Clinical Paper

Heart Failure Epidemiology in Patients With Diabetes Mellitus Without Coronary Heart Disease

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ABSTRACT

Background: Epidemiology of patients with comorbid heart failure (HF) and diabetes mellitus (DM) without coronary heart disease (CHD) is not well described.

Methods and Results: We assessed HF incidence and outcomes in 2896 participants of the Health ABC Study (age 74.0 ± 3.0 years, 48.4% men, 41.1% black, 34.6% with DM) in relation to prio DM and CHD status. During a median follow-up of 11.4 years, 484 participants (16.7%) developed incident HF; 214 (44.2%) had DM of whom 71 (33.1%) had no prio CHD. Incident HF rate was 2.5% per 100 person-years in those with and 1.5% in those without DM (hazard ratio [HR] 1.66, 95% CI 1.39−1.99). In those with DM, incident HF rate was 4.6% in those with and 1.3% in those without CHD (HR 3.75, 95% CI 2.81−4.99). During a median follow-up of 2.1 years after HF onset, 329 (68.0%) of the participants died. Amongst those with DM, annual mortality was 22.6% in those with versus 25.9% without CHD (HR 0.86, 95% CI 0.61−1.22). All-cause hospitalizations after incident HF in DM patients were 55.0 per 100 person-years in those with and 33.3 in those without CHD (rate ratio [RR] 1.64, 95% CI 1.24−2.16); HF hospitalizations were 42.7 and 30.7 per 100-person years (RR 1.39, 95% CI 1.03−1.86) in those with and without CHD. Reduced ejection fraction was seen in 49.6% of HF patients with DM and CHD and in 34.7% of those without CHD ($P = .08$); mortality but not hospitalization risk tended to be lower in those with reduced compared with preserved ejection fraction regardless of CHD status.

Conclusions: A sizeable proportion of HF in patients with DM develops in the absence of prior CHD; these patients are at risk for mortality similar to those with CHD. These data underscore the importance of modulating risk beyond atherosclerosis in patients with comorbid HF and DM. (*J Cardiac Fail 2019;25:78−86*)

Key Words: Heart failure, diabetes mellitus, epidemiology, outcomes, mortality, hospitalization, ejection fraction.

Patients who have diabetes mellitus (DM) are at a high risk for development of incident heart disease. Although coronary heart disease (CHD) in patients with DM has garnered much interest, the importance of heart failure (HF) in patients with DM has recently gained attention.[1] The prevalence of patients with both comorbidities present

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simultaneously is rising,[2,3] and patients have worse outcomes when they are present simultaneously than when either disease is present alone. Such patients with comorbid DM and HF pose complex management challenges owing to difficult polypharmacy and dietary recommendations. The interest in the development and progression of HF among patients with DM has further accelerated with several antihyperglycemic therapies showing a spectrum of impact on HF ranging from increased to neutral to decreased risk.[4–7] Although CHD is a major risk factor for HF, multiple other mechanisms have also been described that put individuals with DM at risk for HF.[8] Although the complications related to CHD in DM are well described, the risk for HF without clinically manifest CHD in patients with DM is not as well known. In the present study, we sought to describe the epidemiology of HF in patients with DM with reference to preexisting and incident CHD in the Health Aging and Body Composition (Health ABC) Study.[9]

Methods

Study Population

The Health ABC Study enrolled 3075 well functioning community dwelling adults aged 70−79 years from April 1997 to June 1998. Participants were identified from a random sample of white Medicare beneficiaries and all age-eligible black residents in designated ZIP codes in Pittsburgh, Pennsylvania, and Memphis, Tennessee. Exclusion criteria included difficulties with activities of daily living, obvious cognitive impairment, inability to communicate, anticipated move within 3 years, or participation in a trial involving lifestyle intervention. The Institutional Review Boards at both study sites approved the protocol, and all participants provided written informed consents. Participants with known or missing HF status at baseline and those with information missing on preceding CHD (n = 179) were excluded from the analysis (Supplemental Table 1). The final cohort analyzed for the present study included 2896 participants.

Outcomes

All participants were asked to report any hospitalizations and every 6 months were asked direct questions about interim events. Medical records for overnight hospitalizations were reviewed at each site. All first admissions with an overnight stay confirmed as related to HF were classified as incident HF. HF diagnosis was adjudicated based on symptoms, signs, chest radiograph results, and echocardiographic findings, with the use of criteria similar to those used in the Cardiovascular Health Study.[10] The criteria required at least an HF diagnosis from a physician and treatment for HF.[11] In addition, data on left ventricular ejection fraction (LVEF) during the index HF hospitalization was available in a subset of HF cases, and baseline characteristics in those with and without LEVF data are presented in Supplemental Table 2. All deaths were reviewed by the Health ABC Study diagnosis and disease ascertainment committee, and underlying causes of death were determined by central adjudication.

Definitions

Glycosylated hemoglobin (Hb_{A1c}) was measured with the use of Tosoh 2.2 Plus (Tosoh Bioscience, Tokyo, Japan), a fully automated Hb_{A1c} analyzer that uses nonporous ion-exchange high-performance liquid chromatography for separation of Hb_{A1c}, with any labile glycohemoglobin subfractions separated from the Shiff base. The Hb_{A1c} assay was NGSP certified and standardized to the Diabetes Control and Complications Trial assay method. DM at baseline was defined as self-report of DM, antihyperglycemic medication use, or $Hb_{A1c} \geq 6.5\%$.

Prevalent CHD was defined as: (1) history of surgical or percutaneous revascularization, (2) electrocardiographic evidence of myocardial infarction, or (3) self-reported history of myocardial infarction or angina accompanied by use of antianginal medications. CHD for the purpose of this study included patients with both prevalent CHD at baseline and incident CHD including hospitalization for myocardial infarction or angina pectoris or elective coronary revascularization occurring after the inception of the cohort but before the onset of HF.[12]

Race was self-defined by the participant. Hypertension was defined as self-reported history of physician diagnosis accompanied by use of antihypertensive medications. Smoking was defined as current, past (≥100 lifetime cigarettes), or never. Left ventricular hypertrophy was diagnosed based on the following criteria; R amplitude >26 mm in either V5 or V6, >20 mm in any of leads I, II, III, or aVF, >12 mm in lead aVL, or R in V5 or V6 plus S amplitude in V1 >35 mm. LVEF was defined as preserved if ≥40% or reduced if <40%.

Risk Factors

We have previously reported independent predictors of incident HF in the Health ABC HF risk model, including age, history of smoking, CHD, left ventricular hypertrophy, systolic blood pressure, heart rate, and serum glucose, albumin, and creatinine levels.[13] To evaluate the prevalence of these risk factors in relation to baseline DM, the continuous predictors were dichotomized with the use of clinically relevant cutoffs. Systolic blood pressure was dichotomized as controlled versus uncontrolled at 140 mm Hg, fasting glucose at ≥126 mg/dL, resting heart rate at 75 beats/min, and albumin at 3.8 mg/dL. Creatinine was converted to estimated glomerular filtration rate (eGFR) with the use of the Modification of Diet in Renal Disease[14] formula and a cutoff of 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ was used to define impaired GFR. Smoking was collapsed into a binary predictor (current yes/no).

Statistical Analysis

The baseline characteristics were compared in individuals who developed HF with and without DM. Continuous variables were compared by means of the *t* test and categoric variables by means of the chi-square test. Cumulative event rates were obtained with the use of the Kaplan-Meier method and compared with the use of the log-rank statistic.

Time-to-event analyses were conducted with the use of Cox proportional hazard models. The proportional hazards assumption was evaluated by examining the Schoenfeld residuals. To assess the association of established risk factors identified in the Health ABC HF model[9,13,15] in participants with versus without baseline DM, multivariable hazard ratios (HR) adjusted for sex were calculated. All-cause and HF-related hospitalizations after HF development were analyzed as count data over time at risk. Hospitalization rates and rate ratios (RRs) with 95% confidence intervals (CIs) were obtained with the use of a Poisson regression model for participants who developed HF with versus without preceding DM, adjusted for age and sex. In a secondary analysis, we examined post-HF outcomes in a subset of participants with LVEF available at the time of HF diagnosis, categorized as preserved (≥40%) or reduced (<40%). All analyses were performed with the use of Stata release 11 (Stata Corp, College Station, Texas).

Results

Baseline Participant Characteristics

The mean age of participants was 74 ± 3 years; 48.4% were men, 41.1% were black, 34.6% had DM, and 32.9% had CHD. The baseline characteristics are presented in Table 1 and Supplemental Table 3. Male sex, smoking, heart rate, hypertension, body mass index, systolic blood pressure, serum creatinine, high triglycerides, and low high-density lipoprotein cholesterol levels were higher or more common in those with than without DM. Compared with participants who did not develop HF, those who did were older and had higher systolic blood pressure, heart rate, and body mass index in both those with and without DM.

Incident Heart Failure

After a median follow-up of 11.4 (interquartile range [IQR] 7.0−11.7) years, 484 (16.7%) participants developed incident HF. Among participants who developed HF, 214 (44.2%) had DM and of these, 71 (33.1%) had no prior CHD. Of patients who did not have DM who developed incident HF, 106 (39.3%) had no prior CHD. The incidence of HF in relations to age, sex, race, and CHD are presented in Fig. 1 and Table 2. Incident HF rates per 100 person years were 1.8% (Interquartile range (IQR) 1.7%−2.0%) overall, 2.5% (2.1%−2.8%) in those with DM, and 1.5% (1.3%−1.7%) in those without DM (HR 1.66, 95% CI

Table 1. Baseline Participant Characteristics

	Entire Cohort (n = 2896)				Incident Heart Failure Cohort (n = 484)		
Characteristic	Overall (n = 2896)	Diabetes (n = 1002)	No Diabetes (n = 1894)	*P* Value	Diabetes (n = 214)	No Diabetes (n = 270)	*P* Value
Age (y)	73.6 (2.9)	73.6 (2.9)	73.6 (2.9)	.817	74.3 (2.8)	74.1 (2.9)	.323
Male (%)	1394 (48.4%)	516 (51.7%)	878 (46.2%)	.008	116 (53.9%)	138 (50.6%)	.498
White (%)	1706 (59.4%)	399 (39.6%)	1307 (69.3%)	<.001	90 (41.8%)	181 (67.1%)	<.001
Smoking status (%)				.007			.718
Never	1281 (44%)	414 (41.8%)	867 (46.2%)		84 (39.6%)	102 (37.4%)	
Current	304 (11%)	127 (13.2%)	177 (9.9%)		29 (13.2%)	32 (12.1%)	
Past	1307 (45.1%)	459 (46.2%)	848 (45.1%)		100 (47.3%)	136 (50.6%)	
Alcohol (%)				<.001			.014
Never	1435 (49.5%)	584 (58.3%)	851 (45.1%)		129 (60.5%)	130 (48.4%)	
Occasional	614 (20.9%)	190 (18.7%)	424 (22%)		40 (18.7%)	52 (19.8%)	
1−7 drinks/wk	620 (22%)	161 (16.5%)	459 (24.2%)		36 (16.5%)	58 (22%)	
≥8 drinks/wk	215 (7.7%)	64 (6.6%)	151 (7.7%)		9 (4.4%)	28 (9.9%)	
Any antihypertensive use (%)	1520 (52.8%)	617 (61.6%)	903 (47.3%)	<.001	165 (77%)	163 (60.5%)	<.001
Any antilipid drug use (%)	396 (13.2%)	152 (15.4%)	244 (13.2%)	.09	47 (22%)	39 (14.3%)	.032
Aspirin use (%)	1069 (37.4%)	387 (38.5%)	682 (36.3%)	.169	108 (50.6%)	110 (40.7%)	.033
Hypertension (%)	1442 (49.5%)	600 (59.4%)	842 (44%)	<.001	169 (79.2%)	199 (73.7%)	.2
Left ventricular hypertrophy (%)	342 (12.1%)	136 (13.2%)	206 (11%)	.032	39 (18.7%)	40 (14.3%)	.313
Body mass index (kg/m^2)	27.3 (4.8)	28.6 (5.1)	26.6 (4.5)	<.001	29.0 (4.9)	27.3 (4.6)	<.001
Systolic blood pressure (mm Hg)	136.0 (20.9)	138.4 (21.4)	134.7 (20.6)	<.001	142.1 (23.7)	140.8 (22.2)	.548
Heart rate (beats/min)	65.3 (11.1)	67.4 (11.7)	64.3 (10.5)	<.001	68.9 (13.4)	65.4 (10.6)	.001
Hemoglobin A_{1c} (%)	6.3 (1.1)	7.4 (1.3)	5.8 (0.4)	<.001	7.6 (1.4)	5.8 (0.4)	<.001
Albumin (g/dL)	4.0 (0.3)	4.0 (0.3)	4.0 (0.3)	.025	4.0 (0.3)	4.0 (0.3)	.825
Creatinine (mg/dL)*	1.0 (0.9−1.2)	1.0 (0.9−1.2)	1.0 (0.9−1.1)	<.001	1.0 (0.9−1.3)	1.0 (0.9−1.1)	.001
Total cholesterol (mg/dL)	203.1 (38.3)	203.1 (39.8)	203.2 (37.5)	.976	197.9 (38.8)	204.0 (37.3)	.083
Low-density lipoprotein (mg/dL)	121.9 (34.6)	122.7 (36.3)	121.4 (33.7)	.363	118.3 (32.3)	123.7 (34.1)	.084
High-density lipoprotein (mg/dL)	54.3 (17.1)	52.5 (16.7)	55.2 (17.2)	<.001	50.3 (16.2)	53.3 (16.9)	.05
Triglycerides (mg/dL)	118.0 (88.0−163.0)	119.5 (89.0−171.0)	117.0 (87.0−158.0)	.003	126.0 (87.0−170.5)	117.0 (89.0−158.0)	.11

Values are presented as mean (SD), n (%), or median (interquartile range) (the latter owing to highly skewed distributions and compared by means of the Mann-Whitney test.

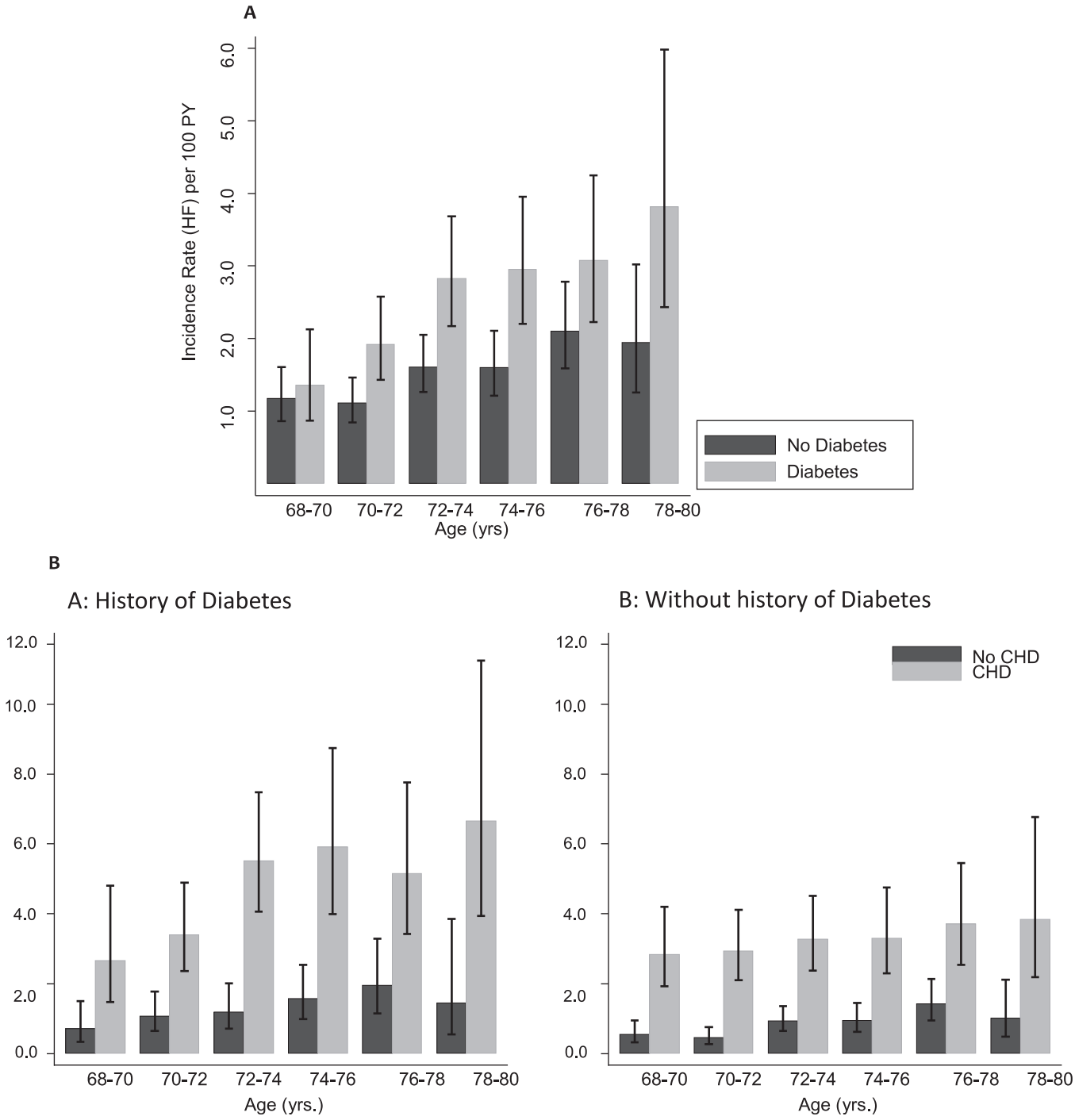

Fig. 1. Incident heart failure (HF) rates per 100 person-years stratified by (**A**) presence and absence of diabetes mellitus and (**B**) coronary heart disease status in those with and without diabetes. Error bars represent 95% confidence intervals.

1.39−1.99; $P < .01$). In individuals with DM, the rates of incidence of HF were 4.6% (3.9%−5.5%) in those with CHD and 1.3% (1.0%−1.6%) in those without CHD (HR 3.75, 95% CI 2.81−4.99; $P < .001$). In those without DM, the incidences of HF in those with and without CHD were, respectively, 3.2% (2.8%−3.8%) and 0.8% (0.7%−1.0%; HR 4.17, 95% CI 3.24−5.37; $P < .001$). Several HF risk variables, including age, albumin, creatinine, heart rate, left ventricular hypertrophy, systolic blood pressure, and smoking, were independently associated with HF in those with and without diabetes at baseline (Supplemental Table 4). No differential association of HF risk factors was observed in those with and without diabetes (Supplemental Table 4).

Table 2. Heart Failure (HF) Incidence by Diabetes Status

	Overall			Diabetes			No Diabetes		
Group	HF	n	Incidence (95% CI)	HF	n	Incidence (95% CI)	HF	n	Incidence (95% CI)
Overall	484	2896	1.8 (1.7−2.0)	214	1002	2.5 (2.1−2.8)	270	1894	1.5 (1.3−1.7)
Race									
White	271	1706	1.7 (1.5−1.9)	90	399	2.5 (2.0−3.0)	181	1307	1.4 (1.2−1.6)
Black	213	1190	2.0 (1.8−2.3)	124	603	2.4 (2.0−2.9)	89	587	1.7 (1.3−2.0)
Sex									
Male	254	1394	2.1 (1.8−2.3)	116	516	2.7 (2.2−3.2)	138	878	1.7 (1. 5−2.0)
Female	230	1502	1.6 (1.4−1.8)	98	486	2.2 (1.8−2.7)	132	1016	1.3 (1.1−1.6)
CHD									
No	177	1941	0.9 (0.8−1.1)	71	608	1.3 (1.0−1.6)	106	1333	0.8 (0.7−1.0)
Yes	307	955	3.8 (3.4−4.2)	143	394	4.6 (3.9−5.5)	164	561	3.2 (2.8−3.8)

Incidence rate calculated per 100 person-years. The rates of incident HF significantly differed by race ($P < .01$), sex ($P < .01$), and diabetes status ($P < .001$) in all subjects. Information on prior coronary heart disease events was missing for 39 participants. CI, confidence interval.

Outcomes

Participants without HF had an annual mortality per 100 person-years of 4.2% (95% CI 3.9%−4.4%) and all-cause hospitalization rate of 2.4 per 100 person-years. During a median follow-up of 2.1 (IQR 0.4−5.0) years after HF onset, 329 participants (68.0%) died. Annual mortality per 100 person-years after HF development was 23.5% (95% CI 20.2%−27.5%) in those with and 21.3% (95% CI 18.3%−24.7%) in those without DM (Fig. 2; HR 1.10, 95% CI 0.89−1.37; $P = .377$).

Among those with DM, annual mortality was 22.6% (18.8%−27.3%) after HF development in those with CHD versus 25.9% (19.5%−34.3%) in those without CHD (HR 0.86, 95% CI 0.61−1.22; $P = .40$). In those without DM,

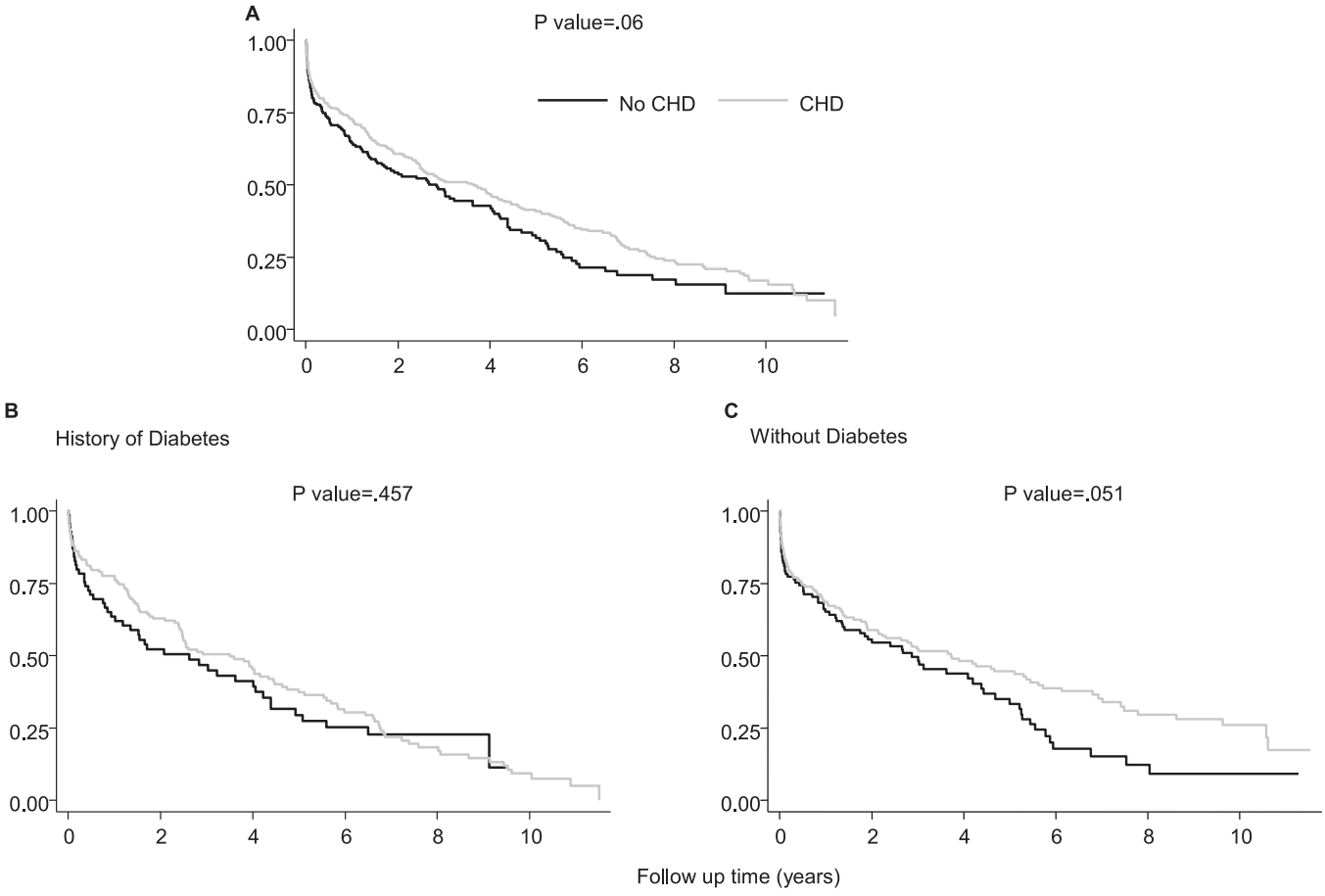

Fig. 2. Survival of patients with heart failure by coronary heart disease (CHD): (**A**) overall, (**B**) patients with diabetes mellitus, and (**C**) patients without diabetes mellitus.

annual mortality was 18.4% (15.1%−22.4%) in those with CHD versus 27.3% (21.6%−34.4%) in those without CHD (HR 0.73, 95% CI 0.53−0.99; $P = .05$).

There were 641 all-cause admissions (43.5 per 100 person-years) after HF development. Of these, 332 (51.7%, 49.1 per 100 person-years) occurred in those with DM and 309 (48.2%, 38.6 per 100 person- years) in those without DM (RR 1.27, 95% CI 1.10−1.48; $P = .02$). All-cause hospitalizations after HF were 270 (55.0 per 100 person-years) and 62 (33.3 per 100 person-years) in DM patients with CHD without CHD, respectively (RR 1.64, 95% CI 1.24−2.16; $P < .001$).

There were 510 HF-related hospitalizations (79.6%, 34.6 per 100 person-years). Of these, 266 (52.2%, 39.4 per 100 person-years) occurred in those with DM and 244 (47.8%, 30.3 per 100 person-years) in those without DM (RR 1.30, 95% CI 1.09−1.54; $P = .03$). HF hospitalizations in DM patients with CHD were 209 (42.7 per 100 person-years) and 57 (30.7 per 100 person-years) in those without CHD (RR 1.39, 95% CI 1.03−1.86; $P < .03$).

Preserved Versus Reduced Ejection Fraction

Data on left ventricular ejection fraction during the index HF hospitalization were available in 372 participants (76.8%; Table 3). Median ejection fraction was 45% (30%−55%); this was numerically but not statistically significantly lower in those with than without DM (40% vs 45%, respectively; $P = .30$). The proportions of participants with reduced versus preserved ejection fraction were, respectively, 45.2% and 54.8% for those with DM and 39.8% versus 60.2% for those without DM ($P = .30$).

Mortality but not hospitalization risk was worse among participants with reduced versus preserved ejection fraction for those with DM (HR 2.10, 95% CI 1.46−2.99 [$P < .001$] for mortality [Fig. 3], RR 1.10, 95% CI 0.87−1.38 [$P = .436$] for all-cause hospitalization, and RR 1.17, 95% CI 0.90−1.51 [$P = .240$] for HF hospitalization) and opposite for those without DM (HR 1.02, 95% CI 0.72−1.45 [$P = .91$] for mortality, RR 1.75, 95% CI 1.37−2.24 [$P < .001$] for all cause hospitalization, and RR 2.12, 95% CI 1.60−2.80 [$P < .001$] for HF hospitalization).

Mean LVEFs in participants with DM with and without CHD were 40% and 45%, respectively ($P = .12$). Reduced ejection fraction was seen in 49.6% of HF patients with DM and CHD and in 34.7% of those without CHD ($P = .08$). In those with DM, hospitalization risk with reduced versus preserved ejection fraction did not differ for participants with CHD (HR 1.50, 95% CI 1.10−2.04 [$P = .01$] for mortality, RR 1.06, 95% CI 0.82−1.38 [$P = .63$] for all-cause hospitalizations, and RR 1.13, 95% CI 0.84−1.51 [$P = .42$] for HF hospitalizations) or those without preceding CHD (HR 1.33, 95% CI 0.87−2.05 [$P = .19$] for mortality, RR 1.47, 95% CI 0.80−2.70 [$P = .21$] for all-cause hospitalization, and RR 1.62, 95% CI 0.87−3.00 [$P = .13$] for HF hospitalizations).

Discussion

In this study, consistently with previous reports, we found that DM was an independent predictor of incident HF in the elderly.[16,17] However, more than one-half of incident HF cases developed in those without DM, and in those who did have DM, one-third did not have history of CHD. These proportions represent a relatively large segment of the at-risk HF population with DM that may not be as aggressively treated for HF prevention if the main risk factor medication focus in patients with DM is to target CHD risk.

As the proportion of older adults in the population increases, the prevalence of HF is predicted to rise substantially.[18,19] Elderly individuals are more likely than younger individuals to develop HF, especially HF with preserved ejection fraction, in part owing to age-related cardiac structural and functional remodeling. Among the elderly, the impact of preexisting DM on HF outcomes has not been ascertained in detail, which is particularly important in the context of newer antihyperglycemic agents that have been shown to increase in some and reduce in other cases the risk of HF hospitalizations.[4−7]

We observed that participants who develop HF with a history of DM were at similar risk for all-cause mortality compared with those without DM. This association, interestingly, was not seen to be modulated by either the presence or the absence of prior CHD in both those with and without DM, although it was clear that DM patients with

Table 3. Incidence of HFpEF and HFrEF

	Overall			HFrEF		HFpEF	
Group	HF	n	Incidence (95% CI)	HFrEF	Incidence (95% CI)	HFpEF	Incidence (95% CI)
Overall	484	2896	1.8 (1.7−2.0)	157	0.6 (05−0.7)	222	0.8 (0.7−0.9)
Diabetes							
No	270	1894	1.5 (1.3−1.7)	82	0.5 (0.4−0.6)	130	0.7 (0.6−0.9)
Yes	214	1002	2.5 (2.1−2.8)	75	0.9 (0.7−1.1)	92	1.1 (0.9−1.3)
CHD							
No	177	1941	0.9 (0.8−1.1)	45	0.2 (0.2−0.3)	89	0.5 (0.4−0.6)
Yes	307	955	3.8 (3.4−4.2)	112	1.4 (1.1−1.7)	133	1.6 (1.4−1.9)

Incidence rate calculated per 100 person-years. Information on ejection fraction was available on a subset if HF patients: 380 (78.5%) of those with HF. CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

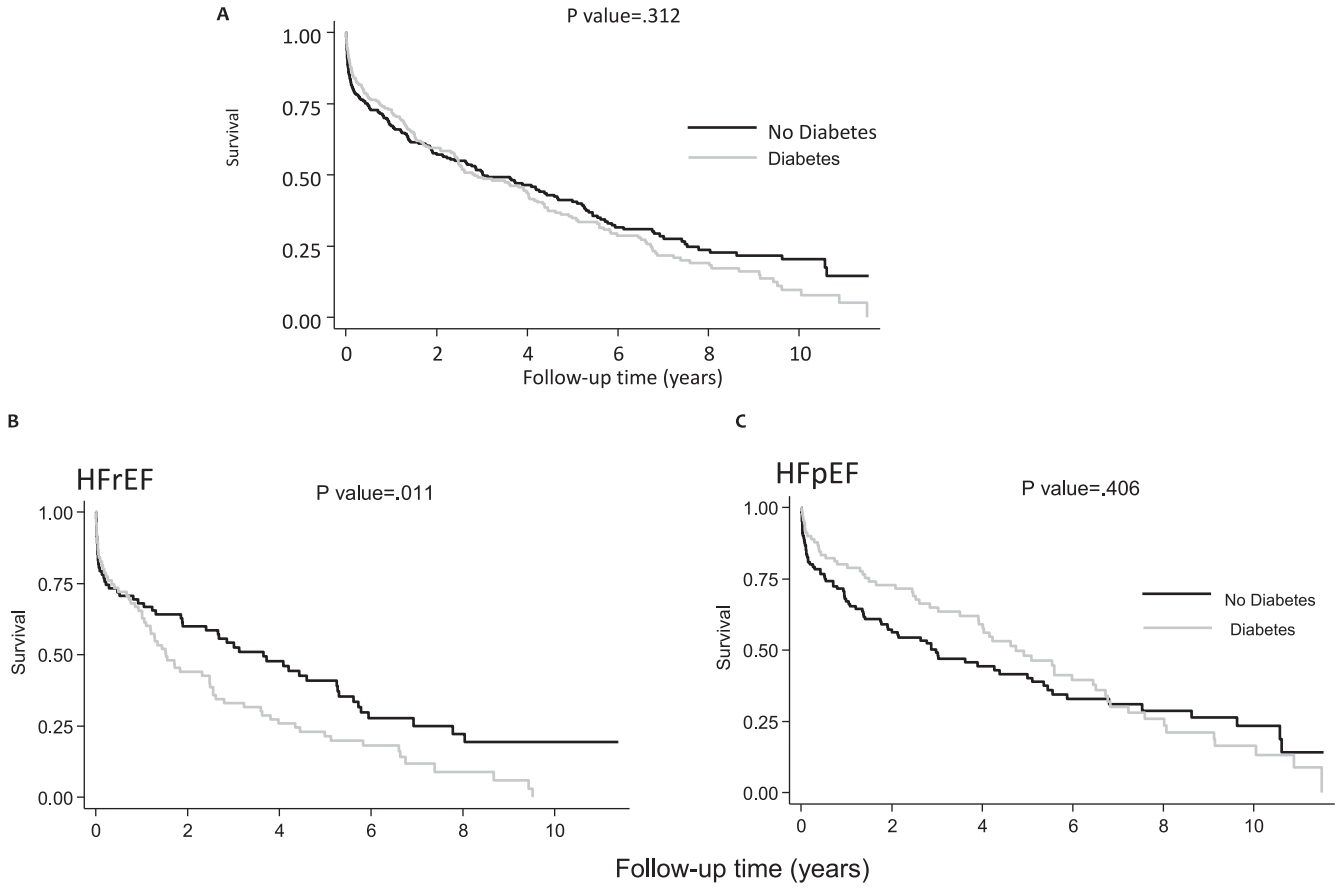

Fig. 3. Survival of patients with heart failure by diabetes mellitus: (**A**) overall, (**B**) patients with heart failure and reduced ejection fraction (HFrEF); and (**C**) patients with heart failure and preserved ejection fraction (HFpEF).

CHD did experience more hospitalizations. Beyond increased prevalence of vascular risk factors, such as hypertension, DM, obesity, and renal dysfunction, all of which lead to cardiomyopathic changes and exert direct negative effects on the myocardium without prior CHD, older adults show higher levels of low-grade inflammation,[20] which has been linked to development of HF[21] potentially through altered response to stressors, enhanced extracellular matrix remodeling, direct effects on the myocardium, and functional vascular changes, including increased vascular stiffness and endothelial dysfunction.[22] Such changes in endothelial function worsen with aging[23] and have been demonstrated to contribute to development of HF independently of traditional risk factors.[10,24] Overall, older participants who developed HF with preceding DM had significantly higher all-cause and HF readmissions than age-matched participants without DM.

There may be physiologic mechanisms specific to development of HF in older people unrelated to DM or vascular disease. For example, it is known that more collagen is deposited in the ventricles with aging.[25,26] This may be related to the aging process or could be secondary to common comorbidities such as diabetes and hypertension.[27,28] Importantly, this could represent a pathophysiologic target to reduce HF in the elderly. Future research is needed to determine the mechanisms relevant to HF development among the elderly beyond that which can be attributed to diabetes and vascular disease.[29,30]

Study Limitations

Our study has several limitations. Incident HF was diagnosed based on HF hospitalization which therefore likely underestimated the true incidence. Echocardiography was not performed at baseline, and therefore we did not have the data on asymptomatic left ventricular dysfunction. However, this does not undermine the significance of clinical HF prevention. In addition, this is consistent with CHD risk prediction and prevention strategies; eg, in such studies, patients do not routinely undergo left heart catheterization or carotid or peripheral angiography to rule out asymptomatic coronary artery, and the focus is on clinically manifest vascular or coronary disease.

Conclusion

This study underscores the importance of DM in relation to the risk for HF as well as reaffirms the existence of an important yet largely underappreciated clinical entity of HF without DM. Importantly, although the risk of micro- and macrovascular atherosclerotic complications of DM have been well researched, including myocardial infarction and stroke, the risk of developing HF in the absence of CHD

has largely not been as much discussed. A sizeable proportion of HF in patients with DM develops in the absence of prior CHD; these patients are also at high risk for mortality compared with those with a history of CHD. These data underscore the importance of modulating risk for adverse outcomes beyond management of atherosclerosis in patients with comorbid HF and DM.

Disclosures

James Januzzi has consulted for Roche Diagnostics, Abbott, Philips, Novartis, Critical Diagnostics, and Janssen, received research support from Prevencio, Singulex, Novartis, and Cleveland Heart Labs, and been on committees/DSMB for Boehringer-Ingelheim, Janssen, Pfizer, Abbvie, Aand mgen. Darren McGuire reports personal fees for trial leadership from Boehringer Ingelheim, Janssen Research and Development, Sanofi US, Merck Sharp and Dohme Corp, Novo Nordisk, GlaxoSmithKline, Astra Zeneca, Lexicon, Eisai, and Esperion and personal consultancy fees from Boehringer Ingelheim, Sanofi US, Merck Sharp and Dohme Corp, Novo Nordisk, Astra Zeneca, and Lilly USA. Naveed Sattar has consulted for Boehringer Ingelheim, Janssen, Eli-Lilly, and Novo-Nordisk and received research support from Boehringer Ingelheim and Astra Zeneca. Javed Butler is a consultant for Amgen, Astra Zeneca, Bayer, BMS, Janssen, Luitpold, Medtronic, Novartis, Relypsa, Vifor, and ZS Pharma. All other authors have no disclosures.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2018.10.015.

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