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Does cardiovascular phenotype explain the association between diabetes and incident heart failure? The Strong Heart Study

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Abstract

Background and Aims—Diabetes remains a predictor of incident heart failure (HF), independent of intercurrent myocardial infarction (MI) and concomitant risk factors. Initial cardiovascular (CV) characteristics, associated with incident heart failure (HF) might explain the association of diabetes with incident HF.

Methods and Results—Participants to the 2nd Strong Heart Study exam, without prevalent HF or coronary heart disease, or glomerular filtration rate <30 mL/min/1.73m², were analyzed (n=2,757, 1,777 women, 1,278 diabetic). Cox regression of incident HF (follow-up 8.91±2.76 years) included incident MI censored as a competing risk event. Acute MI occurred in 96 diabetic (7%) and 84 non-diabetic participants (6%, p=ns). HF occurred in 156 diabetic (12%) and in 68 non-diabetic participants (5%; OR=2.89, p<0.001). After accounting for competing MI and controlling for age, gender, BMI, systolic blood pressure, smoking habit, plasma cholesterol, antihypertensive treatment, heart rate, fibrinogen and C-reactive protein, incident HF was predicted by greater LV mass index, larger left atrium, lower systolic function, greater left atrial systolic force and urinary albumin/creatinine excretion. Risk of HF was reduced with more rapid LV relaxation and anti-hypertensive therapy. Diabetes increases hazard of HF by 66% (0.02<p<0.001). The effect of diabetes could be explained by the level of HbA1c.

Conclusions—Incident HF occurs more frequently in diabetes, independent of intercurrent MI, abnormal LV geometry, subclinical systolic dysfunction and indicators of less rapid LV relaxation, and is influenced by poor metabolic control. Identification of CV phenotype at high-risk for HF in diabetes should be advised.

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Keywords

coronary disease; risk factors; diastolic function; systolic function; hypertrophy; obesity

Introduction

The high incidence of heart failure (HF) currently observed in industrialized countries is still mainly attributable to ischemic heart disease, but an increasing proportion of new cases are not associated with preceding clinically overt myocardial infarction (1,2). The occurrence of non MI-related HF is linked with arterial hypertension (1), but there is increasing evidence that obesity and diabetes can also be powerful risk factors (1,3). We have recently shown that diabetes was a potent predictor of incident HF in the initial Strong Heart Study (SHS) cohort (4), independent of both intercurrent myocardial infarction and other cardiovascular (CV) risk factors, including hypertension and obesity. In contrast, participants with impaired fasting glucose had the same risk of HF as those with normal fasting glucose. Possible link for the independent association of diabetes with incident HF could be the presence of “preclinical cardiovascular disease” that can be assessed by echocardiographic detection of abnormal cardiac geometry and function and/or measurement of proteinuria (5). These abnormalities are associated with diabetes (6), causing or at least facilitating development of HF and might fully explain the link between diabetes and incident HF.

Accordingly, we analyzed the incidence of HF in the diabetic and non-diabetic participants to the 2nd Strong Heart Study (SHS) exam, who were seen four year after the beginning of the study, at the time when echocardiography was performed. We analyzed the relation between diabetes and incident HF in relation to CV risk factors and markers of preclinical cardiovascular disease, to verify whether initial abnormalities of LV function and geometry or albuminuria may explain the association of diabetes with HF.

Methods

Population

The Strong Heart Study (SHS) is a population-based cohort study of CV risk factors and disease in 4,549 American Indians from 3 communities in Arizona, 7 in Southwestern Oklahoma and 3 in South and North Dakota, extensively described previously (6-8) and representative of the source populations (8). For the purpose of the present analysis we analyzed participants of the 2nd exam, which included an echocardiogram (N=3638, 89% of all living); we excluded participants who had history or signs of prevalent HF or coronary heart disease at the time of the 2nd SHS exam (ascertained MI or diagnosis of coronary heart disease by ECG evidence of previous myocardial infarction - by Minnesota code -, coronary angiography, combination of typical symptoms with positive treadmill or imaging stress tests, or need for revascularization procedures). We also excluded participants with glomerular filtration rate (GFR)<30 mL/min/1.73 m², by the simplified MDRD formula. Thus 2,757 participants (1,777 women) were available for the analysis. Both prevalent and incident HF were confirmed by the Strong Heart Study Mortality and Morbidity Committees, as previously reported (4,9). Heart failure was diagnosed when two major, or one major and two minor criteria were present concurrently in the absence of a condition such as end-stage renal failure leading to massive fluid overload. Major criteria were paroxysmal nocturnal dyspnea or orthopnea, neck vein distention, rales, cardiomegaly, acute pulmonary edema, S3 gallop, venous pressure greater than 16 cm water and hepatojugular reflux. Minor criteria were ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, vital capacity less than 2/3 of predicted or heart rate at least 120 beats/min.

Weight loss of at least 4.5 kg in 5 days in response to treatment could serve as a major or minor criterion.

Laboratory tests and definitions

Fasting plasma glucose was measured by standard methods. Diabetes (fasting glucose ≥ 126 mg/dL or ongoing antidiabetic treatment) was diagnosed by 1997 American Diabetes Association recommendations. Severity of diabetes was evaluated by assessing the percent of HbA1c. Obesity was classified by the 1998 NIH guidelines (BMI ≥ 30 kg/m²). Central fat distribution was defined according to NCEP-ATPIII guidelines. Hypertension was defined by JNC-7 criteria (blood pressure $\geq 140/90$ mmHg or use of antihypertensive treatment). C-reactive protein and fibrinogen were measured by standard methods. Microalbuminuria was defined as an urinary albumin/creatinine ratio ≥ 30 and macroalbuminuria as a urinary albumin/creatinine ratio ≥ 300 .

Echocardiography

During the 2nd SHS exam, echocardiograms were performed using phased-array commercial echocardiographs with M-mode, 2-dimensional and Doppler capabilities, as previously reported (6). Left ventricular (LV) dimensions and septal and posterior LV wall thickness were measured by American Society of Echocardiography recommendations (10,11). Antero-posterior left atrial dimension was measured in parasternal long-axis view, by the trailing-edge to leading edge method, and normalized for height. LV mass was obtained by an anatomically validated formula and normalized for body height in m^{2.7} (12). LV volumes were estimated from linear dimensions by the z-derived method (13) and used to derive stroke volume. Stroke volume was also normalized (stroke index) by height in meters to the allometric power of 2.04 (14).

Standard methods were used to calculate relative wall thickness, as a measure of LV geometry, and endocardial and midwall fractional shortening (6,15), as measures of LV systolic function. Myocardial afterload was assessed by computation of circumferential end-systolic wall stress, based on a cylindrical geometry (15). Stress-corrected midwall shortening was used as an estimate of LV contractility. The ratio of pulse pressure to stroke index (PP/SVi) was also computed as a raw indicator of total arterial stiffness, a prognostically validated estimate of vascular load (16,17).

Measurement of diastolic transmitral blood flow was performed as previously described (18). Mitral early (E) and late (A) velocity were recorded at the annular level and used to calculate the E/A ratio. E-deceleration time was also measured (18). The E/A ratio was categorized as normal (≥ 0.6 and ≤ 1.5), abnormal relaxation (<0.6), uncertain filling pattern (>1.5). These partition values have been shown to be associated with increased cardiovascular risk in the cohort of the SHS (18). Also E-deceleration time was categorized, in normal (≥ 160 and <240 ms), abnormal relaxation (≥ 240 ms), uncertain filling pattern with possible restrictive physiology (<160 ms) (19). For Cox analysis, we categorized participants with normal E/A ratio and E deceleration time as a reference subpopulation with normal LV diastolic function, while grouping participants with E/A ratio <0.6 and/or E deceleration time ≥ 240 msec (abnormal relaxation), and those with E/A ratio >1.5 and/or E deceleration time <160 msec (uncertain filling pattern with possible restrictive physiology). Left atrial systolic force (LASF) was also computed, as previously reported and prognostically validated (20).

Statistical analysis

Data were analyzed using SPSS 17.0 (SPSS, Chicago, IL). Descriptive statistics were obtained using chi-square distributions (with Monte Carlo method for computation of exact

2-tailed p value, when appropriate) and analysis of variance. Descriptive statistics are presented for diabetic and non-diabetic participants. Plasma creatinine, GFR, urinary albumin/creatinine ratio, CRP and fibrinogen were log-transformed and presented as medians and interquartile ranges. Indicator variables were included in all multivariate analyses for the three field centers, Arizona, South/North Dakota, and Oklahoma.

Analysis of covariance was used to evaluate whether baseline cardiovascular characteristics were different in diabetic or non-diabetic participants, adjusting for demographics and presence of hypertension.

Log-cumulative adjusted hazard functions for incident HF were generated by Cox regression analysis comparing diabetic with non-diabetic participants. Due to possible cause-effect relationship with incident HF, intercurrent MI was censored as a competing risk event in the Cox model (21). Cox regression was hierarchically programmed by forced entry of primary covariates (in addition to age and sex, we included BMI, systolic blood pressure, antihypertensive therapy, heart rate, fibrinogen, C-reactive protein, plasma cholesterol and smoking habit). In a second block, LV mass index, left atrial dimension, endocardial shortening, end-systolic stress, PP/SVi, categories of diastolic function and LASF were added to the model and a backward selection procedure was used. Finally, diabetes status was forced into the model to verify modifications of the previous model and whether a residual effect of diabetes remained. The same model was also repeated by adding urinary albumin/creatinine ratio among the marker of preclinical cardiovascular diseases included in the second block. To verify whether duration of diabetes and metabolic control could account for by the effect of diabetes, duration and HbA1c were also entered together with diabetes in a further Cox model.

Results

Diabetes was present in 1,278 participants (46%), of whom 886 (69%) were women. Prevalence of diabetes was 50% higher in women than in men (OR=1.49 [CI: 1.27-1.75], $p<0.001$). Diabetic participants also exhibited higher prevalence of obesity (63% vs. 46% in non-diabetic individuals) and hypertension (53% vs. 34%, both $p<0.001$). Smokers (25%) were less frequent, whereas former smokers (42%) and non smokers (33%) were more frequent among diabetic participants than in non diabetic participants (37%, 35% and 28%, respectively, $p<0.001$).

Diabetic participants had higher blood pressure, heart rate and BMI than non-diabetic participants (Table 1). While renal excretory function (creatinine and GFR) and plasma cholesterol were comparable, urinary albumin excretion and inflammatory markers (CRP and fibrinogen) were significantly higher in diabetic than in non-diabetic participants. Microalbuminuria was present in 11% of non diabetic and in 35% of diabetic participants and macroalbuminuria in 2% of non diabetic and 21% of diabetic participants ($p<0.001$).

Table 2 shows that, after adjusting for age, sex, BMI and prevalent hypertension, at the initial echocardiographic examination, diabetic participants exhibited greater LV mass and atrial dimension than non-diabetic participants with more pronounced concentric LV geometry, substantially increased PP/SVi, reduced endocardial and midwall shortening, decreased transmitral E/A ratio and increased left atrial systolic force.

Absolute risk of heart failure

Average follow-up time was 8.91 ± 2.76 years. During the follow-up, 89 diabetic participants (or 7%) suffered for acute myocardial infarction, as opposed to 81 non-diabetic participants (or 6%), a difference that was not statistically significant. In contrast, HF incidence was

nearly 3-fold greater in diabetic (156 cases, or 12%) than in non-diabetic participants (68 cases or 5%; OR=2.89 [CI: 2.15-3.88], $p<0.001$).

HbA1c was higher in participants with than in those without incident HF ($7.92\pm2.47\%$ vs $6.78\pm2.39\%$, $p<0.04$). Duration of diabetes was not significantly different between participants with and without incident HF (11.8 ± 8.3 and 11.0 ± 9.7 yrs, $p=0.09$, even after adjusting for age, sex, BMI, and prevalent hypertension).

Among participants with incident HF, the proportion of individuals with initial ejection fraction $<50\%$ was small: 2% among non diabetic and 2.7% among diabetic persons ($p=ns$).

Independent predictors of HF

The differences reported in table 1 and table 2 could largely explain the increased incidence of HF in diabetic participants. Table 3 (model without diabetes) shows that after accounting for competing intercurrent myocardial infarction and controlling for the effects of age, gender, BMI, systolic blood pressure, heart rate, C-reactive protein, fibrinogen, plasma cholesterol, smoking habit and antihypertensive therapy, significant associations with incident HF were found for greater LV mass index and left atrial dimension, lower endocardial shortening and greater PP/SVi ($0.02<p<0.001$). Risk of incident HF was significantly lower in participants with E-deceleration time <160 msec or E/A ratio >1.5 , and was higher with greater LASF (all $p<0.01$, table 3). Antihypertensive treatment reduced the risk of incident HF by near 40%.

When forced into the model (table 3, model with diabetes), diabetes status did not modify the cardiovascular profile at high risk of HF and remained associated with near 2-fold higher risk of HF ($p<0.001$), independently of confounders and the cardiovascular phenotype emerging from this model. Addition of urinary albumin/creatinine ratio into the model, as an additional marker of preclinical cardiovascular disease, reduced the impact of diabetes on incident HF (table 4), without substantial modification of the other predictors.

In a further Cox model, duration of diabetes and HbA1c were also added to diabetes. This model (table 4) showed that a poor metabolic control could explain the independent predictive effect of diabetes, in addition to urinary albumin/creatinine ratio and to the predictors shown in table 3.

Discussion

This longitudinal study demonstrates that diabetes remains a potent predictor of HF, not only independent of intercurrent MI, but also in addition to what can be predicted by the initial CV phenotype assessed using standard transthoracic echocardiography. Even when adding proteinuria as another marker of preclinical cardiovascular disease, more reflecting microvascular dysfunction (22), the impact of diabetes was only attenuated. These findings suggest that in diabetes an accelerated progression toward cardiac decompensation occurs, which cannot be fully explained by the initial structural and functional CV alterations. However, other elements emerged from our analysis. Severity of diabetes was estimated analyzing the efficacy of the metabolic control (HbA1c) and the duration of the disease. These analyses indicated that the predictive value of diabetes on incident HF is largely explained by the integrated presence of echocardiographic abnormalities, microvascular disease and poor metabolic control. The effect of metabolic control on incident HF might also incorporate effect of duration, given the reported association of HbA1c with age and duration of the disease (23), and implies that further research is needed on impact of anti-diabetic therapy, an unresolved issue of high interest (24,25).

Increased LV mass and left atrial dimension, subtle reduction of LV systolic chamber function, high arterial stiffness and diastolic abnormalities are characteristics associated with increased risk of HF not related to intercurrent MI and independent of presence or absence of diabetes, whereas presence of antihypertensive therapy and more rapid LV relaxation were protective. The CV phenotype predicting incident HF emerging in our analysis is consistent with the features that have been previously reported in general populations (26) and specifically in diabetic populations (6), including abnormalities of LV geometry, systolic and diastolic dysfunction and increased arterial stiffness. Possible errors of classification might have occurred in the group of participants with uncertain LV filling pattern because of the possibility of some subjects with elevated LV filling pressure which could be more exposed to incident HF. We could not be more precise in assessment of a true pseudonormal filling pattern, because in the SHS, pulmonary vein exploration, tissue-Doppler or Valsalva manoeuvre were not systematically done in all participants. However the possibility that a relevant number of subjects could have high LV filling pressure in this group is at least in part ruled out by the generally normal initial ejection fraction (less than 3% had ejection fraction < 50%) and, especially, by the protective effect that this LV filling pattern offers, once the other characteristics are taken into account (see table 3).

The Cox model predicting incident HF not related to intercurrent MI presented internal consistency. Despite ejection fraction at baseline was largely normal in our participants, lower values are sign of a subtle initial systolic dysfunction that accounts for part of the decompensation progressing from asymptomatic LV dysfunction toward clinically overt HF. Diastolic function emerging from the simple methods used in this study is even more interesting. The transmitral filling pattern associated with normal or rapid active relaxation was protective for development of HF, consistent with the evidence that this population had initial normal LV systolic function. This argues also against the possibility that in some participants abnormal relaxation could be masked by coexisting restrictive physiology (what is called “pseudo-normal” filling pattern), and indicates that, in the presence of normal LV systolic function, the amount of LV filling occurring before atrial contraction confers benefit. This LV mechanical profile is also consistent with the evidence that development of high atrial systolic force to complete LV filling is confirmed to be a very negative feature (20). Unfortunately, we do not have information on tissue-Doppler, a method that was not yet consolidated at the time when SHS was designed, and cannot determine whether also LV mid-diastolic filling pressure was increased.

But the key finding of our study is that the reported CV phenotype is not at all sufficient to explain the 2-fold increased risk of HF occurring in diabetic patients independently of incident MI. Comparing the unadjusted odds ratio with the hazard ratio of the Cox model displayed in table 3, revealed that the complexity of structural and functional CV alterations identified as predictors of incident HF only reduced by 1/3 the risk of HF that could be ascribed to diabetes (from 2.9 to 2). However, another marker of preclinical cardiovascular disease, albuminuria, more specifically related to microvascular alterations, could further explain the risk of HF attributable to diabetes, opening interesting questions.

Despite the exclusion of a direct participation of previous myocardial infarction in causing heart decompensation, ischemic myocardial insult could occur in diabetic participants, due to silent MI not detectable at the ECG evaluation and/or microvascular disease. Coronary microvascular disease has been demonstrated in diabetes, by several techniques, even in the presence of normal coronary angiograms (27,28). There is extensive evidence that coronary flow is substantially impaired in diabetic subjects, independent of evident epicardial coronary obstruction. Coronary microvascular abnormalities are also associated with increased aortic impedance and more severe macrovascular disease (27), which is consistent with the increase arterial stiffness found in our diabetic participants. Coronary flow reserve

has been also reported to be negatively correlated with prolonged LV relaxation and negatively impacts LV systolic function (29). The cardiovascular phenotype emerging in diabetes is, therefore, consistent with the possibility that microvascular ischemia associated with microvascular alterations at the kidney level, portends development of HF in diabetic patients through loss of contractile tissue and increase in connective tissue over time (30), a possibility that is gaining confirmations in both experimental and human studies (31,32).

The independent relation of HbA1c with incident HF, which contributes to fully explain the effect of diabetes, also suggests a participation in the structural basis of heart decompensation. Tissue glycation can affect myocardial tissue characteristics and vessel compliance (33) and metabolic abnormalities of diabetes may also directly affect delivery of energy substrates to develop the needed amount of contractile force and normal relaxation (34,35).

In conclusion, this study shows that diabetes remains associated with a doubled risk of HF independent of the general CV profile associated with HF, including abnormal LV geometry, systolic and diastolic dysfunction, increased arterial stiffness and microvascular dysfunction. Due to this evidence, identification of CV phenotype at high-risk for HF in diabetes is advisable, especially when adopting management strategies that might affect loading conditions.

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Abbreviations

HF	Heart Failure
CV	Cardiovascular
SHS	Strong Heart Study
GFR	Glomerular filtration rate
BMI	Body mass index
LV	Left ventricular
PP/SVi	Pulse pressure to stroke index
E	Mitral early velocity
A	Mitral late velocity at atrial contraction

MI	Myocardial infarction
LASF	Left atrial systolic force
OR	Odds ratio
CI	95% confidence interval
HR	Hazard ratio

Table 1

Characteristics of diabetic and non diabetic participants. Significant differences are highlighted in boldface. Abbreviations: BP=blood pressure; GFR = glomerular filtration rate.

	No diabetes (n=1,479)	Diabetes (n=1,278)	p
Age (years)	59.2±8.0	59.6±7.7	0.24
Body Mass Index (kg/m ²)*	30.0±5.9	32.4±6.1	0.001
Systolic BP (mmHg)*	126.0±18.7	131.9±20.0	0.001
Diastolic BP (mmHg)‡	74.5±10.0	75.5±10.2	0.02
Heart rate (bpm)*	66.2±10.4	69.1±10.2	0.001
Creatinine (mg/dL)	0.9 [0.8-1.0]	0.8 [0.7-1.0]	0.50
<i>Plasma cholesterol (mg/dL)</i>	<i>190.5±37.8</i>	<i>190.7±40.4</i>	<i>0.90</i>
GFR (mL/min/1.73 m ²)	79.2 [68.4-93.6]	79.8 [67.1-93.8]	0.68
Urinary albumin/creatinine*	7.9 [4.9-15.4]	38.1 [12.2-206.1]	0.001
C-reactive protein (mg/dL)*	1.19 [0.53-1.80]	1.48 [0.92-2.10]	0.001
Fibrinogen (mg/dL)*	335 [298-378]	368[324-420]	0.001

Table 2

Cardiovascular characteristics of studied population, based on prevalent diabetes status. Comparisons are adjusted for age, sex, BMI and prevalent hypertension.

	No diabetes (n=1,479)	Diabetes (n= 1,278)	p
Cardiac geometry			
LV mass index (g/m ^{2.7})	39.5±9.4	42.4±9.93	0.04
Relative wall thickness	0.34±0.04	0.36±0.05	0.001
Left atrial dimension (cm/m)	2.12±0.29	2.20±0.28	0.04
Afterload			
End-systolic stress (σ , g/cm ²)	148.0±35.6	150.3±38.7	0.793
PP/SVi (mmHg/mL*m ^{-2.04})	2.09±0.67	2.31±0.79	0.001
LV function and chamber contractility			
Endocardial shortening (%)	35.2±5.2	35.0±5.6	0.05
Midwall shortening (mS, %)	17.9±2.1	17.3±2.2	0.001
σ -adjusted mS (%)	97.7±10.8	94.1±11.7	0.001
Diastolic function			
Transmitral E velocity (cm/s)	60.0±16.4	67.0±17.5	0.001
Transmitral A velocity (cm/s)	69.4±15.5	73.4±16.6	0.001
Transmitral E/A ratio	0.89±0.28	0.79±0.25	0.001
E deceleration time (msec)	199.5±63.3	208.6±70.4	0.297
Left atrial systolic force (kdynes)	11.8±4.4	13.0±4.6	0.001

Multivariate Cox regression for incident HF in diabetic and non-diabetic participants of the SHS cohort with or without atrial fibrillation before and after forcing diabetes status. HR=hazard ratio

Table 3

	Model without diabetes			Model with diabetes		
	P	HR	95.0% CI for HR Lower-Upper	P	HR	95.0% CI for HR Lower-Upper
Primary confounders						
Age (5 years)	0.01	1.02	1.00-1.04	0.005	1.13	1.04-1.23
Female gender	0.96	0.99	0.74-1.32	0.70	0.95	0.71-1.26
BMI (kg/m ²)	0.54	0.99	0.97-1.02	0.29	0.99	0.96-1.01
Systolic BP (mmHg)	0.06	0.99	0.98-1.00	0.06	0.99	0.98-1.00
Heart rate (bpm)	0.11	1.01	1.00-1.03	0.13	1.01	1.00-1.03
C-reactive protein (log ₁₀ [mg/dL])	0.63	0.90	0.58-1.39	0.68	0.91	0.59-1.42
Fibrinogen (× 10 mg/dL)	0.007	1.00	1.00-1.00	0.03	1.02	1.00-1.04
Antihypertensive therapy	0.001	0.59	0.45-0.77	0.002	0.66	0.51-0.86
Former smoker	0.02	1.44	1.05-1.97	0.04	1.39	1.01-1.90
Current smoker	0.02	1.49	1.06-2.10	0.03	1.46	1.04-2.05
Plasma cholesterol (mg/dL)	0.19	1.00	1.00-1.01	0.18	1.00	1.00-1.01
Echocardiographic profile						
LV mass index (× 5 g/m ^{2.7})	0.004	1.02	1.01-1.04	0.007	1.11	1.03-1.18
Left atrial dimension (cm/m)	0.006	2.01	1.22-3.33	0.01	1.87	1.13-3.09
Endocardial shortening (%)	0.000	0.95	0.93-0.98	0.001	0.95	0.93-0.98
PP/SVi (mmHg/ml/m ^{2.04})	0.001	1.63	1.23-2.16	0.009	1.46	1.10-1.95
E/A ratio<0.6 and/or E-deceleration time ≥240 msec	0.920	0.99	0.75-1.30	0.95	1.01	0.76-1.33
E/A ratio>1.5 and/or E-deceleration time<160 msec	0.01	0.64	0.46-0.90	0.02	0.65	0.47-0.92
Left atrial systolic force (kdynes)	0.001	1.06	1.03-1.09	0.002	1.05	1.02-1.08
Diabetes status						
Diabetes	--	--	--	0.001	1.98	1.51-2.60

Table 4

Incident HF in relation of diabetes, after sequentially entering urinary/albumin ratio among the markers of preclinical cardiovascular disease, duration and severity of diabetes.

Independent variable	p<	HR	95% Confidence Interval
Urinary albumin/creatinine ratio			
1. Microalbuminuria	<i>0.02</i>	<i>1.46</i>	<i>1.037-1.99</i>
2. Macroalbuminuria	<i>0.001</i>	<i>2.87</i>	<i>1.915-4.22</i>
Diabetes	<i>0.001</i>	<i>1.67</i>	<i>1.245-2.23</i>
Duration and severity			
Duration (years)	<i>0.72</i>	<i>1.00</i>	<i>0.99-1.02</i>
Hba1C (log%)	<i>0.04</i>	<i>1.81</i>	<i>1.04-3.19</i>
Diabetes	<i>0.25</i>	<i>1.27</i>	<i>0.86-1.89</i>