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Glycemic Status and Incident Heart Failure in Elderly without History of Diabetes Mellitus: The Health, Aging, and Body Composition Study

Andreas Kalogeropoulos, MD¹, Vasiliki Georgiopolou, MD¹, Tamara B. Harris, MD MPH², Stephen B. Kritchevsky, PhD³, Douglas C. Bauer, MD⁴, Andrew L. Smith, MD¹, Elsa Strotmeyer, PhD MPH⁵, Anne B. Newman, MD MPH⁵, Peter WF Wilson, MD¹, Bruce M. Psaty, MD PhD⁶, and Javed Butler, MD MPH¹ for the Health ABC Study

¹Emory University, Atlanta GA

²National Institute of Aging, National Institutes of Health, Bethesda MD

³Wake Forest University, Winston Salem SC

⁴University of California San Francisco, San Francisco CA

⁵University of Pittsburgh, Pittsburgh PA

⁶University of Washington, Seattle WA

Abstract

Background—It is unclear whether measures of glycemic status beyond fasting glucose (FG) levels improve incident heart failure (HF) prediction in patients without history of diabetes mellitus (DM).

Methods and Results—The association of measures of glycemic status at baseline (including FG, oral glucose tolerance testing [OGTT], fasting insulin, hemoglobin A_{1c} [HbA_{1c}] levels, and homeostasis model assessment of insulin resistance [HOMA-IR] and insulin secretion [HOMA-B]) with incident HF, defined as hospitalization for new onset HF, was evaluated in 2386 elderly participants without history of DM enrolled in the Health ABC Study (median age 73 years; 47.6% men; 62.5% white, 37.5% black) using Cox models. After a median follow-up of 7.2 years, 185 (7.8%) participants developed HF. Incident HF rate per was 10.7 cases per 1000 person-years with FG <100mg/dL, 13.1 with FG 100–125mg/dL, and 26.6 with FG ≥126mg/dL (P=.002; P=.003 for trend). In adjusted models (for body mass index, age, history of coronary artery disease and smoking, left ventricular hypertrophy, systolic blood pressure and heart rate, and creatinine and albumin levels), FG was the strongest predictor of incident HF (adjusted HR per 10mg/dL, 1.10; 95% CI, 1.02–1.18; P=.009); the addition of OGTT, fasting insulin, HbA_{1c}, HOMA-IR or HOMA-B did not improve HF prediction. Results were similar across race and gender. When only HF with left ventricular ejection fraction (LVEF) ≤40% was considered (n=69), FG showed a strong association in adjusted models (HR per 10mg/dL, 1.15; 95% CI, 1.03–1.29; P=.01). In comparison, when only

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Address correspondence to: Javed Butler, MD MPH, Cardiology Division, Emory University Hospital, 1365 Clifton Road, NE, Suite AT430, Atlanta, GA 30322. Telephone #: (404) 778-5273. Fax #: (404) 778-5285. javed.butler@emory.edu.

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HF with LVEF >40%, was considered (n=71), the association was weaker (HR per 10mg/dL, 1.05; 95% CI; 0.94–1.18; P=.41).

Conclusions—Fasting glucose is a strong predictor of HF risk in elderly without history of DM. Other glycemic measures provide no incremental prediction information.

Keywords (MeSH)

Heart Failure; Elderly; Glucose Metabolism Disorders

Insulin resistance (IR) and related glycemic abnormalities including type 2 diabetes mellitus (DM) have been associated with risk for heart failure (HF).^{1–3} This risk is not entirely explained by the association of glycemic abnormalities with hypertension and dyslipidemia and the ensuing coronary heart disease (CHD) risk.^{1, 4, 5} These metabolic alterations have been associated with non-ischemic HF, and insulin-resistant cardiomyopathy has been described in the literature.⁶ The definitions and categorization of glycemic abnormalities have evolved over time and differences in classification of the various glycemic states exist.^{7–9} Also, it has been suggested that elevated fasting glucose is primarily related to defective insulin secretion whereas impaired two-hour blood glucose level measured by the oral glucose tolerance test (OGTT) is related to IR.¹⁰ Consequently, post-challenge hyperglycemia may relate more strongly than fasting hyperglycemia with cardiovascular outcomes.¹¹ Also, recent data suggest that these categorical definitions might not entirely capture the predictive information conferred by abnormalities of glucose metabolism for HF risk and assessments based on continuous measures may be preferable.^{12, 13} Lastly, other markers of IR beyond serum glucose levels e.g. insulin levels or hemoglobin A_{1c} (HbA_{1c}) have also been shown to predict HF development in patients with DM.^{1, 14}

Increased risk of cardiovascular diseases including HF in patients with DM is undisputed.¹⁵ However, with the increasing obesity and metabolic syndrome prevalence in the United States, many patients without a clinical diagnosis of DM may have IR and may be rendered at risk for HF.¹⁶ It is not clear whether OGTT, fasting insulin levels, or HbA_{1c} have superior or additive predictive value compared to simple fasting glucose levels for HF prediction in patients without history of DM.² Similarly, the importance of assessing IR or β cell function indices versus simple serum glucose levels in this respect is not known. Importantly, none of the previous studies has addressed the possible impact of sex and race on the predictive properties of these markers for incident HF prediction. In this study we sought to assess the predictive value of the different definitions and measures of glycemic and insulin status on incident HF risk. In addition, we sought to assess the value of such markers across sex- and race-based subgroups among the participants of the Health ABC Study.

METHODS

Study Population

The Health ABC Study is a population-based study of 3075 well-functioning, community-dwelling men and women aged 70 to 79 years at inception. Participants were identified from a random sample of white Medicare beneficiaries and all age-eligible black residents in designated zip codes areas surrounding Pittsburgh and Memphis. To be eligible, participants had to report no difficulty in walking one-quarter mile or climbing 10 stairs without resting. Exclusion criteria included difficulties with daily activities, cognitive impairment, inability to communicate, intention of moving within 3 years, or participation in a trial involving a life-style intervention. The institutional review boards at both sites approved the protocol.

Of the 3075 participants, 689 were excluded from this study [95 had definite or possible HF at baseline, 46 had missing data on HF status, 117 had incomplete data to define glycemic status (missing information on DM history or medications in 12, fasting glucose not available or patient not fasted in 66, and OGTT not performed or patient not fasted in 39), and 431 participants had history of DM). The final cohort for this study included 2386 participants.

Baseline Definitions

Baseline data were collected in 1997–1998. Cardiovascular disease status at baseline was based on ICD 9-CM codes as reported by Medicare and Medicaid Services for the years 1995–1998; self-reported history; and use of selected medications. Prevalent HF status at baseline was defined on the basis of history of HF and medications. Heart failure was considered present if the participant reported history of HF accompanied by use of both a) diuretics and b) either a vasodilator or a cardiac glycoside. Reported HF without qualifying (or missing data on) medications was classified as possible HF. Prevalent HF status was classified as missing if the participant was unable to provide adequate information. Diabetes mellitus was considered present if the participant reported history of diabetes or use of anti-diabetes medications. History of coronary revascularization, electrocardiographic evidence of myocardial infarction, or self-reported history of myocardial infarction or angina accompanied by antianginal medications was considered evidence of coronary heart disease (CHD). Hypertension was defined as self-reported history of hypertension or physician diagnosis and use of antihypertensive medications. Smoking was classified as current, past (if ≥ 100 lifetime cigarettes), or never. Cerebrovascular disease was based on history of stroke, transient ischemic attack, or carotid intervention. Depression was defined as self-reported history accompanied by medication use. Left ventricular hypertrophy was determined from baseline electrocardiogram by the following criteria: R > 26 mm in lead V5 or V6, or R > 20 mm in any of leads I, II, III, aVF, or R > 12 mm in lead aVL, or R in lead V5 or V6 plus S in lead V1 > 35 mm.

Baseline Laboratory Measurements

Fasting glucose and OGTT measurements were made after ≥ 8 hours fasting. Immediately after fasting blood draw, participants ingested 75 g glucose solution and a second sample was drawn 2 hours later. Plasma glucose was measured by an automated glucose oxidase reaction (YSI 2300, Yellow Springs, OH). Insulin was assayed with a microparticle enzyme immunoassay (Abbott IMx) in participants who were not on exogenous insulin. For HbA_{1c}, ion-exchange high-performance liquid chromatography (Bio-Rad Variant, Hercules, CA) was used. Since this study focused on participants without history of DM, all three measures (OGTT, insulin and HbA_{1c} levels) were available for the entire study cohort.

Homeostasis model assessment (HOMA) of Insulin Resistance and Insulin Secretion

The homeostasis model assessment (HOMA) of IR and insulin secretion (β -cell function) was developed and validated against hyperinsulinemic-euglycemic clamp (for IR) and hyperglycemic clamp (for insulin secretion).¹⁷ The formulas are as follows:

Insulin resistance (HOMA-IR): $\text{fasting insulin (in } \mu\text{IU/mL)} \times \text{fasting glucose (in mmol/L)} / 22.5$

β -cell function (HOMA-B): $20 \times \text{fasting insulin (in } \mu\text{IU/mL)} / (\text{fasting glucose (in mmol/L)} - 3.5)$

Definitions of Glycemic States

Both the American Diabetes Association (ADA) and the World Health Organization (WHO) classify fasting glucose ≥ 126 mg/dL or 2-h post-OGTT glucose ≥ 200 mg/dL as DM,^{7, 8} but

ADA does not recommend routine use of OGTT. Because of these differences, both the ADA (fasting glucose only) and the combined ADA/OGTT criteria were used to classify glycemic status at baseline in Health ABC Study. Also, WHO defines pre-diabetes fasting glucose at ≥ 110 mg/dL while ADA proposes the 100 mg/dL cut-off point.⁸ Therefore, we assessed the value of all definitions of glycemic status (ADA, ADA/OGTT, WHO, WHO/OGTT) in relation to incident HF. It is recommended, however, that the diagnosis of DM in an asymptomatic person should not be made on the basis of a single abnormal blood glucose value; additional testing on a different day is advisable.¹⁸ If such samples fail to confirm the diagnosis of DM, it is usually advisable to maintain surveillance with periodic re-testing until the diagnostic situation becomes clear. In Health ABC, among participants without clinical history of DM or anti-diabetes medications, 98 participants had fasting glucose ≥ 126 mg/dL. These participants were included in this study as “DM range fasting glucose”. Finally, both ‘intermediate hyperglycemia’ and ‘pre-diabetes’ have been used by the various guidelines for intermediate glycemic states including impaired fasting and/or OGTT glucose; for ease of communication, we referred to this group as ‘pre-diabetes’ in this study.

Outcomes

All participants were asked to report any hospitalizations and every 6 months they were asked direct questions to elicit information about interim cardiovascular events. All first admissions with an overnight stay confirmed to be related to HF by local adjudicators (based on symptoms, signs, chest radiography results, and echo-cardiographic findings) were classified as incident HF. Briefly, HF was confirmed if, in addition to a physician diagnosis of HF, there was (1) documentation in the participants’ medical records of a constellation of symptoms (such as shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and physical signs (such as edema, pulmonary rales, gallop rhythm, displaced left ventricular apical impulse); (2) supporting clinical findings such as evidence of pulmonary edema on chest radiography; or (3) a record of medical therapy for HF, including at least a diuretic and a vasodilator and/or digitalis. Although echocardiography was not available for all HF hospitalizations, when it was available it was considered part of the clinical picture. Since HF was not allowed as a cause of death, there were no deaths considered as incident HF. Deaths were reviewed by the Health ABC diagnosis and disease ascertainment committee; cause of death was determined by central adjudication. Information on left ventricular ejection fraction (LVEF) post-HF development was abstracted from echocardiography or left ventriculography reports from the hospital medical records

Statistical Analysis

Incident HF rates for baseline categories of glycemic status were compared using the log-rank χ^2 statistic. The discrimination properties of the various definitions of baseline glycemic status for incident HF prediction were assessed using the corresponding c statistics. Raw and adjusted hazard ratios (HR) for baseline categories and markers of glycemic status were calculated using Cox proportional hazards models. Adjusted models included body mass index (BMI), which has been shown to be associated both with incident HF in younger individuals¹⁹ and insulin resistance,²⁰ and previously identified independent predictors of incident HF in Health ABC (age, history of CAD and smoking, baseline systolic blood pressure and heart rate, log creatinine and albumin levels, and left ventricular hypertrophy by electrocardiogram).¹³ Proportionality was checked by the Schoenfeld residuals. The appropriate form (i.e. linear vs. non-linear relation to incident HF risk) for markers of glycemic status (fasting glucose, 2-hour glucose, fasting insulin, HbA_{1c}, and HOMA-derived measures of IR and β -cell function) was determined using fractional polynomials and natural cubic splines. Interaction terms with sex and race were fitted as appropriate to test for modification effects. We assessed the possible incremental value of additional markers of glycemic status beyond fasting glucose by entering 2-hour glucose, fasting insulin, HbA_{1c} levels, and HOMA-derived measures of IR and β -cell

function in incremental models including BMI, previously identified independent predictors of incident HF in Health ABC, and fasting glucose. A threshold of $P < .05$ (by Wald χ^2) was set to retain an additional marker.

In a secondary analysis, we evaluated the association between fasting glucose and risk for HF with reduced ($\leq 40\%$) vs. preserved ($> 40\%$) LVEF. For these analyses, only incident HF cases with documented LVEF were considered as events in separate (reduced and preserved LVEF, respectively) Cox models.

Analyses were performed with Stata 10. A two-sided P-value of .05 or less was considered statistically significant.

RESULTS

The median age of participants was 73 years (interquartile range [IQR], 71–76 years); 47.6% were men and 62.5% white. After a median follow-up of 7.2 years (IQR, 6.9–7.5 years), 185/2386 participants (7.8%) developed HF (11.9 per 1000 person-years; 95% confidence interval [CI], 10.3–13.7). The baseline characteristics of participants and incident HF rates according to glycemic status (classified by the ADA fasting glucose criteria) are shown in Table 1.

Glycemic Status Categorization and Incident Heart Failure

Based on the ADA criteria, fasting glucose in the pre-diabetes range was detected in 527 participants (22.1%), and 98 (4.1%) had DM-range fasting glucose. When both fasting and OGTT glucose were considered, 827 (34.7%) participants had pre-diabetes fasting and/or OGTT glucose, and 234 (9.8%) had levels in the DM range. Figure 1 shows the Kaplan-Meier estimates of incident HF rate in the various subgroups based on glycemic status. Based on the log-rank χ^2 statistic, fasting glucose based ADA and WHO criteria provided the maximal prognostic separation without any improvement with the addition of OGTT values (Figure 1). The c statistics for incident HF prediction were 0.538 (95% CI, 0.503–0.572) and 0.534 (95% CI, 0.506–0.561) for the ADA and WHO fasting glucose-only classifications, respectively; the OGTT-added definitions did not improve discrimination (c statistics, 0.533 [95% CI, 0.494–0.572] and 0.529 [95% CI, 0.491–0.566], respectively). No significant modification effect of race or sex on the association of baseline glycemic status with HF risk was observed.

Markers of Insulin Resistance and Incident Heart Failure

We found a continuous association between fasting glucose levels and risk for incident HF (unadjusted HR per 10mg/dL, 1.12; 95% CI, 1.05–1.18; $P < .001$; adjusted HR, 1.10; 95% CI, 1.02–1.18; $P = .009$); there was no statistical evidence of a non-linear or ‘step’ relation.

Table 2 shows the raw and adjusted HR for incident HF for the markers of glycemic status. Fasting glucose, OGTT 2-hour glucose, and HbA_{1c} were associated with incident HF, while fasting insulin and HOMA-derived measure of IR and β cell function were not. In adjusted analyses, fasting glucose had the strongest association with HF risk. When entered in a base model including other independent predictors of incident HF and fasting glucose, additional markers of glycemic status (HbA_{1c}, OGTT 2-hour glucose, fasting insulin, and HOMA-derived measures of IR and β -cell function) did not improve the model (all Wald χ^2 $P > .4$). The association of markers of glycemic status with incident HF was similar across sex and race subgroups (data not shown).

Heart Failure with Preserved vs. Reduced LVEF

Data on ventricular function during hospitalization for HF were not prospectively collected in the Health ABC Study; therefore, the available data are based on medical record reviews. Data on LVEF from echocardiography or left ventriculography reports during the index HF hospitalization were available in 140 of 185 (75.7%) of participants. Median LVEF was 42% (interquartile range, 26%–55%). When only HF with LVEF $\leq 40\%$ ($n=69$; 49.3%) was considered as endpoint, fasting glucose was strongly associated with the endpoint in the fully-adjusted model (HR per 10mg/dL, 1.15; 95% CI, 1.03–1.29; $P=.01$). In comparison, when only HF with LVEF $>40\%$ ($n=71$; 50.7%) was considered as endpoint, fasting glucose had a weaker association with the endpoint (HR per 10mg/dL, 1.05; 95% CI, 0.94–1.18; $P=.41$).

DISCUSSION

In this study, we show that serum glucose levels were strongly associated with risk for HF development in elderly who did not have diabetes mellitus at baseline. This risk was independent of other HF risk factors and was consistent in both sexes, and in whites and blacks. Importantly, other glycemic measures did not provide incremental predictive information. With the increasing obesity and metabolic syndrome prevalence in the United States and the related worsening of glycemic abnormalities in the general population, our findings have important clinical implications.

Although various definitions have been developed and modified over time to characterize glycemic status into sub-groups, we and other investigators have shown in the past that the relation between serum glucose levels and incident HF is continuous.^{5, 12, 13} Notably, previous studies included both subjects with and without clinical DM; in the current study, we found a continuous relation in subjects without history of DM. Moreover, risk increases even within a range of levels that is currently considered normal by all criteria. However, analysis using categorization of glucose levels into normal, pre-diabetes range, and DM-range failed to detect increased risk for incident HF in persons with pre-diabetes range in our study. This most likely represents the effect of sub-group analysis and beta-error related to lack of power to detect a difference. Thus, our results underscore the risk of loss of information associated with categorization of biologically continuous variables. One may contest that the importance of pre-diabetes and cardiovascular risk is primarily shown in younger populations, and part of the risk might be mediated through risk of new onset DM over time. The potent relationship between serum glucose levels as an independent predictor of HF risk even after adjusting for other risk factors makes this assertion less likely.

The biological association of serum glucose levels and HF risk has been studied well in patients with DM; the same mechanisms may underlie this risk association in patients without history of DM and may be mediated through IR. In the presence of IR, the heart rapidly modifies its metabolism, resulting in augmented fatty acid and decreased glucose consumption.^{6, 21} This alteration is central in the development of diabetic cardiomyopathy, a condition that affects both systolic and diastolic function of the heart and predisposes to HF.^{22, 23} Additional mechanisms linking IR and HF include adverse effects of hyperglycemia on endothelial function,²⁴ effects of excess circulating glucose and fatty acids on myocyte structure,²⁵ intracellular signaling and gene expression,²⁶ and impaired recruitment of the myocardial insulin-responsive glucose transport system in response to ischemia.²⁷ In line with these findings, we recently reported that fasting glucose is an independent predictor of incident HF prediction in the elderly participants of the Health, Aging, and Body Composition (Health ABC) Study,¹³ superseding baseline diabetes status (as defined by self-reported history and use of medications).

The WHO definition of glycemic status suggests incorporation of OGTT, which is expected to uncover latent DM (or at risk for DM) subjects based on a challenge as opposed to a fasting value. With respect to prediction of HF risk, we did not detect any incremental value of OGTT over fasting glucose alone. When used as a categorical value, OGTT rather reduced the specificity of the fasting glucose based categorization of glycemic abnormalities, and when studied as a continuous variable, it did not add anything to the prediction of incident HF beyond fasting glucose. Thus, OGTT did not help identify persons at greater risk for subsequent HF. Indeed, neither switching to WHO criteria (which are more liberal on normal fasting glucose values) nor addition of OGTT resulted in net improvement in HF risk classification above ADA fasting glucose based definitions.

Although we found significant unadjusted relations between markers of glycemic status and HF risk, serum glucose levels remained the most potent risk predictor. Once controlled for all other predictors of HF risk including serum glucose, none of the other markers -- fasting insulin, 2 hour post challenge glucose levels, Hemoglobin A_{1c}, and HOMA-based IR and β cell function assessment -- provided additional prognostic information. These results obviously neither test nor suggest any pathophysiologic association of any of these markers with HF risk, but they provide important practical information. Fasting glucose levels may help to identify persons who are at risk for HF, and risk detection with respect to glycemic status may best be achieved with a simple and inexpensive blood test.

Interestingly, in our study fasting glucose was more strongly associated with incident HF with depressed as compared to preserved LVEF. Although some data suggest that the outcomes for these two groups of patients are similar, the distribution of demographic characteristics still differ significantly between the two groups,²⁸ i.e. patients with HF and preserved EF are more likely to be older and women. This may impact on the risk factor profile for incident HF for the two groups, something that is also suggested by our solitary risk factor analysis, i.e. fasting glucose. However, due to the restricted number of patients in our subgroup analysis and the lack of uniform LVEF assessment, these data are preliminary. Differences in risk factors and their population attributable risks for HF with preserved vs. low LVEF need further study.

Our study has several limitations. Diagnosis of incident HF in our study was based on HF hospitalization and therefore we likely underestimated the true incidence of HF. Echocardiography was not performed at baseline in the Health ABC Study. Thus, participants with subclinical prevalent structural heart disease may have been included in the analysis. Ninety-eight participants in this study had fasting glucose in the DM range. We are not certain what proportion of these individuals represents undiagnosed DM vs. spurious finding, what proportion were subsequently clinically diagnosed and treated vs. not; and who required intensive medical therapy vs. just diet control for borderline elevated glucose levels. These issues are however important as undiagnosed and untreated DM would not only heighten the risk for HF development, but it may also represent more complex social (inadequate access to care) and medical (poorly treated comorbidities) issues which may also predispose an individual to develop HF. Because ventricular function during hospitalization for HF was not prospectively assessed, we could not reliably assess the differential impact of fasting glucose on development of HF with preserved vs. reduced LVEF. The available data on LVEF were based on medical record reviews and are not derived from a single modality. Therefore, we cannot be confident that the distribution of LVEF in our data is representative of the investigated population. Finally, the findings of this study are limited to the elderly population and are not transferable to the general population. Further work is needed.

In conclusion, our study demonstrates that simple fasting serum glucose levels were the strongest predictor of incident HF risk among glycemic status markers; that this relationship is continuous; and starts at a level considered normal for serum glucose. This relationship was

not affected by either white or black race, or sex. Testing for other glycemic measures did not add to our ability to identify individuals at risk for incident HF. Whether identification of such high-risk individuals and subsequent glucose lowering intervention would reduce HF risk needs further study.

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Figure 1. Incident heart failure by baseline glycemic status

The fasting glucose -only based definitions of glycemic status (upper panels) provide better prognostic separation for incident heart failure as compared to the respective OGTT-added definitions (lower panels), as indicated by the log-rank χ^2 statistics. Note that the risk for incident HF among participants in the intermediate glycemic categories (i.e., impaired FG in upper panels and impaired FG or OGTT in lower panels, respectively) is not distinctly different as compared to that among participants with normal glycemic status (Mantel-Cox χ^2 statistics for the comparisons between impaired and normal glycemic status all correspond to $P>.25$).

ADA, American Diabetes Association;

FG, Fasting glucose;

OGTT, Oral glucose tolerance test;

WHO, World Health Organization

Table 1
Baseline Participant Characteristics by Glycemic Status (American Diabetes Association Criteria)

Variable	Normal fasting glucose (n=1761)	Pre-diabetes fasting glucose (n=527)	Diabetes-range fasting glucose (n=98)	P	P (trend)
Incident heart failure % (N)	7.1 (125)	8.3 (44)	16.3 (16)	.002	.003
Rate, per 1000 person-years	10.7	13.1	26.6		
Age, years	73 (71, 76)	73 (71, 76)	73 (71, 76)	.90	.81
Sex, % male	43.8	56.2	68.4	<.001	<.001
Race, % white	63.5	60.5	55.1	.136	.050
Systolic blood pressure, mmHg	133 (121, 148)	134 (123, 148)	135 (122, 150)	.097	.038
Diastolic blood pressure, mmHg	71 (64, 79)	72 (65, 81)	71 (65, 79)	.093	.075
Body mass index, kg/m ²	25.9 (23.3, 28.8)	28.1 (25.4, 31.6)	29.3 (25.9, 31.9)	<.001	<.001
Heart rate, beats per minute	63 (57, 70)	66 (59, 74)	68 (61, 77)	<.001	<.001
Hypertension, %	41.3	51.9	50.5	<.001	<.001
Current smokers, %	10.7	9.3	9.2	.63	.36
Coronary heart disease, %	13.6	19.8	25.8	<.001	<.001
Left ventricular hypertrophy, %	11.9	10.8	11.2	.83	.56
Creatinine, mg/dL	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	.002	.001
Albumin, g/dL	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)	4.1 (3.9, 4.3)	<.001	<.001
Total cholesterol, mg/dL	201 (178, 227)	204 (180, 229)	204 (175, 233)	.44	.21
High density lipoprotein, mg/dL	54 (44, 65)	49 (41, 59)	45 (38, 55)	<.001	<.001
Low density lipoprotein, mg/dL	120 (99, 143)	123 (101, 145)	118 (103, 143)	.31	.17
Triglycerides, mg/dL	113 (85, 115)	130 (98, 179)	142 (105, 236)	<.001	<.001
Fasting glucose, mg/dL	90 (85, 94)	106 (102, 111)	141 (131, 165)	NA	NA
Hemoglobin A _{1c} , %	5.9 (5.6, 6.2)	6.2 (5.9, 6.6)	7.4 (6.8, 8.1)	<.001	<.001
2-Hour glucose, mg/dL	115 (95, 139)	142 (118, 177)	270 (223, 329)	<.001	<.001
Fasting Insulin, μ U/dL	6.1 (4.5, 8.8)	9.1 (6.5, 12.9)	11.3 (6.2, 15.1)	<.001	<.001
Insulin resistance (HOMA)*	1.35 (0.97, 1.98)	2.41 (1.73, 3.46)	4.02 (2.50, 5.39)	<.001	<.001
β -cell function (HOMA) [†]	88 (64, 124)	74 (53, 109)	43 (26, 73)	<.001	<.001

Numbers for continuous variables are median (25th percentile, 75th percentile)

HOMA= homeostasis model assessment, NA=not applicable

Table 2
Markers of Insulin Resistance and Incident Heart Failure Risk at Baseline (N=2386)

Variable	Unadjusted			BMI-Adjusted		
	HR (95% CI)	Wald	P	HR (95% CI)	Wald	P
Fasting glucose, per SD	1.22 (1.10–1.35)	14.32	<.001	1.21 (1.09–1.34)	13.66	<.001
Hemoglobin A _{1c} , per SD	1.26 (1.13–1.41)	17.07	<.001	1.25 (1.11–1.41)	13.86	<.001
2-Hour glucose, per SD	1.22 (1.07–1.39)	9.09	.002	1.20 (1.05–1.38)	6.83	.009
Fasting insulin, per SD	1.06 (0.90–1.25)	0.45	.50	0.97 (0.84–1.13)	0.12	.73
Insulin resistance, per SD	1.10 (0.97–1.24)	2.19	.14	1.05 (0.91–1.21)	0.42	.52
β-cell function, per SD	0.91 (0.77–1.07)	1.34	.27	0.86 (0.73–1.01)	3.48	.06

Variable	Model 1 [*]			Model 2 [†]		
	HR (95% CI)	Wald	P	HR (95% CI)	Wald	P
Fasting glucose, per SD	1.19 (1.04–1.35)	6.80	.009	1.08 (0.90–1.28)	0.65	.42
Hemoglobin A _{1c} , per SD	1.19 (1.03–1.38)	5.27	.02	1.01 (0.83–1.23)	0.01	.91
2-Hour glucose, per SD	1.15 (0.97–1.36)	2.63	.11	0.88 (0.74–1.06)	1.74	.19
Fasting insulin, per SD	0.92 (0.77–1.10)	0.84	.36	0.89 (0.74–1.07)	1.58	.21
Insulin resistance, per SD	0.99 (0.84–1.17)	0.01	.92	0.93 (0.78–1.10)	0.76	.38
β-cell function, per SD	0.86 (0.72–1.03)	2.82	.09			

^{*} Adjusted for BMI, age, history of coronary artery disease and smoking, systolic blood pressure and heart rate, left ventricular hypertrophy on electrocardiogram, and creatinine and albumin levels

[†] Adjusted for variables included in model 1 plus fasting glucose levels

SD: standard deviation