# Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes According to Diabetes Status in Patients With Heart Failure and Preserved Ejection Fraction

## A Report From the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction)

Editorial, see p 736

**BACKGROUND:** In patients with heart failure and preserved ejection fraction, little is known about the characteristics of, and outcomes in, those with and without diabetes mellitus.

**METHODS:** We examined clinical and echocardiographic characteristics and outcomes in the I-Preserve trial (Irbesartan in Heart Failure With Preserved Ejection Fraction) according to history of diabetes mellitus. Cox regression models were used to estimate hazard ratios for cardiovascular outcomes adjusted for known predictors, including age, sex, natriuretic peptides, and comorbidity. Echocardiographic data were available in 745 patients and were additionally adjusted for in supplementary analyses.

**RESULTS:** Overall, 1134 of 4128 patients (27%) had diabetes mellitus. Compared with those without diabetes mellitus, they were more likely to have a history of myocardial infarction (28% versus 22%), higher body mass index (31 versus 29 kg/m$^2$), worse Minnesota Living With Heart Failure score (48 versus 40), higher median N-terminal pro-B-type natriuretic peptide concentration (403 versus 320 pg/mL; all $P<0.01$), more signs of congestion, but no significant difference in left ventricular ejection fraction. Patients with diabetes mellitus had a greater left ventricular mass and left atrial area than patients without diabetes mellitus. Doppler E-wave velocity (86 versus 76 cm/s; $P<0.0001$) and the E/e' ratio (11.7 versus 10.4; $P=0.010$) were higher in patients with diabetes mellitus. Over a median follow-up of 4.1 years, cardiovascular death or heart failure hospitalization occurred in 34% of patients with diabetes mellitus versus 22% of those without diabetes mellitus (adjusted hazard ratio, 1.75; 95% confidence interval, 1.49–2.05), and 28% versus 19% of patients with and without diabetes mellitus died (adjusted hazard ratio, 1.59; confidence interval, 1.33–1.91).

**CONCLUSIONS:** In heart failure with preserved ejection fraction, patients with diabetes mellitus have more signs of congestion, worse quality of life, higher N-terminal pro-B-type natriuretic peptide levels, and a poorer prognosis. They also display greater structural and functional echocardiographic abnormalities. Further investigation is needed to determine the mediators of the adverse impact of diabetes mellitus on outcomes in heart failure with preserved ejection fraction and whether they are modifiable.

**CLINICAL TRIAL REGISTRATION:** URL: http://www.clinicaltrials.gov. Unique identifier: NCT00095238.

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Sources of Funding, see page 733

**Key Words:** diabetes mellitus ■ echocardiography ■ heart failure

## Clinical Perspective

### What Is New?

- Among individuals with heart failure and preserved ejection fraction, those with diabetes mellitus have more evidence of congestion and higher N-terminal pro-B-type natriuretic peptide concentrations compared with patients with heart failure and preserved ejection fraction without diabetes mellitus.
- The former patients also reported worse health-related quality of life and had a higher risk of cardiovascular mortality and hospitalization.
- They had more structural and functional echocardiographic abnormalities, including evidence of elevated left ventricular filling pressure, which may, at least in part, mediate the adverse consequences of diabetes mellitus in patients with heart failure and preserved ejection fraction.

### What Are the Clinical Implications?

- The study underlines the need for further investigation of which treatment approaches to both heart failure and diabetes mellitus might improve outcomes in patients with both conditions.
- The finding of more signs of congestion, higher N-terminal pro-B-type natriuretic peptide levels and echocardiographic evidence of higher filling pressures in patients with compared with those without diabetes mellitus raises the possibility that more intensive diuretic therapy might be therapeutically helpful, although this hypothesis needs to be tested prospectively in a clinical trial.

Diabetes mellitus is common in patients with heart failure (HF) and preserved ejection fraction (HFpEF). It has been suggested that diabetes mellitus plays a central pathophysiological role in the development of HFpEF, although the exact mechanisms are debated and there are few comparative data on cardiac structure and function in patients with HFpEF with and without diabetes mellitus.[1–4] In addition, although it is well known that diabetes mellitus is associated with worse outcomes in patients with HF and reduced ejection fraction, less is known about the clinical and echocardiographic characteristics of and outcomes in patients with HFpEF with diabetes mellitus compared with those without diabetes mellitus.[1–3] The importance of better understanding the relationship between diabetes mellitus and HF has been underscored by recent trials in patients with type 2 diabetes mellitus that have suggested that some drugs (thiazolidinediones and possibly certain dipeptidyl peptidase-4 inhibitors) may increase the risk of HF[4–6] and others (the sodium glucose cotransporter 2 inhibitor empagliflozin) may decrease the risk.[7] Three glucagon-like peptide-1 agonist trials have shown no clear-cut effect on HF.[8–10] The aforementioned trials largely reported incident HF, and there are few data on the effect of antidiabetes drugs in patients with established HF. One notable exception is a recent trial demonstrating no benefit of liraglutide in patients with HF and reduced ejection fraction recently hospitalized with decompensation.[11]

Although the type of HF affected by these treatments was not characterized in any of the trials mentioned, it is likely that many or even most cases were HFpEF.[12] With this study, we aimed to give clinicians a better understanding of the consequences of diabetes mellitus in patients with HFpEF and to give insight into potential pathophysiological mechanisms and therapeutic targets for future research.

In the present study, we examined the risk of adverse cardiovascular outcomes according to diabetes status adjusted for known risk factors in the I-Preserve trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). In a subgroup of patients, a full echocardiographic examination was performed[13] that allowed a detailed comparison of cardiac structure and function in patients with HFpEF with and without diabetes mellitus.

## METHODS

I-Preserve was a randomized trial that examined the effects of the angiotensin II receptor antagonist irbesartan on morbidity and mortality in patients with HFpEF.[14] The rationale, design, and findings from I-Preserve have previously been reported.[14–16] Briefly, patients enrolled in the trial were ≥60 years of age and had HF symptoms and a left ventricular (LV) ejection fraction (LVEF) ≥45%. In addition, patients who had been hospitalized for HF during the previous 6 months were required to have current New York Heart Association class II, III, or IV symptoms and echocardiographic, electrocardiographic, or chest x-ray findings supporting a diagnosis of HF or underlying cardiac disease. If they had not been recently hospitalized for HF, they were required to have ongoing class III or IV symptoms with the corroborative evidence described above. The corroborative evidence required was at least one of pulmonary congestion on a chest x-ray, LV hypertrophy or an enlarged left atrium on an echocardiogram, or LV hypertrophy or left bundle-branch block on an ECG. Details of these criteria have been described previously.[14]

Angiotensin-converting enzyme inhibitor therapy was limited to those patients with a specific indication other than hypertension (eg, diabetes mellitus with complications and significant coronary or peripheral artery disease). In addition, only one third of randomized patients at each site were permitted to be treated with an angiotensin-converting enzyme inhibitor. Treatment with an angiotensin II receptor blocker was prohibited, although a patient could be enrolled if angiotensin II receptor blocker treatment was discontinued at least 14 days earlier. Exclusion criteria included a systolic blood pressure <100 or >160 mm Hg or a diastolic blood pressure >95 mm Hg despite antihypertensive therapy, a creatinine level >2.5 mg/dL (221 μmol/L), or a potassium concentration >5.2 mmol/L. The ethics committee of each of the 293 participating sites in 25 countries approved the trial, and all patients provided informed

consent. Detailed echocardiographic measurements were made in a subset of 745 patients at baseline, as described previously.[8] Cardiovascular outcomes and all-cause mortality did not differ between patients randomly assigned to irbesartan or placebo.[15]

## Outcomes

For this report, the primary outcome examined was the composite of cardiovascular death or HF hospitalization, as well as each of the components of this composite separately. This composite was slightly different from the original primary outcome of I-Preserve, which was all-cause mortality or protocol-specified cardiovascular hospitalization (HF, myocardial infarction, stroke, unstable angina, ventricular or atrial dysrhythmia), but in keeping with the primary composite outcome of most recent HF trials. We also report all-cause mortality.

All deaths and hospitalizations were adjudicated by an independent end-point committee.

## Statistical Analyses

Baseline characteristics are presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences in baseline characteristics according to diabetes mellitus were assessed with a $\chi^2$ test for categorical covariates and 2-sided *t* tests and Kruskal-Wallis test as appropriate. Tests for interactions between diabetes mellitus and age, sex, and ischemic origin were performed, but none were significant. Incidence rates of the outcomes of interest are presented per 100 person-years, and the risks of HF hospitalization, cardiovascular death, and the composite outcome were estimated as hazard ratios in Cox regression models with those with no history of diabetes mellitus used as reference. The adjusted model included variables previously validated for the I-Preserve study[16]: age, sex, quality of life, hospitalization for HF in the past 6 months, LVEF, heart rate, ischemic origin, estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide (NT-proBNP; log transformed), neutrophils (log transformed), chronic obstructive pulmonary disease/asthma, and previous myocardial infarction. The outcomes of interest were also assessed by cumulative incidence plots with the Nelson-Aalen method. We conducted competing-risk analyses for all nonfatal events (and for cardiovascular death, the competing risk of all-cause death) using the Fine and Gray approach for the subdistribution of a competing risk.[17] As a supplementary analysis, we stratified patients with diabetes mellitus according to insulin use and nonuse.

In patients with echocardiographic measurements available, we further adjusted for LV systolic and diastolic properties and measurements of LV structure. These results are presented separately as a subgroup analysis. To explore the potential for overfitting of the model with echocardiographic data that were available in only a subset of patients, we conducted sensitivity analyses. In the first, we removed end-systolic left atrial area and LV mass from the model, and in the second, we calculated a single continuous risk score variable from the previously described multivariable risk score for I-Preserve and added this to a model with the echocardiographic measurements. We did not adjust for randomization arm because irbesartan had no effect on any outcome in I-Preserve and no interaction with diabetes mellitus was found. All *P* values are 2 sided, and a value of $P<0.05$ was considered significant. All analyses were performed separately with Stata version 14 (StataCorp, College Station, TX).

# RESULTS

## Baseline Characteristics

Overall, 1134 of 4128 patients (27%) enrolled in I-Preserve had a diagnosis of diabetes mellitus at baseline. The characteristics of patients with and without diabetes mellitus at baseline are shown in Table 1. Patients with diabetes mellitus were slightly younger and had higher heart rate and body mass index but not statistically different blood pressure and renal function. Furthermore, patients with diabetes mellitus had higher NT-proBNP, despite no difference in LVEF and prevalence of atrial fibrillation. They were more likely to have an ischemic origin, were about twice as likely to have undergone percutaneous coronary intervention or coronary artery bypass grafting (20% versus 11%), and were more likely to have had a stroke. Although patients with and without diabetes mellitus did not differ in distribution of New York Heart Association class, those with diabetes mellitus had a significantly worse quality of life as measured by the Minnesota Living With Heart Failure score. Background use of medications was comparable except for angiotensin-converting enzyme inhibitor and lipid-lowering drugs, both of which were more common in patients with diabetes mellitus. Signs and symptoms of HF and electrocardiographic findings of LV hypertrophy, left bundle-branch block, and atrial fibrillation/flutter did not differ significantly between those with and those without diabetes mellitus at baseline.

## Echocardiographic Measurements

Of the 745 patients in the echocardiographic substudy, 187 (25%) had diabetes mellitus (Table 2). The echocardiographic data were incomplete, especially for certain measurements of diastolic function. We had a measurement of LVEF in all 745 patients, left atrial area in 696 patients, and end-systolic LV volume in 581 patients. The E/A ratio was available in 647 patients, but the E/e ratio was available in only 515 patients. The baseline characteristics of this subset of patients are presented in Table I in the online-only Data Supplement. The differences between patients with and without diabetes mellitus in this subset reflected those in the overall trial.

In terms of LV structure, patients with diabetes mellitus had a larger end-systolic dimension (3.3±0.7 versus 3.2±0.7 cm; $P=0.02$), larger end-diastolic dimension (4.9±0.6 versus 4.8±0.6 cm; $P=0.044$), and greater LV


*Circulation.* 2017;135:724–735. DOI: 10.1161/CIRCULATIONAHA.116.024593

**Table 1. Baseline Characteristics Stratified by Presence of Diabetes Mellitus in I-Preserve**

| | All Patients (N=4128) | No Diabetes Mellitus (n=2994) | Diabetes Mellitus (n=1134) | *P* Value |
|---|---|---|---|---|
| Age, mean, y, n (%) | 72±7 | 72±7 | 71±7 | 0.0006 |
| ≥65 y | 3388 (82) | 2480 (83) | 908 (80) | 0.04 |
| ≥75 y | 1413 (34) | 1036 (35) | 377 (33) | 0.41 |
| Female sex, n (%) | 2491 (60) | 1802 (60) | 689 (61) | 0.74 |
| Race, n (%) | | | | <0.0001 |
| White | 3859 (94) | 2829 (95) | 1030 (91) | |
| Black | 82 (2) | 47 (2) | 35 (3) | |
| Other | 187 (4) | 118 (4) | 69 (6) | |
| EF, % | 59±9 | 59±9 | 60±9 | 0.45 |
| Body mass index, kg/m$^2$, n (%) | 30±5 | 29±5 | 31±6 | <0.0001 |
| Underweight (<18.5 kg/m$^2$) | 20 (1) | 20 (1) | 0 (0) | <0.0001 |
| Normal (18.5–24.9 kg/m$^2$) | 624 (15) | 514 (17) | 110 (10) | |
| Overweight (25–29.9 kg/m$^2$) | 1744 (42) | 1311 (44) | 433 (38) | |
| Obese (≥30 kg/m$^2$) | 1740 (42) | 1149 (38) | 591 (52) | |
| Symptoms, n (%) | | | | |
| NYHA class | | | | 0.07 |
| I | 1 (0) | 0 (0) | 1 (0) | |
| II | 870 (21) | 653 (22) | 217 (19) | |
| III | 3144 (76) | 2264 (76) | 880 (78) | |
| IV | 112 (3) | 76 (3) | 36 (3) | |
| Minnesota Living With Heart Failure score | 42 (28–58) | 40 (27–55) | 48 (30–55) | <0.0001 |
| Examination findings | | | | |
| Rales, n (%) | 1158 (28) | 811 (27) | 347 (31) | 0.0250 |
| CXR congestion, n (%) | 1590 (39) | 1086 (36) | 505 (44) | <0.0001 |
| Jugular venous distention, n (%) | 346 (8) | 229 (8) | 117 (10) | 0.0060 |
| Edema, n (%) | 2255 (55) | 1609 (54) | 646 (57) | 0.0631 |
| Third heart sound, n (%) | 338 (8) | 227 (8) | 111 (10) | 0.0217 |
| Heart rate, bpm | 71±10 | 71±10 | 72±10 | <0.0001 |
| Systolic blood pressure, mm Hg | 136±15 | 136±15 | 137±15 | 0.64 |
| ECG findings | | | | |
| Left bundle-branch block, n (%) | 336 (8) | 247 (8) | 89 (8) | 0.67 |
| LV hypertrophy, n (%) | 1260 (31) | 934 (31) | 326 (29) | 0.13 |
| QRS duration (no pacemaker), ms | 0.10±0.05 | 0.10±0.06 | 0.10±0.06 | 0.1784 |
| Atrial fibrillation/flutter, n (%) | 697 (17) | 497 (17) | 200 (18) | 0.47 |
| Laboratory measurements | | | | |
| NT-proBNP, median (quartiles 1–3), pg/mL | 339 (134–964) | 320 (128–945) | 403 (154–1023) | 0.0074 |
| eGFR, ml/min/1.73m$^2$ | 70 (55–85) | 70 (56–84) | 69 (53–86) | 0.3362 |
| CKD (eGFR <60 ml/min/1.73m$^2$), n (%) | 1363 (33) | 962 (32) | 401 (35) | 0.0488 |
| Hemoglobin, g/dL | 14.0±1.5 | 14.1±1.4 | 13.8±1.6 | <0.0001 |
| Anemia (<11 women/<13 men), n (%) | 514 (13) | 304 (11) | 210 (19) | <0.0001 |
| Neutrophils (quartiles 1–3), cells/μL | 4.3 (3.4–5.3) | 4.2 (3.3–5.2) | 4.6 (3.7–5.6) | <0.0001 |

(*Continued*)

**Table 1. Continued**

| | All Patients (N=4128) | No Diabetes Mellitus (n=2994) | Diabetes Mellitus (n=1134) | *P* Value |
|---|---|---|---|---|
| Medical history, n (%) | | | | |
| HF hospitalization within 6 mo | 1816 (44) | 1294 (43) | 522 (46) | 0.1042 |
| Ischemic origin | 1036 (25) | 710 (24) | 326 (29) | 0.0009 |
| Hypertensive origin | 2622 (64) | 1960 (66) | 662 (58) | <0.0001 |
| Myocardial infarction | 969 (23) | 655 (22) | 314 (28) | <0.0001 |
| Stable angina pectoris | 1652 (40) | 1217 (41) | 435 (38) | 0.1804 |
| Unstable angina pectoris | 315 (8) | 197 (7) | 118 (10) | <0.0001 |
| Hypertension | 3650 (88) | 2625 (88) | 1025 (90) | 0.0150 |
| Atrial fibrillation | 1209 (29) | 868 (29) | 341 (30) | 0.50 |
| Stroke | 399 (10) | 263 (9) | 136 (12) | 0.002 |
| COPD/asthma | 391 (10) | 262 (9) | 129 (11) | 0.0101 |
| PCI or CABG | 548 (13) | 327 (11) | 221 (20) | <0.0001 |
| ICD | 12 (0) | 6 (0) | 6 (1) | 0.08 |
| Pacemaker | 252 (6) | 168 (6) | 84 (7) | 0.0314 |
| Medication, n (%) | | | | |
| Any diuretic | 3418 (83) | 2462 (82) | 956 (84) | 0.11 |
| Loop diuretic | 2150 (52) | 1480 (50) | 670 (59) | <0.0001 |
| ACE inhibitor | 1033 (25) | 615 (21) | 418 (37) | <0.0001 |
| β-Blocker | 2427 (59) | 1774 (59) | 653 (58) | 0.33 |
| Calcium channel blocker | 1637 (40) | 1179 (39) | 458 (40) | 0.55 |
| Long-acting nitrates | 1108 (27) | 775 (26) | 333 (29) | 0.02 |
| Mineralocorticoid antagonists | 633 (15) | 451 (15) | 182 (16) | 0.43 |
| Digoxin | 561 (14) | 390 (13) | 171 (15) | 0.09 |
| Lipid-lowering drugs | 1047 (25) | 667 (22) | 380 (34) | <0.0001 |
| Antiplatelets, any | 2416 (59) | 1723 (58) | 693 (61) | 0.04 |
| Metformin | 284 (7) | 0 (0) | 284 (25) | <0.0001 |
| Other oral antidiabetic agents | 544 (13) | 2 (0) | 542 (48) | <0.0001 |
| Insulin | 339 (8) | 0 (0) | 339 (30) | <0.0001 |

ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention. NT-proBNP was available for 3479 patients (84%) and Minnesota Living With Heart Failure for 3181 patients (77%).

mass (173±48 versus 161±48 g; *P*=0.004), but the relative wall thickness was similar (0.40±0.08 versus 0.40±0.08; *P*=0.40). No significant differences were seen for LV systolic properties, although fractional shortening tended to be lower in diabetic patients (33±10% versus 35±10%; *P*=0.09).

Details of LV diastolic function are shown in Table 2. Early diastolic mitral inflow velocity (E) was significantly higher in patients with diabetes mellitus (86±32 versus 76±27 cm/s; *P*≤0.0001), as was the E/e' ratio (11.7 versus 10.4; *P*=0.001), where e' is the average of lateral and septal annular velocities by tissue Doppler. Twenty-seven percent of patients with diabetes mellitus and 14% of those without had an $E/e'_{avg}$ >14 (*P*=0.001), suggesting significantly more diastolic dysfunction among patients with diabetes mellitus.[18] E/A was also higher among patients with diabetes mellitus (1.18±0.97 versus 1.00±0.65; *P*=0.01). Left atrial area was greater (24±6 versus 23±6 $cm^2$; *P*=0.003), as was the proportion of individuals with an enlarged left atrium (75% versus 66%; *P*=0.02), compared with patients without diabetes mellitus.

**Table 2. Echocardiographic Data According to Diabetes Status**

| | No Diabetes Mellitus (n=558) | Diabetes Mellitus (n=187) | *P* Value | Normal Range |
|---|---|---|---|---|
| Age, y | 72±7 | 72±7 | 0.97 | |
| Female, n (%) | 351 (63) | 108 (58) | 0.21 | |
| LV structure | | | | |
| End-diastolic dimension, cm | 4.8±0.6 | 4.9±0.6 | 0.044 | 4.0–6.0 |
| End-diastolic volume, mL | 93±38 | 98±38 | 0.15 | 80–180 |
| End-systolic dimension, cm | 3.2±0.7 | 3.3±0.7 | 0.02 | 2.0–4.0 |
| End-systolic volume, mL | 34±18 | 37±19 | 0.074 | 25–50 |
| Septum wall thickness, cm | 0.97±0.16 | 1.00±0.16 | 0.04 | 0.8–0.9 |
| Mass, g | 161±48 | 173±48 | 0.004 | 80–140 |
| Relative wall thickness | 0.40±0.08 | 0.40±0.08 | 0.40 | 0.36–0.40 |
| LV hypertrophy, n (%) | 384 (69) | 147 (79) | 0.01 | |
| LV systolic properties | | | | |
| Fractional shortening, % | 35±10 | 33±10 | 0.09 | 30–45 |
| EF, % | 64±9 | 63±10 | 0.13 | 55–75 |
| Stroke volume, mL | 59±24 | 61±25 | 0.405 | 50–70 |
| S´ lateral | 8.2±2.3 | 8.2±2.3 | 0.72 | 6–14 |
| LV diastolic properties | | | | |
| Diastolic dysfunction | | | 0.30 | |
| Grade I, n (%) | 194(38) | 54 (32) | | |
| Grade II, n (%) | 28 (6) | 14 (8) | | |
| Grade III, n (%) | 282 (55) | 95 (57) | | |
| Grade IV, n (%) | 7 (1) | 4 (2) | | |
| E, cm/s | 76±27 | 86±32 | <0.0001 | 40–90 |
| $E/e´_{lateral}$ ratio | 9.5±3.9 | 10.5±5.9 | 0.03 | 4.5–11.5 |
| $E/e´_{average}$ ratio | 10.4±3.9 | 11.7±6.4 | 0.001 | <10 |
| A, cm/s | 82±25 | 84±28 | 0.41 | 40–100 |
| E/A | 1.00±0.65 | 1.18±0.97 | 0.01 | 0.6–1.4 |
| E´ lateral annulus, cm/s | 9.1±3.5 | 9.4±3.2 | 0.35 | 7.0–11.5 |
| E´ septal annulus, cm/s | 7.4±2.3 | 7.1±2.5 | 0.26 | 5.0–11.0 |
| IVRT, ms | 97±22 | 93±21 | 0.053 | 4.5–11.5 |
| E deceleration time | 217±78 | 211±75 | 0.38 | 60–130 |
| Left atrial area, $cm^2$ | 23±6 | 24±6 | 0.003 | 10–20 |
| Enlarged left atria, n (%) | 366 (66) | 140 (75) | 0.02 | |
| Left atrial volume index | 44.1±17.8 | 46.8±19.1 | 0.15 | 16–34 |
| RV systolic pressure, mm Hg | 26±13 | 28±14 | 0.28 | 15–25 |

EF indicates ejection fraction; IVRT, isovolumic relaxation time; and RV, right ventricular. LV hypertrophy is LV mass >140 g.

## Clinical Outcomes

The unadjusted rates of the composite end point of cardiovascular death or HF hospitalization and all-cause mortality were higher in patients with diabetes mellitus (Table 3 and Figures 1 and 2).

Over a median of 4.1 years of follow-up, the composite end point occurred in 391 patients (34%) with diabetes mellitus compared with 662 patients without (22%), with event rates of 10.2 and 5.7 per 100 person-years, respectively. After adjustments for known predictive variables (see Methods), the hazard ratio for patients with diabetes mellitus compared with those without was 1.75 (95% confidence interval, 1.49–2.05). Competing-risk analyses gave comparable results (Table II in the

**Table 3. Outcomes According to Diabetes Mellitus in I-Preserve**

| | Patients, n | Events, n (%) | Event Rate, n/ 100 Patient-y | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) |
|---|---|---|---|---|---|
| Cardiovascular death or HF hospitalization | | | | | |
| No history of diabetes mellitus | 2994 | 662 (22) | 5.7 (5.3–6.2) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 391 (34) | 10.2 (9.2–11.3) | 1.76 (1.55–1.99) | 1.75 (1.49–2.05) |
| Cardiovascular death | | | | | |
| No history of diabetes mellitus | 2994 | 393 (13) | 3.2 (2.9–3.5) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 220 (19) | 5.0 (4.4–5.7) | 1.61 (1.36–1.89) | 1.59 (1.28–1.96) |
| HF hospitalization | | | | | |
| No history of diabetes mellitus | 2994 | 408 (14) | 3.5 (3.2–3.9) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 253 (22) | 6.6 (5.8–7.5) | 1.82 (1.55–2.13) | 1.77 (1.45–2.16) |
| All-cause mortality | | | | | |
| No history of diabetes mellitus | 2994 | 567 (19) | 4.6 (4.2–5.0) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 314 (28) | 7.2 (6.4–8.0) | 1.59 (1.39–1.83) | 1.59 (1.33–1.91) |
| Noncardiovascular death | | | | | |
| No history of diabetes mellitus | 2994 | 174 (6) | 1.4 (1.2–1.6) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 94 (8) | 2.1 (1.8–2.6) | 1.57 (1.22–2.02) | 1.60 (1.14–2.25) |
| All-cause hospitalization | | | | | |
| No history of diabetes mellitus | 2994 | 1520 (51) | 17.3 (16.5–18.2) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 708 (62) | 26.2 (24.3–28.2) | 1.45 (1.33–1.59) | 1.51 (1.34–1.70) |
| Cardiovascular hospitalization | | | | | |
| No history of diabetes mellitus | 2994 | 815 (27) | 7.8 (7.3–8.4) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 374 (33) | 10.7 (9.7–11.8) | 1.33 (1.17–1.50) | 1.34 (1.14–1.57) |
| Noncardiovascular hospitalization | | | | | |
| No history of diabetes mellitus | 2994 | 699 (23) | 6.5 (6.0–7.0) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 1134 | 331 (29%) | 9.2 (8.3–10.2) | 1.37 (1.21–1.57) | 1.41 (1.19–1.68) |

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction.

*Adjusted for age, sex, quality of life, log N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, heart rate, neutrophils, ejection fraction, hospitalization for HF in past 6 months, ischemic origin, history of myocardial infarction, and history of chronic obstructive pulmonary disease/asthma.

online-only Data Supplement). The pattern of higher risk associated with diabetes mellitus (hazard ratio, 1.79; confidence interval, 1.28–2.51 for the composite end point) was also seen in the echocardiography subgroup, although this risk was no longer statistically significant (hazard ratio, 1.45; confidence interval, 0.82–2.59) after further adjustment for echocardiographic variables (see Methods and Table 4), possibly because of the smaller sample size. The sensitivity analyses of the models that included echocardiographic data showed similar results.

Diabetes mellitus was associated with higher rates of all-cause death, cardiovascular death, and noncardiovascular death. The elevated risks of these outcomes persisted after adjustments for known prognostic variables (Table 3). Mode of death according to the presence or absence of diabetes mellitus is depicted in Table 5. Pump failure and sudden cardiac death were more frequent in patients with diabetes mellitus, whereas rates of fatal myocardial infarction and stroke were similar.

HF hospitalization occurred in 253 patients (22%) with diabetes mellitus compared with 408 patients (14%) without diabetes mellitus, yielding event rates of 6.6 and 3.5 per 100 person-years, giving a diabetes mellitus/no diabetes mellitus–adjusted hazard ratio of 1.77 (95% confidence interval, 1.45–2.16). When repeat HF hospitalizations were included, 708 admissions occurred in those with diabetes mellitus and 468 in individuals without diabetes mellitus, resulting in event rates of 9.3 and 5.7 per 100 person-years, respectively. The number and rates of admission to hospital for any reason and for cardiovascular and noncardiovascular reasons separately were also higher in individuals with diabetes mellitus compared with those without (Table 3). Results stratified by use/nonuse of insulin treatment in patients with diabetes mellitus are

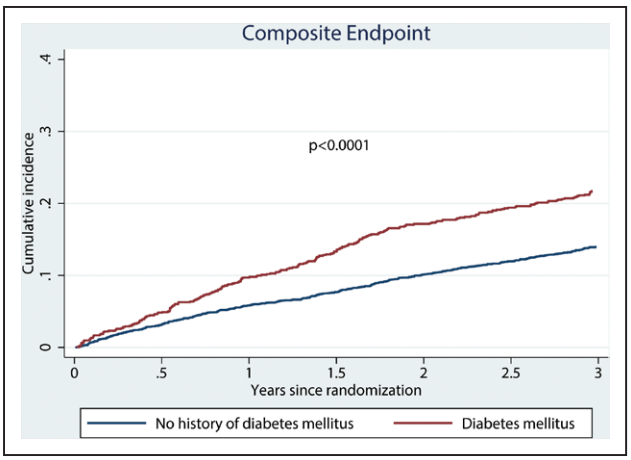


**Figure 1. Cumulative incidence plot for the composite end point of cardiovascular death or heart failure hospitalization according to history of diabetes mellitus.**

shown in Table III in the online-only Data Supplement, which displays a step-wise worsening, with the highest risk in patients with diabetes mellitus who were treated with insulin.

## Adverse Events

Serious adverse events and drug discontinuation because of adverse events (excluding death) are listed in Table IV in the online-only Data Supplement. Overall, serious adverse events were rare, but increased potassium, chronic kidney disease, and cough were more prevalent in patients with diabetes mellitus (all $P<0.05$). Drug discontinuation as a result of adverse events other than death was also more likely in patients with diabetes mellitus (23% versus 17%; $P=0.0008$).

# DISCUSSION

There is only 1 other report from a large clinical trial comparing the characteristics of and outcomes in patients with HFpEF with and without diabetes mellitus. However, in that publication from the CHARM program (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity), an LVEF cut point of 40% was used, natriuretic peptides were not measured, echocardiography data were unavailable, and health-related quality of life was not reported.[5] In the present study, we fill these gaps and describe a number of novel findings. We found that patients with diabetes mellitus, despite no statistically significant differences in age, sex distribution, and average LVEF, had a different pattern of comorbidity/pathogenesis (more coronary heart disease/less hypertension), a higher median NT-proBNP (despite a greater prevalence of obesity), more evidence of congestion, worse quality of life, and more cardiac remodeling with higher LV mass and more evidence of diastolic dysfunction than patients without diabetes mellitus. In addition, we found that the relationship between diabetes mellitus and higher risk of cardiovascular outcomes persisted after adjustment for NT-proBNP.

It was notable that despite a similar distribution of New York Heart Association class and LVEF, variables commonly used to characterize the severity of HF, patients with diabetes mellitus had a higher (worse) Minnesota Living With Heart Failure score, with values similar to those found in patients with HF and reduced ejection fraction with diabetes mellitus. The differential between patients with HFpEF with and without diabetes mellitus in I-Preserve (48 versus 40) was very similar to that seen in another study of the effects of phosphodiesterase-5 inhibition in HFpEF: Patients without diabetes mellitus (n=123) had a mean score of 42 compared with 47 in patients with diabetes mellitus (n=93).[19] This worse self-reported HF-related quality of life may have a number of explanations, one of which may be the greater severity of congestion documented by edema, rales, and jugular venous distension in patients with diabetes mellitus (and supported by greater diuretic use, elevated natriuretic peptides, and left atrial enlargement; see below). The phosphodiesterase-5 inhibitor trial mentioned above also found more edema in patients with diabetes mellitus, and those patients had reduced functional capacity compared with patients without diabetes mellitus. That patients with diabetes mellitus exhibit more congestion may be relevant to the increased risk of HF with hypoglycemic drugs causing sodium and water retention (thiazolidinediones) and reduced risk with those acting as a diuretic (sodium-glucose cotransporter-2 inhibitors).[12,18] These findings might also help clinicians decide in which patients to target new treatments in HFpEF, depending on their mode of action. The substantially worse Minnesota Living With Heart Failure score in patients with HFpEF and diabetes mellitus also suggests that health-

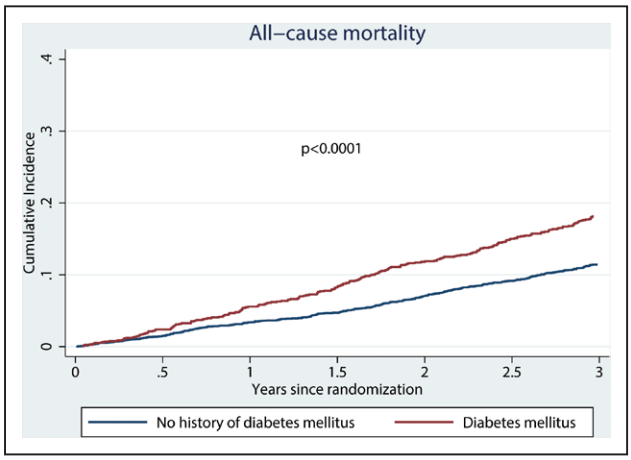


**Figure 2. Cumulative incidence plot for all-cause mortality according to history of diabetes mellitus.**

**Table 4. Outcomes According to Diabetes Mellitus in I-Preserve (Only Patients With Echocardiographic Data)**

| | Patients, n | Events, n (%) | Event Rate, n/ 100 Patient-y | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) |
|---|---|---|---|---|---|
| Cardiovascular death or HF hospitalization | | | | | |
| No history of diabetes mellitus | 558 | 96 (17) | 4.8 (3.9–5.9) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 52 (28) | 8.8 (6.7–11.5) | 1.79 (1.28–2.51) | 1.45 (0.82–2.59) |
| Cardiovascular death | | | | | |
| No history of diabetes mellitus | 558 | 44 (8) | 2.1 (1.5–2.8) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 28 (15) | 4.1 (2.8–6.0) | 1.99 (1.24–3.19) | 1.84 (0.76–4.45) |
| HF hospitalization | | | | | |
| No history of diabetes mellitus | 558 | 61 (11) | 3.1 (2.4–3.9) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 36 (19) | 6.1 (4.4–8.4) | 1.94 (1.29–2.93) | 1.55 (0.76–3.20) |
| All-cause mortality | | | | | |
| No history of diabetes mellitus | 558 | 74 (13) | 3.5 (2.8–4.4) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 43 (23) | 6.3 (4.7–8.5) | 1.82 (1.25–2.65) | 2.12 (1.07–4.18) |
| Noncardiovascular death | | | | | |
| No history of diabetes mellitus | 558 | 30 (5) | 1.4 (1.0–2.0) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 15 (8) | 2.2 (1.3–3.7) | 1.57 (0.85–2.93) | 3.63 (1.08–12.20) |
| All-cause hospitalization | | | | | |
| No history of diabetes mellitus | 558 | 273 (49) | 17.8 (15.8–20.0) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 115 (61) | 28.2 (23.5–33.8) | 1.53 (1.23–1.90) | 1.50 (1.04–2.18) |
| Cardiovascular hospitalization | | | | | |
| No history of diabetes mellitus | 558 | 133 (24) | 7.2 (6.1–8.6) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 54 (29) | 10.0 (7.7–13.1) | 1.34 (0.98–1.84) | 1.11 (0.63–1.96) |
| Noncardiovascular hospitalization | | | | | |
| No history of diabetes mellitus | 558 | 140 (25) | 7.7 (6.5–9.1) | 1.00 (Referent) | 1.00 (Referent) |
| Diabetes mellitus | 187 | 61(33) | 11.1 (8.7–14.3) | 1.42 (1.05–1.92) | 1.64 (1.01–2.67) |

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction.

*Adjusted for age, sex, quality of life, log N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, heart rate, neutrophils, ejection fraction, hospitalization for HF in past 6 months, ischemic origin, history of myocardial infarction, history chronic obstructive pulmonary disease/asthma, left ventricular end-systolic volume, left ventricular mass, ejection fraction, E/E' ratio, and left atrial area.

related quality of life may be a worthwhile end point in future trials in these patients.

Also notable was the considerably higher median NT-proBNP concentration in patients with diabetes mellitus, especially given the greater prevalence of obesity that is associated with lower natriuretic peptide concentrations.[19] Again, there may be a number of explanations for this. Greater congestion, as alluded to above, may be one. Impaired renal function (which was slightly more common in patients with diabetes mellitus) may be another. Atrial fibrillation was not more common in patients with diabetes mellitus, but those patients had more functional and structural cardiac abnormalities than patients without diabetes mellitus.

The echocardiography substudy from I-Preserve provides some of the most unique data in the present report. Specifically, patients with diabetes mellitus had slightly larger LV dimensions and greater LV mass compared with patients without diabetes mellitus. The latter finding, along with the differences we found in mitral inflow and tissue Doppler measurements, suggests increased LV stiffness, impaired LV filling, and higher left atrial pressure (supported by higher NT-proBNP concentrations) in patients with compared with those without diabetes mellitus.[20] The phosphodiesterase-5 inhibitor trial also reported echocardiographic findings that were largely consistent with ours, although the differences between patients with and without diabetes mellitus were less often significant, possibly because of the small sample size. One community-based cohort study also reported that patients with HFpEF with diabetes mellitus had a greater LV mass and higher E/e' than patients without diabetes mellitus.[20] Collectively, however, the differences in diastolic function between patients with and

**Table 5. Mode of Death According to Diabetes Mellitus in I-Preserve**

| Death | No Diabetes Mellitus (n=2994) | Diabetes Mellitus (n=1134) | *P* Value |
|---|---|---|---|
| All causes | 567 (19) | 314 (28) | <0.0001 |
| Cardiovascular | 393 (13) | 220 (20) | <0.0001 |
| Pump failure | 72 (2) | 53 (5) | 0.0001 |
| Sudden cardiac death | 144 (5) | 87 (8) | 0.0004 |
| Myocardial infarction | 32 (1) | 13 (1) | 0.83 |
| Stroke | 57 (2) | 19 (2) | 0.63 |
| Other cardiovascular | 85 (3) | 42 (4) | 0.15 |
| Noncardiovascular | 174 (6) | 94 (8) | 0.004 |

I-Preserve indicates Irbesartan in Heart Failure With Preserved Ejection Fraction.

without diabetes mellitus in our study and the other studies mentioned were relatively modest despite the prevalent view that diastolic dysfunction is a pathognomonic feature of diabetes-related cardiac disease.

Last, we found that patients with HFpEF and diabetes mellitus had worse outcomes than patients with HFpEF without diabetes mellitus. This was also true in the CHARM program and the DIG trial (Digitalis Investigators Group) ancillary study in patients with an LVEF >45% (285 of the 987 patients had diabetes mellitus).[7] In the Olmsted County epidemiological study, diabetes mellitus was independently predictive of death (and cardiovascular death) in a community HF cohort, regardless of ejection fraction.[21] However, unlike in these earlier trials, we were able to adjust outcomes for NT-proBNP levels. Despite adjustment for NT-proBNP and other prognostic variables, patients with diabetes mellitus were 1.5 to 2.0 times as likely to have an adverse clinical outcome. In contrast, we found that, after additional adjustment for LV end-systolic volume, LV mass, E/e', and left atrial area in the echocardiographic subgroup, the risk associated with diabetes mellitus was no longer statistically significant (Table 4), possibly because of either the smaller sample size of the echocardiographic subgroup or because adverse LV remodeling is an important mediator of the risk associated with diabetes mellitus. The excess risk associated with diabetes mellitus was seen for death and for HF hospitalization and was apparent for both cardiovascular and noncardiovascular death; that is, no specific type of event seemed to be particularly increased in patients with diabetes mellitus. Adjustment for echocardiographic findings did not attenuate the risk of noncardiovascular outcomes.

Our study has a number of limitations. The analyses were retrospective rather than preplanned. The diagnosis of diabetes mellitus was investigator reported and not standardized. Although similar to that in DIG and CHARM trials, the prevalence of diabetes mellitus in I-Preserve was lower than in many more recent trials, presumably reflecting the steadily increasing prevalence of diabetes mellitus.[2,22] The small numbers of events in those with echocardiographic data may have led to "overfitting" of the model, although sensitivity analyses found similar results after the removal of variables from the model. Last, patient selection in clinical trials limits the external validity of findings when extrapolated to a typical community population.

## CONCLUSIONS

Among patients with HFpEF, those with diabetes mellitus have more signs of congestion, worse quality of life, higher NT-proBNP levels, greater structural and functional echocardiographic abnormalities, and worse outcomes than those without diabetes mellitus. Further investigation is needed to determine the mediators of the adverse impact of diabetes mellitus on outcomes in HFpEF and whether they are modifiable.

## SOURCES OF FUNDING

Dr Kristensen is supported by a postdoctoral grant from the Danish Independent Research Council and a Research Fellowship from the Heart Failure Association of the European Society of Cardiology.

## DISCLOSURES

Dr Komajda is on the Speakers Bureau for Bristol-Myers Squibb, Sanofi, AstraZeneca, Menarini, MSD, and Servier and is a consultant for Servier and Amgen. Dr Mogensen reports speaker fees from Novo Nordisk and MSD. Dr Køber has received honoraria as a steering committee member from AstraZeneca. Dr Jhund reports consulting and speaker fees from Novartis and research funding from Boehringer Ingelheim. Dr Petrie reports speaker fees from Astellas, AstraZeneca, Bayer, Takeda, Boerhinger Ingelheim, Novartis, Roche, and GlaxoSmithKline. Dr Zile reports consultant fees from Amgen, A-Z, Bayer, Bristol Myers Squibb, Capricor, Corvia, Eli Lilly, Giliad, Ironwood, Medtronic, Merck, Novartis, and St. Jude Medical and research support from the National Heart, Lung, and Blood Institute, Veterans Affairs, US Department of Defense, Medtronic, and Novartis. Dr McMurray´s employer, the University of Glasgow, has received fees for his consulting or trial committee work with Abbvie, Amgen, AstraZeneca/Medimmune, Bayer, Bristol Myers Squibb, DalCor, GlaxoSmithKline, Merck, Novartis, Resverlogix, Sanofi-Aventis, and Stealth Therapeutics. Drs Kristensen, Preiss, Anand, and Gottdiener report no relevant conflicts.

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## FOOTNOTES

Received July 21, 2016; accepted December 9, 2016.

The online-only Data Supplement, podcast, and transcript are available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.024593/-/DC1.

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