10.1161/CIRCULATIONAHA.116.024593

Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes According to Diabetes Status in Patients with Heart Failure and Preserved Ejection Fraction. A Report from the Irbesartan in Heart Failure with Preserved Ejection Fraction Trial (I-Preserve)

Running Title: *Kristensen et al.; Diabetes in HFpEF*

Søren L. Kristensen, MD, PhD[1,2]; Ulrik M. Mogensen, MD, PhD[1,2]; Pardeep S. Jhund, MD, PhD[1]; Mark C. Petrie MB ChB[1]; David Preiss, MD, PhD[3]; Sithu Win, MD[4]; Lars Køber, MD, DMSc[2]; Robert S. McKelvie, MD PhD[5]; Michael R. Zile, MD[6]; Inder S. Anand, MD, DPhil (Oxon.)[7]; Michel Komajda, MD[8]; John S. Gottdiener, MD[9]; Peter E. Carson, MD[10]; John J.V. McMurray, MD[1]

[1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, UK; [2]Department of Cardiology, Rigshospitalet University Hospital, Copenhagen, Denmark; [3]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, UK; [4]Mayo Clinic, Rochester,MN; [5]Western University, London, ON, Canada; [6]Ralph H. Johnsons Veterans Affairs Medical Center and Medical University of South Carolina, Charleston, SC; [7]Division of Cardiology, University of Minnesota, Minneapolis, MN; [8]Université Paris 6 and Hospital Pitié-Salpétrière, Paris, France; [9]University of Maryland Medical Center, Baltimore, MD; [10]Georgetown University and Washington DC Veterans Affairs Medical Center, Washington DC

Address for Correspondence:

John JV McMurray, MD
Institute of Cardiovascular and Medical Sciences,
BHF Cardiovascular Research Centre,
University of Glasgow,
Glasgow, G12 8TA
United Kingdom
Tel: +44 141 330 3479
Fax: +44 141 330 6955
Email: john.mcmurray@glasgow.ac.uk

Journal Subject Terms: Diabetes, Type 2; Heart Failure; Echocardiography; Clinical Studies

Abstract

***Background*—**In patients with HF and preserved ejection fraction (HFpEF), little is known about the characteristics of and outcomes in those with and without diabetes.
***Methods*—**We examined clinical and echocardiographic characteristics and outcomes in the Irbesartan in Heart Failure with Preserved Ejection Fraction trial (I-Preserve), according to history of diabetes. Cox regression models were used to estimate hazard ratios (HR) 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. Compared to those without diabetes, they were more likely to have a history of myocardial infarction (28% vs. 22%), higher BMI (31kg/m^2 vs. 29kg/m^2), worse Minnesota living with HF score (48 vs. 40), higher median NT-proBNP concentration (403 vs 320 pg/ml; all $p<0.01$), more signs of congestion but no significant difference in LVEF. Patients with diabetes had a greater left ventricular (LV) mass and left atrial area than patients without diabetes. Doppler *E* wave velocity (86 vs 76 cm/sec, $p<0.0001$) and the ratio of E/e' (11.7 vs 10.4, $p=0.010$) were higher in patients with diabetes. Over a median follow-up of 4.1 years, cardiovascular death or HF hospitalization occurred in 34% of patients with diabetes vs. 22% of those without diabetes; adjusted HR 1.75 (95% CI 1.49-2.05) and 28% vs. 19% of patients with and without diabetes died; adjusted HR 1.59 (1.33-1.91).
***Conclusions*—**In HFpEF, patients with diabetes have more signs of congestion, worse quality of life, higher NT-proBNP 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 on outcomes in HFPEF, and whether they are modifiable.

***Clinical Trial Registration*—**http://www.clinicaltrials.gov Unique Identifier NCT00095238

Key-words: heart failure; diabetes mellitus; echocardiography

Clinical Perspective

What is new?

- Among individuals with heart failure and preserved ejection fraction (HFpEF), those with diabetes have more evidence of congestion and higher N-terminal pro B-type natriuretic peptide (NT proBNP) concentrations, compared to HFpEF patients without diabetes.
- The former patients also reported worse health-related quality of life and had a higher risk of cardiovascular mortality and hospitalization.
- They also 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 in patients with HFpEF.

What are the clinical implications?

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

Introduction

Diabetes is common in patients with heart failure and preserved ejection fraction (HFpEF). It has been suggested that diabetes 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 HFpEF patients with and without diabetes.[1-4] Also, while it is well known that diabetes is associated with worse outcomes in patients with heart failure and reduced ejection fraction (HFrEF), less is known clinical and echocardiographic characteristics of, and outcomes in, HFpEF patients with diabetes compared to those without.[1-3] The importance of better understanding the relationship between diabetes and heart failure has been underscored by recent trials in patients with type 2 diabetes mellitus which have suggested that some drugs may increase the risk of heart failure (thiazolidinediones and possibly certain dipeptidyl-peptidase-4 inhibitors)[4-6] and others may decrease the risk (the sodium glucose cotransporter 2 inhibitor empagliflozin).[7] Three GLP-1 agonist trials have shown no clear cut effect on heart failure.[8-10] The aforementioned trials largely reported incident heart failure and there are few data on the effect of anti-diabetes drugs in patients with established heart failure. One notable exception is a recent trial demonstrating no benefit of liraglutide in patients with HFrEF 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 in patients with HFpEF and to give insight into potential pathophysiologic 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 Irbesartan in Heart Failure with Preserved Ejection Fraction trial (I-Preserve). In a subgroup of patients, a full echocardiographic examination was performed[13] which allowed a detailed comparison of cardiac structure and function in HFpEF patients with and without diabetes.

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 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 (NYHA) class II, III, or IV symptoms and echocardiographic, electrocardiographic or chest X-ray findings supporting a diagnosis of heart failure and/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, left ventricular hypertrophy and/or an enlarged left atrium on an echocardiogram and left ventricular hypertrophy or left bundle branch block on an ECG. The details of these criteria have been described previously.[14]

Angiotensin-converting enzyme (ACE) inhibitor therapy was limited to those patients with a specific indication other than hypertension (such as 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 ACE inhibitor. Treatment by an angiotensin II receptor blocker (ARB) was prohibited although a patient could be enrolled if ARB treatment was discontinued at least 14 days earlier. Exclusion criteria included a systolic blood pressure <100mmHg or >160mmHg or a diastolic blood pressure >95mmHg despite antihypertensive therapy; a creatinine level >2.5mg/dl [221μmol/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 were assessed using a chi-squared test for categorical covariates and two-sided t-tests and kruskall-wallis test, as appropriate. Tests for interactions between diabetes and

age, sex and ischemic etiology 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 HRs in Cox regression models with those with no history of diabetes 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 last 6 months, LVEF, heart rate, ischemic etiology, eGFR, NT-proBNP (log-transformed), neutrophils (log-transformed), chronic obstructive pulmonary disease (COPD)/asthma, and previous myocardial infarction. The outcomes of interest were also assessed by cumulative incidence plots using the Nelson Aalen method. We also conducted competing risk analyses for all non-fatal events (and for CV 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 according to insulin use and non-use, respectively.

In patients with echocardiographic measurements available, we further adjusted for left ventricular (LV) systolic and diastolic properties as well as 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 which was only available in a subset of patients we conducted sensitivity analyses. In the first, we removed end-systolic left atrial area and left ventricular 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 as irbesartan had no effect on any outcome in I-Preserve, and no interaction with diabetes was found. All p values are two-sided, and a p value of <0.05 was considered significant. All

analyses were performed separately using Stata version 14 (Stata Corp. College Station, Texas, USA).

Results

Baseline characteristics

Overall, 1134 (27%) of 4128 patients enrolled in I-Preserve had a diagnosis of diabetes at baseline. The characteristics of patients with and without diabetes at baseline are shown in Table 1. Patients with diabetes were slightly younger and had higher heart rate and body mass index (BMI), but not statistically different blood pressure and renal function. Furthermore, patients with diabetes had higher NT-proBNP, despite no difference in LVEF and prevalence of atrial fibrillation. They were more likely to have an ischemic etiology, were about twice as likely to have undergone percutaneous coronary intervention or coronary artery bypass grafting (20% vs. 11%) and were more likely to have had a stroke. Although patients with and without diabetes did not differ in distribution of NYHA class, those with diabetes 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 ACE inhibitor and lipid-lowering drugs, both of which were more common in patients with diabetes. Signs and symptoms of HF as well as electrocardiographic findings of left ventricular (LV) hypertrophy, left bundle branch block and atrial fibrillation/flutter did not differ significantly between those with and without diabetes at baseline.

Echocardiographic measurements

Of the 745 patients in the echocardiographic substudy, 187 (25%) had diabetes (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 and end-systolic LV volume in 581 patients. E/A ratio was available in 647 patients but E/e ratio was available in only 515 patients. The baseline characteristics of this subset of patients are presented in Supplementary Table 1. The differences between patients with and without diabetes in this subset reflected those in the overall trial.

In terms of LV structure, patients with diabetes had a larger end systolic dimension (3.3±0.7 vs. 3.2±0.7 cm, p=0.02), end-diastolic dimension (4.9 ±0.6 vs 4.8±0.6 cm, p=0.044) and greater LV mass (173±48 vs. 161±48 grams, p=0.004), but the relative wall thickness was similar (0.40±0.08 vs. 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% vs. 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 (86±32 vs 76±27 cm/sec, p=<0.0001), as was the ratio of E/e' (11.7 vs 10.4, p=0.001), where e' is the average of lateral and septal annular velocities by tissue Doppler. There were 27% of patients with diabetes and 14% of those without with an E/e'_{avg} >14 (p=0.001) suggesting significantly more diastolic dysfunction among patients with diabetes.[18] E/A was also higher among patients with diabetes (1.18±0.97 vs 1.00±0.65, p=0.01). Left atrial area was greater (24±6 vs. 23±6 cm^2, p=0.003), as were the proportion of individuals with an enlarged left atrium (75 vs. 66%, P=0.02), all compared to patients without diabetes.

Clinical Outcomes

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

Over a median of 4.1 years of follow-up, the composite endpoint occurred in 391 of patients (34%) with diabetes compared with 662 of those without (22%), with event rates per 100 person years of 10.2 and 5.7, respectively. After adjustments for known predictive variables (see Methods), the hazard ratio (HR) for patients with diabetes, compared to those without, was 1.75 (95% CI 1.49-2.05). Competing risk analyses gave comparable results (Supplementary Appendix Table 2). The pattern of higher risk associated with diabetes (HR 1.79 [1.28-2.51] for the composite endpoint) was also seen in the echocardiography subgroup, although this risk was no longer statistically significant (HR 1.45 [0.82-2.59]) after further adjustment for echocardiographic variables (see Methods and Table 4) possibly due to the smaller sample size. **The results of the sensitivity analyses of the models that included echocardiographic data showed similar results.**

Diabetes was associated with higher rates of all-cause death, as well as cardiovascular death and non-cardiovascular 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 is depicted in Table 5. Pump failure and sudden cardiac death were more frequent in patients with diabetes, whereas rates of fatal myocardial infarction and stroke were similar.

HF hospitalization occurred in 253 patients (22%) with diabetes, compared to 408 patients (14%) without diabetes, yielding event rates per 100 person-years of 6.6 and 3.5, giving a diabetes/no diabetes adjusted hazard ratio of 1.77 (1.45-2.16). When repeat HF hospitalizations were included, 708 admissions occurred in those with diabetes and 468 in individuals without diabetes, resulting in event rates per 100 person-years of 9.3 and 5.7, respectively. The number and rates of admission to hospital for any reason, and for cardiovascular and non-cardiovascular reasons separately, were also higher in individuals with diabetes compared to those without

(Table 3). Results stratified by use/non-use of insulin treatment in patients with diabetes are shown in Supplementary Table 3, which displays a step-wise worsening, with the highest risk in patients with diabetes who were insulin-treated.

Adverse events

Serious adverse events and drug discontinuation due to adverse events (excluding death) are listed in Supplementary Appendix Table 4. Overall, serious adverse events were rare, but increased potassium, chronic kidney disease and cough were more prevalent in patients with diabetes (all p-values<0.05). Drug discontinuation due to adverse events other than death was also more likely in patients with diabetes (23% vs. 17%, p-value 0.0008).

Discussion

There is only one other report from a large clinical trial comparing the characteristics of, and outcomes in, HFpEF patients with and without diabetes mellitus. However, in that publication from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Programme, a 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, despite no statistically significant differences in age, sex distribution, and average LVEF, had a different pattern of comorbidity/etiology (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 remodelling with higher LV mass and more evidence of diastolic dysfunction than patients without diabetes.

Additionally, we found that the relationship between diabetes and higher risk of cardiovascular outcomes persisted after adjustment for NT-proBNP.

It was notable that despite a similar distribution of NYHA class and LVEF, variables commonly used to characterise the severity of heart failure, patients with diabetes had a higher (worse) Minnesota Living with Heart Failure score with values similar to those found in HFrEF patients with diabetes. The differential between HFpEF patients with and without diabetes in I-Preserve (48 vs 40) was very similar to that seen in another study of the effects of phosphodiesterase-5 inhibition in HFpEF: patients without diabetes (n=123) had a mean score of 42 vs patients with diabetes (n=93) who had a mean score of 47.[19] This worse self-reported heart failure-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 (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 and those patients had reduced functional capacity compared to patients without diabetes. That patients with diabetes exhibit more congestion may be relevant to the increased risk of heart failure 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 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 also suggests that health-related quality of life may be a worthwhile endpoint in future trials in these patients.

Also notable was the considerably higher median NT-proBNP concentration in patients with diabetes, especially given the greater prevalence of obesity which 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) may be another. Atrial fibrillation was not more common in patients with diabetes but those patients did have more functional and structural cardiac abnormalities than patients without diabetes.

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

Finally, we found that HFpEF patients with diabetes had worse outcomes than HFpEF patients without diabetes. This was also true in the CHARM Programme and the Digitalis Investigators Group trial (DIG) ancillary study in patients with a LVEF >45% (285 of the 987 patients had diabetes).[7] In the Olmsted county epidemiological study, diabetes was

independently predictive of death (and cardiovascular death) in a community heart failure cohort, irrespective 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 as well as other prognostic variables, patients with diabetes 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 was no longer statistically significant (Table 4), possibly due either to the smaller sample size of the echocardiographic subgroup or because adverse LV remodelling is an important mediator of the risk associated with diabetes. The excess risk associated with diabetes was seen for each of death and heart failure hospitalization and was apparent for both cardiovascular and non-cardiovascular death i.e. there was no specific type of event that seemed to be particularly increased in patients with diabetes. Adjustment for echocardiographic findings did not attenuate the risk of non-CV outcomes.

Our study has a number of limitations. The analyses were retrospective rather than pre-planned. The diagnosis of diabetes was investigator-reported and not standardised. Although similar to that in DIG and CHARM trials, the prevalence of diabetes in I-Preserve was lower than in most more recent trials, presumably reflecting the steadily increasing prevalence of diabetes.[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 removing variables from the model. Finally, patient selection in clinical trials limits the external validity of findings when extrapolating to a typical community population.

In summary, among patients with HFpEF, those with diabetes 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. Further investigation is needed to determine the mediators of the adverse impact of diabetes 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 (ESC).

Disclosures

Drs. Kristensen, Preiss, Anand and Gottdiener reports no relevant conflicts of interests.

Dr. Komajda is on the speakers bureau for Bristol-Myers Squibb, Sanofi, AstraZeneca, Menarini, MSD, and Servier and is consultant for Servier and Amgen. Dr Mogensen reports speakers fees from Novo Nordisk and MSD. Dr. Køber has received honoraria as steering committee member from AstraZeneca. Dr Jhund reports consulting and speakers fees from Novartis and research funding from Boehringer Ingelheim. Dr. Petrie reports speakers fees from Astellas, AstraZeneca, Bayer, Takeda, Boerhinger Ingelheim, Novartis, Roche, GlaxoSmithKline. Dr. Zile reports consultant fees from Amgen, A-Z, Bayer, Bristol Myers Squibb, Capricor, Corvia, Eli Lilly, Giliad, Ironwood, Medtronic, Merck, Novartis, St. Jude Medical and research support from NHLBI, VA, DOD, Medtronic and Novartis. Dr. McMurray´s employer, 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.

References

1. Aguilar D, Deswal A, Ramasubbu K, Mann DL and Bozkurt B. Comparison of patients with heart failure and preserved left ventricular ejection fraction among those with versus without diabetes mellitus. *Am J Cardiol*. 2010;105:373-7.
2. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ and Investigators C. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29:1377-85.
3. Seferovic PM and Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *Eur Heart J*. 2015;36:1718-27, 1727a-1727c.
4. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED and Trial Evaluating Cardiovascular Outcomes With Sitagliptin Study G. Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus: Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. 2016;1:126-35.
5. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB and Investigators E. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385:2067-76.
6. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL, Committee S-TS and Investigators*. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014;130:1579-88.
7. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE and investigators E-ROt. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. *Eur Heart J*. 2016;37:1526-34.
8. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC and Investigators E. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373:2247-57.
9. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB, Committee LS and Investigators LT. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375:311-22.
10. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J and Vilsbøll T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2016;375:1834-1844.
11. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, McNulty SE, Anstrom KJ, Shah MR, Braunwald E, Cappola TP and Network NHFCR. Effects of Liraglutide on Clinical Stability Among Patients

With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA*. 2016;316:500-8.
12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE and Investigators E-RO. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373:2117-28.
13. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, Baicu CF, Massie BM, Carson PE and Investigators IP. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124:2491-501.
14. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, Ptaszynska A, Frangin G and Investigators I-P. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial: Rationale and design. *Journal of Cardiac Failure*. 2005;11:576-585.
15. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A and Investigators IP. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456-67.
16. Komajda M, Carson PE, Hetzel S, McKelvie R, McMurray J, Ptaszynska A, Zile MR, Demets D and Massie BM. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail*. 2011;4:27-35.
17. Fine JP and Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94:496-509.
18. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA and Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277-314.
19. Lindman BR, Davila-Roman VG, Mann DL, McNulty S, Semigran MJ, Lewis GD, de las Fuentes L, Joseph SM, Vader J, Hernandez AF and Redfield MM. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. *J Am Coll Cardiol*. 2014;64:541-9.
20. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA and Redfield MM. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. *Circ Heart Fail*. 2012;5:710-9.
21. Henkel DM, Redfield MM, Weston SA, Gerber Y and Roger VL. Death in heart failure: a community perspective. *Circ Heart Fail*. 2008;1:91-7.
22. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM and Investigators T. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383-92.

Table 1. Baseline Characteristics stratified by presence of diabetes in I-Preserve

	All patients N=4128	No diabetes n=2994	Diabetes n=1134	P-value
Age, mean – years	72 ± 7	72 ± 7	71 ± 7	0.0006
>/=65 years	1975 (48%)	1444 (48%)	531 (47%)	0.12
>/=75 years	1413 (34%)	1036 (35%)	377 (33%)	
Female sex, no. (%)	2491 (60%)	1802 (60%)	689 (61%)	0.74
Race, no (%):				<0.0001
Caucasian	3859 (94%)	2829 (95%)	1030 (91%)	
Black	82 (2%)	47 (2%)	35 (3%)	
Other	187 (4%)	118 (4%)	69 (6%)	
Ejection fraction	59 ± 9	59 ± 9	60 ± 9	0.45
Body mass index	30 ± 5	29 ± 5	31 ± 6	<0.0001
Underweight (<18.5)	20 (1%)	20 (1%)	0 (0%)	<0.0001
Normal (18.5-24.9)	624 (15%)	514 (17%)	110 (10%)	
Overweight (25-29.9)	1744 (42%)	1311 (44%)	433 (38%)	
Obese (≥30)	1740 (42%)	1149 (38%)	591 (52%)	
Symptoms				
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 HF score	42 (28-58)	40 (27-55)	48 (30-55)	<0.0001
Examination findings				
Rales	1158 (28%)	811 (27%)	347 (31%)	0.0250
CXR congestion	1590 (39%)	1086 (36%)	505 (44%)	<0.0001
Jugular venous distention	346 (8%)	229 (8%)	117 (10%)	0.0060
Edema	2255 (55%)	1609 (54%)	646 (57%)	0.0631
3rd heart sound	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	336 (8%)	247 (8%)	89 (8%)	0.67
Left ventricular hypertrophy	1260 (31%)	934 (31%)	326 (29%)	0.13
QRS duration, (no pacemaker)	0.10 ± 0.05	0.10 ± 0.06	0.10 ± 0.06	0.1784
Atrial fibrillation/flutter	697 (17%)	497 (17%	200 (18%)	0.47
Laboratory measurements				
NT-proBNP, median (Q1-Q3)	339 (134-964)	320 (128-945)	403 (154-1023)	0.0074
eGFR – l/min/1.73m^2	70 (55-85)	70 (56-84)	69 (53-86)	0.3362
CKD (eGFR<60 l/min/1.73m^2)	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)	514 (13%)	161 (5%)	119 (11%)	<0.0001
Neutrophils, cells/μL (Q1-Q3)	4.3 (3.4-5.3)	4.2 (3.3-5.2)	4.6 (3.7-5.6)	<0.0001
Medical history, no. (%)				
HF hospitalization within 6 months	1816 (44%)	1294 (43%)	522 (46%)	0.1042
Ischemic etiology	1036 (25%)	710 (24%)	326 (29%)	0.0009
Hypertensive etiology	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, no. (%)				
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
Beta-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

HF – heart failure, CXR – chest x-ray, bpm – beats per minute, eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease, PCI – percutaneous coronary intervention, CABG - coronary artery bypass graft, ICD – Implantable cardioverter defibrillator. NT-pro BNP was available for 3479 (84%) of patients and Minnesota living with HF for 3181 patients (77%).

Table 2. Echocardiographic data according to diabetes status

	No diabetes n=558	Diabetes n=187	p-value	Normal Range
Age	72±7	72±7	0.97	
Female	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	384 (69%)	147 (79%)	0.01	
LV systolic properties				
Fractional shortening, %	35±10	33±10	0.09	30-45
Ejection fraction, %	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	194(38%)	54 (32%)		
Grade II	28 (6%)	14 (8%)		
Grade III	282 (55%)	95 (57%)		
Grade IV	7 (1%)	4 (2%)		
E, cm/sec	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/sec	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/sec	9.1±3.5	9.4±3.2	0.35	7.0-11.5
E´ septal annulus, cm/sec	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	366 (66%)	140 (75%)	0.02	
Left atrial volume Index (LAVI)	44.1±17.8	46.8±19.1	0.15	16-34
RV systolic pressure	26±13	28±14	0.28	15-25

LV hypertrophy – LV mass>140 gram

Table 3. Outcomes according to diabetes in I-Preserve

	No. patients	No. events	Event rate per 100 py	Unadjusted HR	Adjusted* HRs
CV death or HF hospitalization					
No history of diabetes	2994	662 (22%)	5.7 (5.3-6.2)	1.00 (ref)	1.00 (ref.)
Diabetes	1134	391 (34%)	10.2 (9.2-11.3)	1.76 (1.55-1.99)	1.75 (1.49-2.05)
CV death					
No history of diabetes	2994	393 (13%)	3.2 (2.9-3.5)	1.00 (ref.)	1.00 (ref.)
Diabetes	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	2994	408 (14%)	3.5 (3.2-3.9)	1.00 (ref.)	1.00 (ref.)
Diabetes	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	2994	567 (19%)	4.6 (4.2-5.0)	1.00 (ref.)	1.00 (ref.)
Diabetes	1134	314 (28%)	7.2 (6.4-8.0)	1.59 (1.39-1.83)	1.59 (1.33-1.91)
Non CV death					
No history of diabetes	2994	174 (6%)	1.4 (1.2-1.6)	1.00 (ref.)	1.00 (ref.)
Diabetes	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	2994	1520 (51%)	17.3 (16.5-18.2)	1.00 (ref.)	1.00 (ref.)
Diabetes	1134	708 (62%)	26.2 (24.3-28.2)	1.45 (1.33-1.59)	1.51 (1.34-1.70)
CV hospitalization					
No history of diabetes	2994	815 (27%)	7.8 (7.3-8.4)	1.00 (ref.)	1.00 (ref.)
Diabetes	1134	374 (33%)	10.7 (9.7-11.8)	1.33 (1.17-1.50)	1.34 (1.14-1.57)
Non-CV hospitalization					
No history of diabetes	2994	699 (23%)	6.5 (6.0-7.0)	1.00 (ref.)	1.00 (ref)
Diabetes	1134	331 (29%)	9.2 (8.3-10.2)	1.37 (1.21-1.57)	1.41 (1.19-1.68)

HF – heart failure. CV-cardiovascular, Py- person-years, ref - reference

*adjusted for age, sex, quality of life, log NT-proBNP, eGFR, Heart rate, neutrophils, ejection fraction, hospitalization for HF in last 6 months, ischemic etiology, Hx myocardial infarction, Hx COPD/Asthma

Table 4. Outcomes according to diabetes in I-Preserve (only patients with echocardiographic data)

	No. patients	No. events	Event rate per 100 py	Unadjusted HR	Adjusted* HRs
CV death or HF hospitalization					
No history of diabetes	558	96 (17%)	4.8 (3.9-5.9)	1.00 (ref.)	1.00 (ref.)
Diabetes	187	52 (28%)	8.8 (6.7-11.5)	1.79 (1.28-2.51)	1.45 (0.82-2.59)
CV death					
No history of diabetes	558	44 (8%)	2.1 (1.5-2.8)	1.00 (ref.)	1.00 (ref.)
Diabetes	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	558	61 (11%)	3.1 (2.4-3.9)	1.00 (ref.)	1.00 (ref.)
Diabetes	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	558	74 (13%)	3.5 (2.8-4.4)	1.00 (ref.)	1.00 (ref.)
Diabetes	187	43 (23%)	6.3 (4.7-8.5)	1.82 (1.25-2.65)	2.12 (1.07-4.18)
Non CV death					
No history of diabetes	558	30 (5%)	1.4 (1.0-2.0)	1.00 (ref.)	1.00 (ref.)
Diabetes	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	558	273 (49%)	17.8 (15.8-20.0)	1.00 (ref.)	1.00 (ref.)
Diabetes	187	115 (61%)	28.2 (23.5-33.8)	1.53 (1.23-1.90)	1.50 (1.04-2.18)
CV hospitalization					
No history of diabetes	558	133 (24%)	7.2 (6.1-8.6)	1.00 (ref.)	1.00 (ref.)
Diabetes	187	54 (29%)	10.0 (7.7-13.1)	1.34 (0.98-1.84)	1.11 (0.63-1.96)
Non-CV hospitalization					
No history of diabetes	558	140 (25%)	7.7 (6.5-9.1)	1.00 (ref.)	1.00 (ref.)
Diabetes	187	61(33%)	11.1 (8.7-14.3)	1.42 (1.05-1.92)	1.64 (1.01-2.67)

Py - person-years, ref – reference

*adjusted for age, sex, quality of life, log NT-proBNP, eGFR, Heart rate, neutrophils, ejection fraction, hospitalization for HF in last 6 months, ischemic etiology, Hx myocardial infarction, Hx COPD/Asthma , LV end systolic volume, LV mass, ejection fraction, E/E' ratio, Left atrial area.

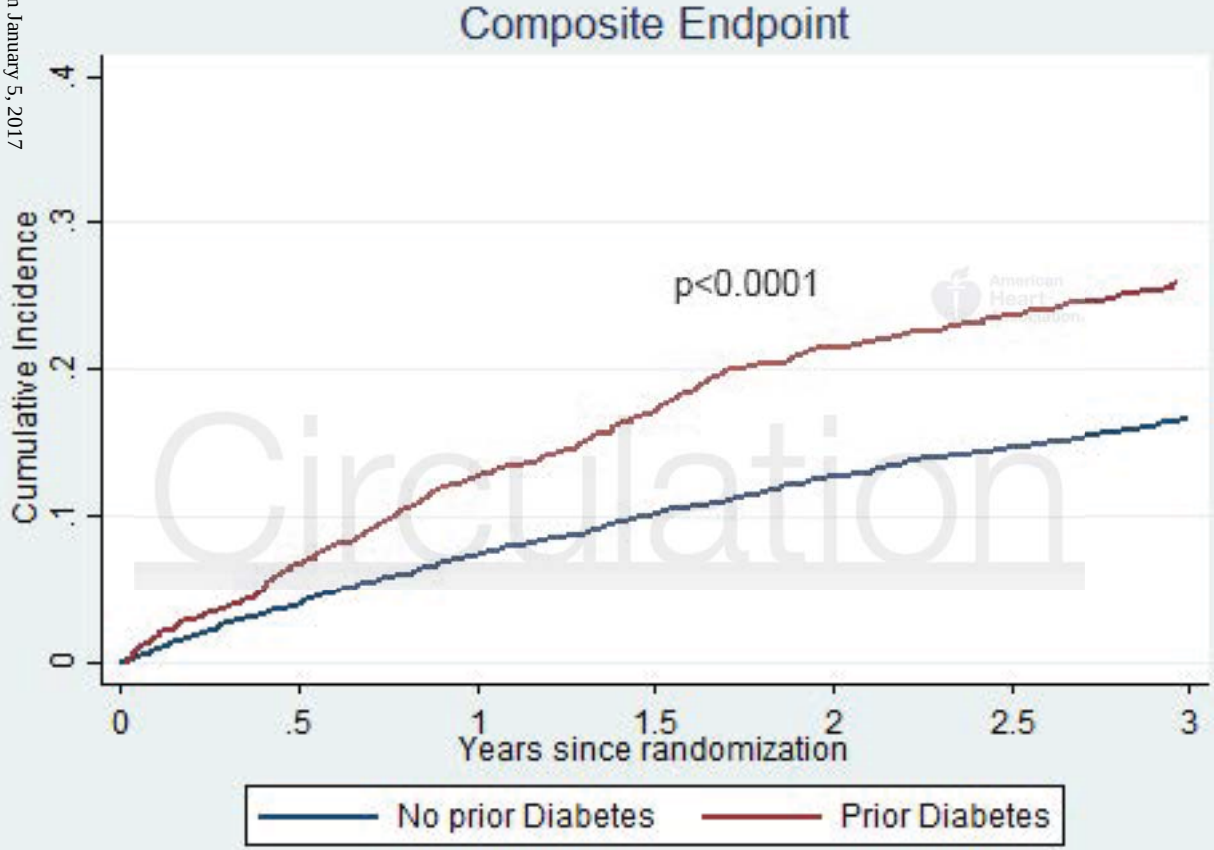
Table 5. Mode of death according to diabetes in I-Preserve

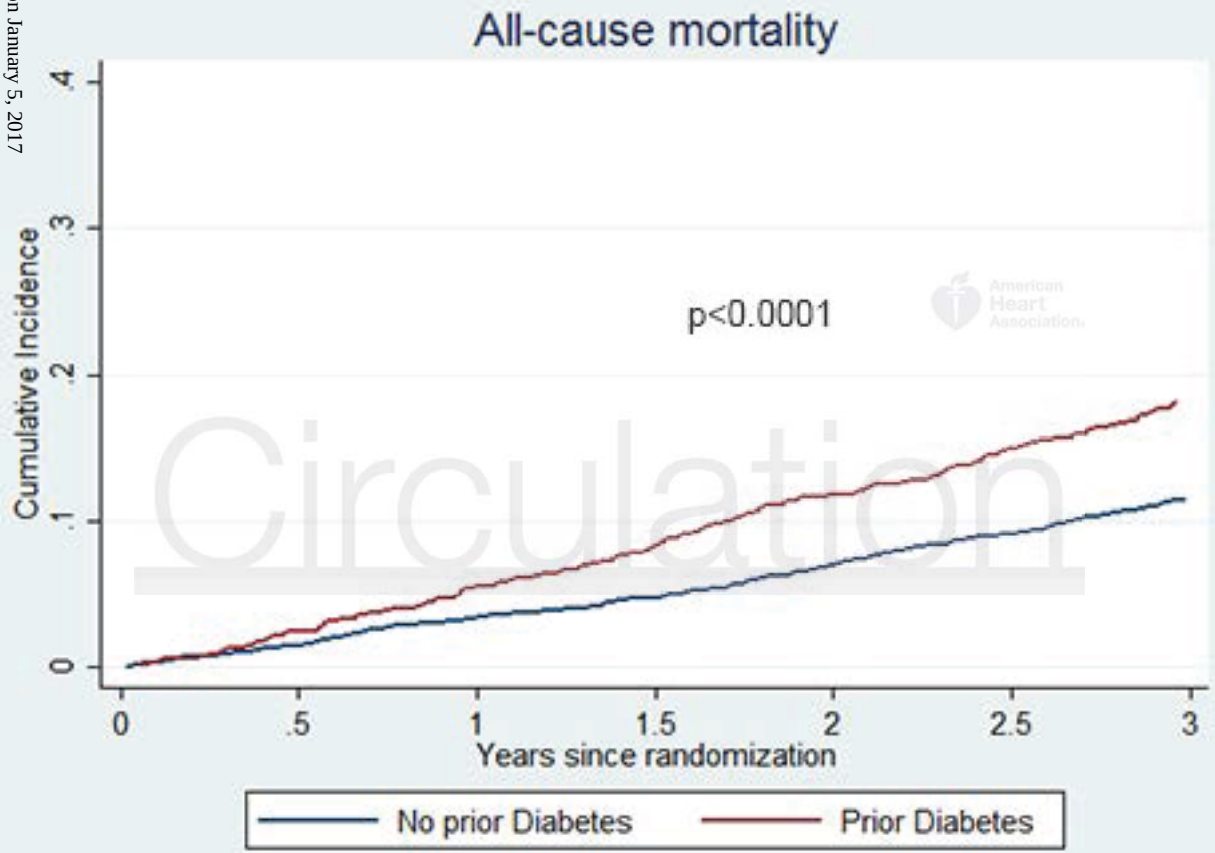
	No diabetes (n=2994)	Diabetes (n=1134)	p-value
Death			
All causes	567 (19%)	314 (28%)	<0.0001
Cardiovascular	393 (13%)	220 (20%)	<0.0001
Pump failure	72 (2%)	53 (5%)	0.0001
Sudden cardiac death	144 (5%)	87 (8%)	0.0004
Myocardial infarction	32 (1%)	13 (1%)	0.83
Stroke	57 (2%)	19 (2%)	0.63
Other cardiovascular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

Figure Legends

Figure 1. Cumulative incidence plot for composite endpoint of cardiovascular death or HF hospitalization according to history of diabetes

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





Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes According to Diabetes Status in Patients with Heart Failure and Preserved Ejection Fraction. A Report from the Irbesartan in Heart Failure with Preserved Ejection Fraction Trial (I-Preserve)

Søren L. Kristensen, Ulrik M. Mogensen, Pardeep S. Jhund, Mark C. Petrie, David Preiss, Sithu Win, Lars Køber, Robert S. McKelvie, Michael R. Zile, Inder S. Anand, Michel Komajda, John S. Gottdiener, Peter E. Carson and John J.V. McMurray

Circulation. published online January 4, 2017;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Supplementary Table 1: Baseline Characteristics stratified by history of diabetes among patients with full echocardiographic examination

	All patients n=745	No diabetes n=558	Diabetes n=187	P-value
Age, mean – years	72±7	72±7	72±7	0.9747
>/=65 years	480 (64.4%)	271 (49%)	83 (44%)	0.6070
>/=75 years	265 (36%)	194 (35%)	71 (58%)	
Female sex, no. (%)	459 (62%)	351 (63%)	108 (58%)	0.2102
Race, no (%):				0.0248
Caucasian	713 (96%)	537 (96%)	176 (94%)	
Black	12 (2%)	5 (1%)	7 (4%)	
Other	20 (3%)	16 (3%)	5 (3%)	
Ejection fraction	60±9	60±9	60±9	0.5429
Body mass index	30±5	29±5	32±5	<0.0001
Underweight (<18.5)	2 (0%)	2 (0%)	0	<0.0001
Normal (18.5-24.9)	105 (14%)	92 (17%)	13 (7%)	
Overweight (25-29.9)	302 (41%)	239 (43%)	63 (34%)	
Obese (≥30)	336 (45%)	225 (40%)	111 (59%)	
Symptoms				
NYHA class				0.8429
II	164 (22%)	120 (22%)	44 (24%)	
III	560 (75%)	422 (76%)	138 (74%)	
IV	21 (3%)	16 (3%)	5 (3%)	
Minnesota living with HF, median	40 (27-54)	39 (27-52)	43 (26-58)	0.2623
Examination findings				
Rales	182 (24%)	140 (25%)	42 (23%)	0.4689
CXR congestion	287 (39%)	205 (37%)	82 (44%)	0.0837
Jugular venous distention	65 (9%)	43 (8%)	21 (11%)	0.1367
Edema	448 (60%)	332 (60%)	116 (62%)	0.5402
3rd heart sound	41 (6%)	32 (6%)	9 (5%)	0.6323
Heart rate /bpm	70±10	69±10	71±11	0.0937
Systolic blood pressure /mm Hg	136±15	136±14	137±15	0.4641
ECG findings				
Left bundle branch block	48 (6%)	37 (7%)	11 (6%)	0.7183
Left ventricular hypertrophy	210 (28%)	161 (29%)	49 (26%)	0.4858
QRS duration	0.10±0.06	0.10 ± 0.06	0.10 ± 0.07	0.2645
Atrial fibrillation/flutter	106 (14%)	74 (13%)	32 (17%)	0.1921
Laboratory examinations				
NT-proBNP, median (Q1-Q3)	299 (129-916)	272 (114- 801)	415 (177-1237)	0.0021
eGFR - l/min/1.73m^2, median (Q1-Q3)	70 (56-84)	70 (56-84)	70 (56-83)	0.6748
CKD (eGFR<60 l/min/1.73m^2)	239 (32%)	179 (32%)	60 (32%)	0.9986
Hemoglobin, g/dl	14.0±1.4	14.1±1.4	13.7±1.5	0.0020
Anemia (Hb<11 Women <13 Men)	76 (11%)	48 (9%)	28 (16%)	0.0029
Neutrophils, cells/µL (Q1-Q3)		4.0 (3.3-5.0)	4.5 (3.5-5.6)	0.0003

Medical history, no. (%)				
HF hospitalization within 6 months	308 (41%)	218 (39%)	90 (48%)	0.0295
Ischemic etiology	150 (20%)	105 (19%)	45 (24%)	0.1215
Hypertensive etiology	529 (71%)	408 (73%)	121 (65%)	0.0282
Myocardial infarction	148 (20%)	103 (19%)	45 (24%)	0.1215
Stable angina pectoris	277 (37%)	218 (39%)	59 (32%)	0.0656
Unstable angina pectoris	58 (8%)	41 (7%)	17 (9%)	0.4413
Hypertension	683 (92%)	507 (91%)	176 (94%)	0.1628
Atrial fibrillation	192 (26%)	136 (24%)	56 (30%)	0.1315
Stroke/TIA	77 (10%)	53 (10%)	24 (13%)	0.1947
PCI or CABG	98 (13%)	68 (12%)	30 (16%)	0.1769
ICD	0	0	0	NA
Pacemaker	50 (7%)	31 (6%)	19 (10%)	0.0294
Medication, no. (%)				
Any diuretic	614 (82%)	455 (82%)	159 (85%)	0.2785
Loop diuretic	371 (50%)	256 (46%)	115 (62%)	0.0002
ACE-I	227 (31%)	145 (26%)	82 (44%)	<0.0001
Beta-blocker	468 (63%)	356 (64%)	112 (60%)	0.3388
Calcium-channel blocker	331 (44%)	243 (44%)	88 (47%)	0.4031
Long-acting nitrates	173 (23%)	129 (23%)	44 (24%)	0.9083
Mineralocorticoid antagonists	120 (16%)	85 (15%)	35 (19%)	0.2621
Digoxin	65 (9%)	42 (8%)	23 (12%)	0.0453
Lipid lowering drugs	179 (24%)	121 (22%)	58 (31%)	0.0097
Antiplatelets, any	434 (58%)	325 (58%)	109 (58%)	0.9914
Metformin	53 (28%)	0 (0%)	53 (28%)	<0.0001
Other oral antidiabetic agents	92 (12%)	0 (0%)	92 (49%)	<0.0001
Insulin	47 (6%)	0 (0%)	47 (25%)	<0.0001

HF – heart failure, CXR – chest x-ray, bpm – beats per minute, eGFR – estimated glomerular filtration rate, CKD – chronic kidney disease, PCI – percutaneous coronary intervention, CABG - coronary artery bypass graft, ICD – Implantable cardioverter defibrillator

Supplementary Table 2: Comparison of results applying Cox regression and competing risk analyses

	Event rate per 100 py	Unadjusted HR	Unadjusted SHR (comp risk)	Adjusted HR	Adjusted SHR (Comp risk)
CV death or HF hospitalization					
No history of diabetes	5.7 (5.3-6.2)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	10.2 (9.2-11.3)	1.76 (1.55-1.99)	1.73 (1.53-1.96)	1.75 (1.49-2.05)	1.73 (1.45-2.02)
CV death					
No history of diabetes	3.2 (2.9-3.5)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	5.0 (4.4-5.7)	1.61 (1.36-1.89)	1.58 (1.34-1.86)	1.59 (1.28-1.96)	1.54 (1.24-1.91)
HF hospitalization					
No history of diabetes	3.5 (3.2-3.9)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	6.6 (5.8-7.5)	1.82 (1.55-2.13)	1.75 (1.49-2.04	1.77 (1.45-2.16)	1.69 (1.37-2.08)
All-cause mortality					
No history of diabetes	4.6 (4.2-5.0)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	7.2 (6.4-8.0)	1.59 (1.39-1.83)	NA	1.59 (1.33-1.91)	NA
Non CV death					
No history of diabetes	1.4 (1.2-1.6)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	2.1 (1.8-2.6)	1.57 (1.22-2.02)	1.48 (1.15-1.90)	1.60 (1.14-2.25)	1.50 (1.07-2.09)
All-cause hospitalization					
No history of diabetes	17.3 (16.5-18.2)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	26.2 (24.3-28.2)	1.45 (1.33-1.59)	1.42 (1.30-1.55)	1.51 (1.34-1.70)	1.46 (1.29-1.64)
CV hospitalization					
No history of diabetes	7.8 (7.3-8.4)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	10.7 (9.7-11.8)	1.33 (1.17-1.50)	1.29 (1.14-1.46)	1.34 (1.14-1.57)	1.29 (1.10-1.52)
Non-CV hospitalization					
No history of diabetes	6.5 (6.0-7.0)	1.00 (ref)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diabetes	9.2 (8.3-10.2)	1.37 (1.21-1.57)	1.32 (1.16-1.51)	1.41 (1.19-1.68)	1.36 (1.14-1.62)

HR – Hazard ratio, SHR – Sub hazard ratios, CV –cardiovascular, HF – heart failure

Supplementary Table 3 **Outcomes stratified by use of insulin in patients with diabetes**

	No. patients	No. events	Event rate per 100 py	Unadjusted HR	Adjusted* HR
CV death or HF hosp.					
No history of diabetes	2994	662 (22%)	5.7 (5.3-6.2)	1.00 (ref)	1.00 (ref)
Diabetes - non-insulin	795	256 (32%)	9.2 (8.1-10.4)	1.59 (1.37-1.83)	1.71 (1.43-2.04)
Diabetes insulin treated	339	135 (40%)	12.9 (10.9-15.3)	2.20 (1.83-2.65)	1.85 (1.44-2.40)
CV death					
No history of diabetes	2994	393 (13%)	3.2 (2.9-3.5)	1.00 (ref.)	1.00 (ref.)
Diabetes - non-insulin	795	145 (18%)	4.6 (3.9-5.4)	1.48 (1.22-1.79)	1.55 (1.22-1.97)
Diabetes insulin treated	339	75 (22%)	6.0 (4.8-7.6)	1.94 (1.51-2.48)	1.67 (1.19-2.33)
HF hospitalization					
No history of diabetes	2994	408 (14%)	3.5 (3.2-3.9)	1.00 (ref.)	1.00 (ref.)
Diabetes - non-insulin	795	160 (20%)	5.7 (4.9-6.7)	1.59 (1.32-1.91)	1.70 (1.36-2.13)
Diabetes insulin treated	339	93 (27%)	8.9 (7.3-10.9)	2.41 (1.93-3.02)	1.94 (1.42-2.65)
All-cause mortality					
No history of diabetes	2994	567 (19%)	4.6 (4.2-5.0)	1.00 (ref.)	1.00 (ref.)
Diabetes - non-insulin	795	205 (26%)	6.5 (5.7-7.5)	1.45 (1.24-1.70)	1.53 (1.25-1.88)
Diabetes insulin treated	339	109 (32%)	8.8 (7.3-10.6)	1.96 (1.60-2.41)	1.76 (1.32-2.33)
Non CV death					
No history of diabetes	2994	174 (6%)	1.4 (1.2-1.6)	1.00 (ref.)	1.00 (ref.)
Diabetes - non-insulin	795	60 (8%)	1.9 (1.5-2.5)	1.37 (1.04-1.86)	1.48 (1.00-2.18)
Diabetes insulin treated	339	34 (10%)	2.7 (2.0-3.8)	2.03 (1.40-2.93)	1.95 (1.15-3.32)
All-cause hospitalization					
No history of diabetes	2994	1520 (51%)	17.3 (16.5-18.2)	1.00 (ref.)	1.00 (ref.)
Diabetes - non-insulin	795	459 (58%)	22.2 (20.2-24.3)	1.25 (1.13-1.39)	1.35 (1.18-1.55)
Diabetes insulin treated	339	248 (73%)	39.0 (34.4-44.1)	2.09 (1.83-2.39)	2.04 (1.70-2.46)
CV hospitalization					
No history of diabetes	2994	815 (27%)	7.8 (7.3-8.4)	1.00 (ref.)	1.00 (ref.)
Diabetes - non-insulin	795	252 (32%)	9.9 (8.7-11.2)	1.24 (1.08-1.43)	1.37 (1.15-1.63)
Diabetes insulin treated	339	121 (36%)	12.7 (10.7-15.2)	1.56 (1.29-1.89)	1.27 (0.97-1.65)
Non-CV hospitalization					
No history of diabetes	2994	699 (23%)	6.5 (6.0-7.0)	1.00 (ref.)	1.00 (ref)
Diabetes - non-insulin	795	204 (26%)	7.6 (6.7-8.8)	1.16 (0.99-1.35)	1.16 (0.94-1.42)
Diabetes insulin treated	339	127 (37%)	13.7 (11.5-16.3)	2.00 (1.65-2.41)	2.28 (1.76-2.95)

Supplementary Table 4 **Serious adverse events and drug discontinuation according to diabetes**

	No diabetes (n=2994)	Diabetes (n=1134)	p-value
Serious Adverse events			
Increased potassium	8 (1%)	13 (2%)	0.0027
Hypotension	33 (2%)	18 (2%)	0.5666
Chronic kidney disease	64 (4%)	55 (7%)	0.0004
Dizziness	13 (1%)	7 (1%)	0.7428
Drug discontinuation due to adverse event (not death)	289 (17%)	178 (23%)	0.0008