUSSION

In a community-based sample of Blacks, we found that increasing levels of HbA_{1C} and FPG, as well as the diabetes status (as defined by a combination of HbA_{1C} and FPG) were independently associated with a higher risk incident HF hospitalization. HbA_{1C} was significantly associated with higher risks of both HFpEF and HFrEF, and to a similar extent. FPG was associated with a higher risk of both HFpEF.

Our observations provide additional insights into the relation of dysglycemia and HF. Several studies have reported on the association of glycemic markers or hyperglycemia

status and incident HF, but have these included a limited number of participants of African descent both (3). These studies have reported relative risk for the diabetes and HF association of similar magnitude to that reported in our investigation (3).The prior studies have generally focused on HbA_{1C} (6,7), other on FPG and others on both (3), showing positive association of these markers with incident HF (7,17,18). Other studies of HbA_{1C} have focused on individuals with diabetes only (6,19). There is a paucity of studies on the relation of glycemia with the subtypes of HF (20). The extant studies of HF subtypes have shown that diabetes status is associated with both HFpEF and HFrEF, in similar fashion (20), but have not estimated the individual associations with FPG HbA_{1C} or, and have not accounted for HbA_{1C} in their definition of diabetes. Our observations extend the literature on this topic, by providing additional evidence on the association between glycemic markers and the future risk of incident HF, as well as it subtypes. Our study attempts to capture the whole spectrum of dysglycemia (including prediabetes and diabetes), as well as the various pathways representing the metabolic milieu associated with dysglycemia that contribute to cardiac dysfunction, as possibly captured by various glycemic markers. These pathways include glucotoxicity, lipotoxicity, and hyperinsulinemia (captured by FPG but also by HbA_{1C}), or increased tissue glycation leading to fibrosis (captured by HbA_{1C}) (8). Our finding of a lack of a significant association between the diabetes status and HF subtypes (HFpEF or HFrEF) may be due to a lack of power. Futhermore, the observed significant association of HbA_{1C} with HF suggests that the diabetes status is not the only determinant of HF, and confirms that the extent of blood glucose control matters (19).

Our study suggests that although HbA_{1C} may differ by racial/ethnic groups, its has a important prognostic value among Blacks in terms of HF. Our study highlight diabetes as a high-risk condition that should be the focus of HF preventive efforts among Blacks, who are disproportionally affected by both diabetes and HF compared to other racial/ethnic groups in the US (1,2). Such a preventative approach can combine lifestyle changes and the use of of novel diabetes therapies wih a cardiovascular benefit such as sodium-glucose co-transporter-2 (SGLT-2) inhibitors showing improved HF outcomes among individuals with diabetes in clinical trials including those with HFrEF (21,22) and those with HFpEF. (23,24). This importance is recognized in contemporary guidelines that recommend the use of specific therapies in the context of HF and diabetes, to optimize management (25,26).

In a hypothesis-generating study, we studied the association of HF with several glycemic biomarkers, namely FPG and HbA_{1C}, which may all represent distinct biological pathways that would contribute to HF occurrence. Data from labaratory-based studies suggest the potential pathways through which hyperglycemia leads to HF include among others : i) increased concentration of advanced glycation end products (AGEs) may promote myocardial collagen deposition and fibrosis; ii) hyperglycemia-related oxidative stress may induce myocardial injury and fibrosis; iii) mitochondrial dysfunction and autonomic perturbations related to diabetes may also contribute to myocardial dysfunction and iv) hyperinsulinemia related to insulin resistance (8). While laboratory-based studies suggest distinct pathways by which diabetes leads to HFpEF (27), we did not find significant differences in the risk of HFpEF and HFrEF related to hyperglycemia.

Some limitations of our study should be acknowledged. First, the participants were Blacks from Jackson in Mississippi; thus, our results may not be generalizable to Blacks elsewhere in the US and to other racial/ethnic groups. Second, we did not have data on 2 hour-post load glucose levels, and thus we may have underestimated the effect of diabetes on HF risk. Third, the ascertainment of the incidence of HF relied solely on hospitalizations, and did not include outpatient HF cases, which may have led to an underestimation of cases of HF in the community. Fourth, we may have been underpowered to examine the association with the HF subtypes, as evidenced by the low event rates for each subtype. Lastly, because of the observational nature of our analysis, the study findings may be predisposed to residual confounding.

The strengths of this study include a well-characterized community-based sample of Blacks, the availability of several glycemic markers, the examination of various HF subtypes, a rigorous adjustment that included accounting for CHD as time-varying covariates in our analyses.

CONCLUSION

In conclusion, in a community-based sample of Blacks adults, high levels of several glycemic markers were associated with an increased risk of incident HF. These results suggest that the link to abnormal glucose metabolism could represent the combined influence of different biological pathways leading to heart failure. Overall, our findings are of contemporary significance given the rising burden of HF among patients with diabetes in the United States, especially among Blacks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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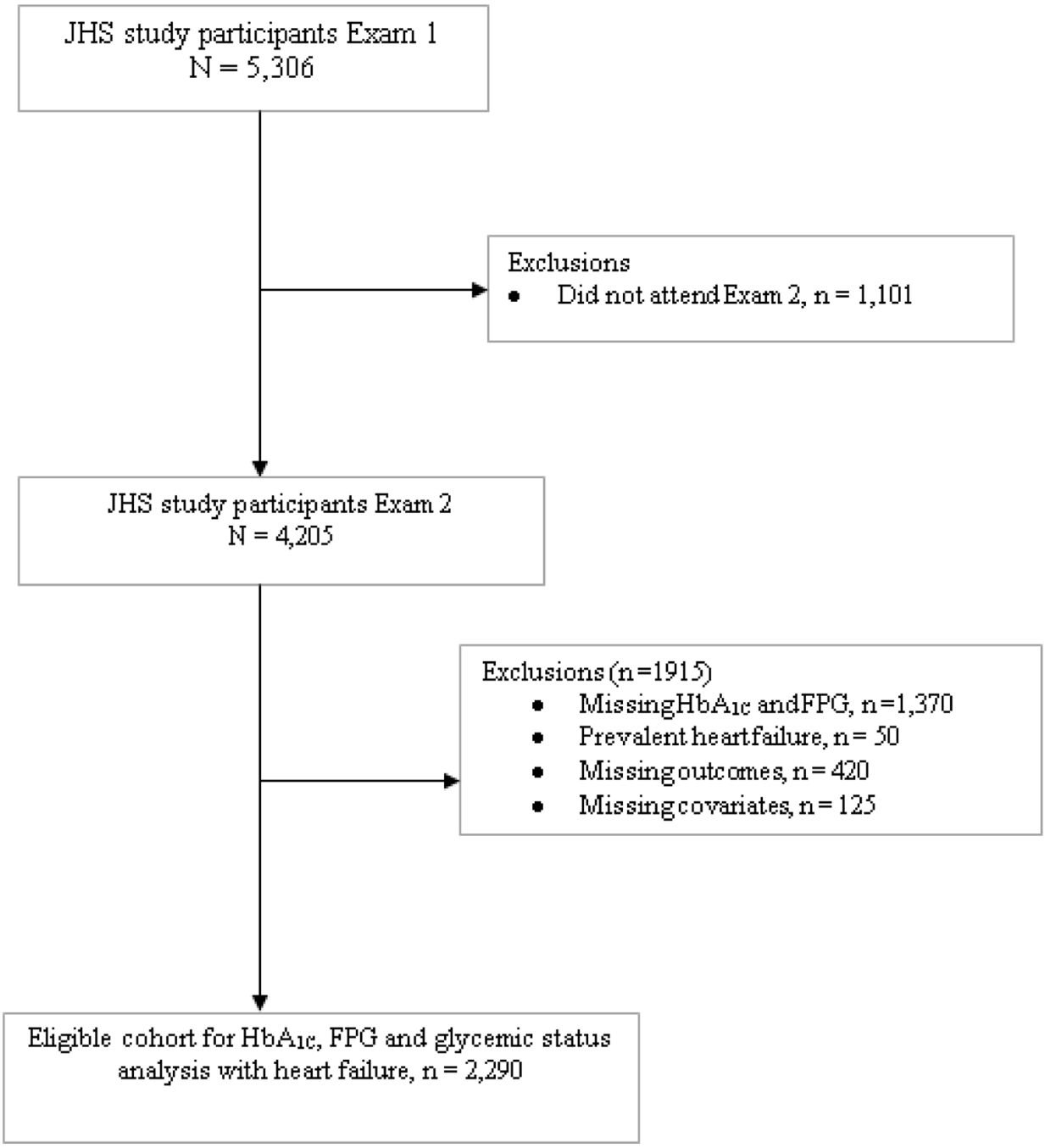

Figure 1:
Process of selecting eligible participants for the analyses

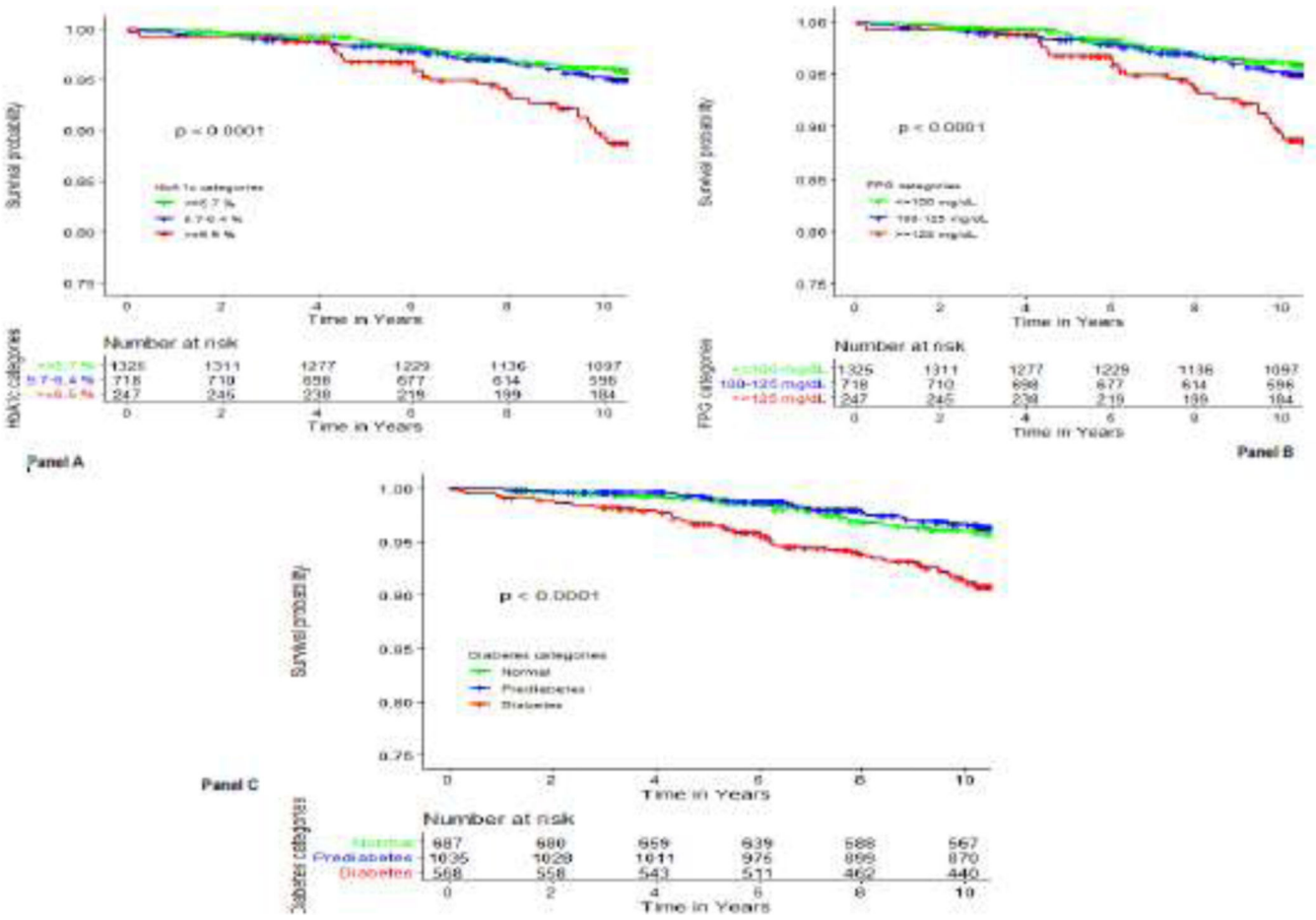

Figure 2:

Survival plot comparing the risk of heart failure hospitalization across levels of glycemic markers.

Panel A: by levels of glycosylated hemoglobin (HbA_{1C}), Panel B: by levels of by levels of fasting plasma glucose (FPG), Panel C: by glycemic status categories

Table 1:

Characteristics of Jackson Heart Study participants by categories of glycated hemoglobin at Examination2

	Glycated hemoglobin (HbA_{1C}) categories				
Characteristics	**Total (N=2,290)**	**<5.7 % (N=1050)**	**5.7 – 6.4 % (N = 834)**	**≥6.5 % (N = 406)**	***P-value***
Age, years	57 (12)	54.7 + 0.36	58.7 + 0.40	60.6 + 0.58	*<.0001*
Male, n (%)	830 (36.2)	395 (37.6)	288 (34.5)	147 (36.2)	*0.3835*
Low income status, n (%)	250 (11.0)	108 (10.3)	92 (11.0)	45 (11.1)	
Current Smokers, n (%)	225 (9.8)	91 (8.7)	100 (12.0)	34 (8.4)	*0.0307*
Physical Activity categories:					
Low	1021 (44.5)	420 (40.0)	390 (46.8)	211 (52.0)	*<0.0001*
Moderate	771 (33.7)	362 (34.5)	279 (33.5))	130 (32.0)	
Ideal	498 (21.8)	268 (25.5)	165 (19.8)	65 (16.0)	
Body mass index, kg/m^2	31.9 (6.9)	30.5 + 0.21	32.2 + 0.23	34.7 + 0.33	*<.0001*
Obese (BMI>30 kg/m^2), n (%)	1252 (54.7)	474 (45.1)	484 (58.0)	294 (72.4)	*<.0001*
Fasting plasma glucose (FPG), mg/dL		93.3 + 0.78	99.9 + 0.88	144.3 + 1.26	*<.0001*
Hemoglobin A_{1C}, %		5.4 + 0.02	6.0 + 0.02	7.6 + 0.03	*<.0001*
FPG <100 mg/dL	1325 (57.9)	842 (80.2)	445 (53.4)	155 (9.4)	*<.0001*
FPG: 100 – 125 mg/dL	718 (31.4)	200 (19.0)	363 (43.5)	155 (38.2)	
FPG: >126 mg/dL	247(10.8)	8 (0.8)	26 (3.1)	213 (52.5)	
Diabetes, n (%)	568 (24.8)	51 (4.9)	111 (13.3)	406 (100.0)	*<.0001*
Systolic blood pressure, mmHg	127 (19)	125.4 + 0.57	126.9 + 0.64	131.5 + 0.92	*<.0001*
Diastolic blood pressure, mmHg	75 (10)	75.1 + 0.31	74.0 + 0.35	74.3 + 0.50	*<.0.06*
Hypertension, n (%)	1502 (65.6)	578 (55.0)	588 (70.2)	336 (82.8)	*<.0001*
Antihypertensive medications, n (%)	127 (19)	528 (50.3)	544 (65.2)	336 (82.8)	*<.0001*
Total cholesterol, mg/dL	197 (41)	196.5 + 1.25	200.2 + 1.41	191.2 + 2.02	*0.005*
HDL-cholesterol, mg/dL	54.2 (15.1)	55.5 + 0.46	53.9 + 0.52	51.2 + 0.75	*<.0001*
Total to HDL-cholesterol ratio	123.0 (36.8)	3.75 + 0.04	3.94 + 0.04	3.96 + 0.06	*0.0004*
LDL -cholesterol, mg/dL	3.86 (1.21)	123.2 + 1.13	126 + 1.27	116.9 + 1.85	*0.0003*
eGFR, mL/min/1.73 m^2	97.2 (19.7)	99.6 + 0.61	95.3 + 0.68	95.2 + 0.97	*0.011*
Prevalent CHD, n (%)	88 (3.8)	23 (2.2)	40 (4.8)	25 (6.2)	*0.0004*

Values are reported as mean ± SD for continuous traits and n (%) for dichotomous traits. BP: blood pressure, CHD: coronary heart disease, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein

Table 2:

Event Rates of Incident of Heart Failure Rates among Jackson Heart Study Participants

	Cases/No. at Risk	1000-Person Years	Event Rates (per 1000 Person-Years)
Glycated hemoglobin (HbA_{1C})			
≤5.7 %	40/1050	10591	3.8 (2.77, 5.15)
5.7 – 6.4 %	36/834	8447	4.26 (3.07, 5.91)
≥ 6.4 %	43/406	3972	10.8 (8.03, 14.6)
Pooled	119/2290	23012	5.17 (4.32, 6.19)
Fasting Plasma Glucose (mg/dL)			
<100 mg/dL	54/1325	13334	4.05 (3.1, 5.29)
100–125 mg/dL	35/718	7273	4.81 (3.46, 6.70)
≥ 125 mg/dL	30/247	2404	12.5 (8.72, 17.8)
Pooled	119/2290	19945	5.17 (4.32, 6.19)
Hyperglycemia status			
Normal	27/687	6903	3.91 (2.68, 5.70)
Pre-diabetes	39/1035	10538	3.70 (2.70, 5.06)
Diabetes	53/568	5569	9.52 (7.27, 12.50)
Pooled	119/2290	21587	5.17 (4.32, 6.19))

Table 3:

Estimates of the Multivariable Adjusted Association of glycemic markers and incident heart failure

	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	*P-value*
Glycated hemoglobin (HbA_{1C})			
≤5.7 %	1 (Reference)	1 (Reference)	
5.7 – 6.4 %	1.12 (0.72, 1.77)	0.84 (0.52, 1.33)	0.45
≥ 6.5 %	2.90 (1.88, 4.45)	1.65 (1.03, 2.62)	0.0355
1 SD increment of HbA_{1C}	1.38 (1.24, 1.52)	1.30 (1.12, 1.51)	*0.0007*
Fasting Plasma Glucose (mg/dL)			
<100 mg/dL	1 (Reference)	1 (Reference)	
100–125 mg/dL	1.19 (0.78, 1.81)	0.81 (0.51, 1.26)	0.34
≥ 125 mg/dL	3.13 (2.00, 4.89)	1.92 (1.20, 3.08)	0.0070
1-SD increment of fasting Glucose	1.29 (1.17, 1.42)	1.32 (1.17, 1.48)	<0.0001
Hyperglycemia status (defined by both fasting plasma glucose and HbA_{1C})			
Normal	1 (Reference)	1 (Reference)	
Pre-diabetes	0.96 (0.58, 1.57)	0.68 (0.41, 1.13)	0.14
Diabetes	2.36 (2.03, 3.79)	1.24 (1.02, 2.05)	0.03

Values are hazard ratios (95% confidence interval [CI]) and *P* values. The hazard ratios are adjusted for age, sex, smoking, income, alcohol use, physical activity, body mass index, ratio of total to HDL-cholesterol, systolic blood pressure, use of antihypertensive medications, use of statins, eGFR, and CHD (time-varying covariate).