

Title: Risk related to pre-diabetes and diabetes in heart failure with reduced ejection fraction: Insights from PARADIGM-HF.

Short title: Pre-diabetes and diabetes in PARADIGM-HF

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ABSTRACT

Background: The prevalence of pre-diabetes and its consequences in patients with heart failure and reduced ejection fraction (HF-REF) are not known. We investigated these in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF).

Methods: We examined clinical outcomes in 8,399 patients with HF-REF according to history of diabetes, and glycemic status (baseline hemoglobin A1c [HbA1c] <6.0% (<42mmol/mol), 6.0-6.4% (42-47mmol/mol) [pre-diabetes] and ≥6.5% (≥48mmol/mol) [diabetes]), in Cox regression models adjusted for known predictors of poor outcome.

Results: Patients with a history of diabetes (n=2,907 [35%]) had a higher risk of the primary composite outcome of heart failure hospitalization or cardiovascular mortality compared to those without a history of diabetes: adjusted hazard ratio [HR] 1.38, 95% confidence interval 1.25-1.52; p<0.001. HbA1c measurement showed that an additional 1,106 (13% of total) patients had undiagnosed diabetes and 2,103 (25%) had pre-diabetes. The HR for patients with undiagnosed diabetes (HbA1C >6.5%) and known diabetes compared to those with HbA1c<6.0% was 1.39 (1.17-1.64); p<0.001 and 1.64 (1.43-1.87); p<0.001, respectively. Patients with pre-diabetes were also at higher risk (HR 1.27 [1.10-1.47]; p<0.001), compared to those with HbA1c<6.0%. The benefit of LCZ696 (sacubitril/valsartan) compared with enalapril was consistent across the range of HbA1c in the trial.

Conclusion: In patients with HF-REF, dysglycemia is very common and pre-diabetes is associated with a higher risk of adverse cardiovascular outcomes (compared to patients with no diabetes and HbA1c <6.0%). LCZ696 was beneficial compared to enalapril, irrespective of glycemic status.

INTRODUCTION

Heart failure and type 2 diabetes mellitus are two of the great epidemics of modern times.^{1,2} Although each begets the other, the links between the two conditions are not fully elucidated.³ While it is widely acknowledged that diabetes is a risk marker for the development of heart failure and greatly heightens the risk of worse outcomes once heart failure develops⁴⁻⁶, the relationship between heart failure and the development of diabetes is less well understood. Even though heart failure seems to be a state of insulin resistance, the mechanisms underlying this are not clear.⁷ Few studies have investigated the prevalence of “pre-diabetic” dysglycemia in patients with heart failure, and even fewer its clinical consequences (and with conflicting findings).^{8,9} Identification of an association, if any, between pre-diabetes and adverse clinical outcomes is of clinical importance from two contrasting perspectives. There has been recent concern that hypoglycemic agents might contribute to the poor cardiovascular outcomes, including heart failure, in patients with diabetes.³ Demonstration that patients with pre-diabetes, untreated with hypoglycemic agents, have worse outcomes than normoglycemic patients would support the view that dysglycemia *per se* is harmful in heart failure. If so, treatment of such patients with hypoglycemic agents might prevent the development of diabetes and improve heart failure outcomes. We therefore investigated the prevalence of diabetes and pre-diabetes in patients with heart failure and reduced ejection fraction (HF-REF) who participated in the Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF)¹⁰ and examined the relationship between glycemic status and clinical outcomes in this trial. We also compared the effect of sacubitril-valsartan (LCZ696) with enalapril in patients in PARADIGM-HF according to glycemic status.

METHODS

The design and primary results of the PARADIGM-HF trial have been described in detail.¹⁰⁻¹²

Study Patients: The inclusion criteria for PARADIGM-HF included: New York Heart Association (NYHA) class II-IV symptoms, ejection fraction $\leq 40\%$ (changed to $\leq 35\%$ by amendment), and a plasma B-type natriuretic peptide (BNP) ≥ 150 pg/mL (or N-terminal pro-BNP [NTproBNP] ≥ 600 pg/mL). Patients who had been hospitalized for heart failure within the preceding 12 months could be enrolled with a lower natriuretic peptide concentration (BNP ≥ 100 pg/mL or NTproBNP ≥ 400 pg/mL). Patients were required to be taking an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) at a dose equivalent to enalapril 10 mg daily for at least 4 weeks before screening, along with a stable dose of a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist, if indicated. The exclusion criteria included history of intolerance of an ACE inhibitor or ARB, symptomatic hypotension (or a systolic blood pressure < 100 mmHg at screening/ < 95 mmHg at randomization), an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², a serum potassium concentration > 5.2 mmol/L at screening (> 5.4 mmol/L at randomization) or a history of angioedema.

Study Procedures: On trial entry, existing treatment with an ACE inhibitor or ARB was stopped, but other treatments for heart failure were continued. Patients first received enalapril 10 mg twice daily for two weeks (single-blind) and then LCZ696 (single-blind) for an additional 4 to 6 weeks, initially at 100 mg twice daily and then 200 mg twice daily. Patients tolerating both drugs at target doses were randomly assigned in a 1:1 ratio to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily. The dose of enalapril was selected based on its effect to reduce the risk of death compared with placebo in the Studies of Left

Ventricular Dysfunction (SOLVD) Treatment Trial.¹³ LCZ696 200 mg twice daily delivers the equivalent of valsartan 160 mg twice daily and significant and sustained neprilysin inhibition.

Definition of pre-diabetes, undiagnosed diabetes and diabetes: For the purposes of this study, patients *without* a prior diagnosis of diabetes were divided into three categories according to HbA1c level using The International Diabetes Expert Committee criteria^{14, 15}: 1) “Normal” <6.0% (<42 mmol/mol) 2) Pre-diabetes 6.0 -6.4% (42-47 mmol/mol) and 3) Undiagnosed diabetes $\geq 6.5\%$ (≥ 48 mmol/mol). Patients with a prior diagnosis of diabetes (irrespective of HbA1c level) were considered to have diabetes.

Study Outcomes: PARADIGM-HF was designed to recruit ~8400 patients and continue until 1229 patients experienced cardiovascular deaths and 2410 patients experienced either a first hospitalization for heart failure, or cardiovascular death (primary outcome). However, an independent Data and Safety Monitoring Board recommended early termination of the study when the pre-specified boundary for overwhelming benefit for both cardiovascular mortality and the primary outcome had been crossed. The primary outcome of this analysis was a composite of death from cardiovascular causes or a first hospitalization for heart failure. The secondary outcomes of PARADIGM-HF were the time to death from any cause, the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure), the time to a new onset of atrial fibrillation, and the time to the first occurrence of a decline in renal function (which was defined as end-stage renal disease or as a decrease in the estimated glomerular filtration rate (eGFR) of at least 50% or a decrease of more than 30 ml per minute per 1.73 m² from randomization to less than 60 ml per minute per 1.73 m²); there were too few patients with new onset atrial fibrillation and decline in renal function for meaningful analysis in the current study of HbA1c sub-groups. Adjudication

of these outcomes was carried out in a blinded fashion by a clinical-end-points committee according to pre-specified criteria. Safety outcomes included hypotension, elevation of serum creatinine, hyperkalemia, cough and angioedema, as previously reported.¹¹

Statistical Analysis: Baseline characteristics are presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. Unadjusted event rates are reported per 100 patient years of follow-up according to diabetic status. Cox proportional hazard models were applied to calculate hazard ratios (HR) for the outcomes in patients with pre-diabetes, undiagnosed diabetes and diabetes with normoglycemic patients as reference, as well as treatment effect of LCZ696 for the outcomes according to glycemic status. In additional Cox models we examined the relation between diabetic status and outcomes stratified by ejection fraction and kidney function (Figures 2 and 3). The adjusted Cox regression models included information on age, sex, race (Caucasian vs. all other), geographical region, heart failure duration, NYHA class, ejection fraction, heart rate, KCCQ score, body mass index, eGFR, NTproBNP, ischemic etiology and history of myocardial infarction, stroke, and atrial fibrillation. We compared frequency of a ≥ 5 point decline in KCCQ score at 8 months follow-up according to diabetes status, and used logistic regression to calculate odds ratios for this reduction in patients with diabetes and pre-diabetes compared to normoglycemic patients. We applied a cubic spline model to assess the relationship between HbA1c and the primary composite outcome in patients not treated with glucose-lowering drugs. All p values are two-sided, and a p value of <0.05 was considered significant. Analyses were performed using Stata version 13 (Stata Corp. College Station, Texas, USA), and SAS version 9.4 (SAS Institute, North Carolina, USA).

RESULTS

Overall, 8,274 patients had known diabetes or a measurement of HbA1c at baseline. Of these, 2,907 (35%) had a history of diabetes. Of the 5,369 (65%) patients with no history of diabetes, 2,158 (40% [26% of total]) had HbA1c < 6.0%, 2,103 (39% [25% of total]) had HbA1c 6.0 - < 6.5% and 1,106 (21% [13% of total]) had HbA1c \geq 6.5% (“undiagnosed diabetes”). A total of 4,013 (49%) patients were therefore defined as having diabetes based upon history (n=2,907) or HbA1c \geq 6.5% (n=1,106). The median follow-up in patients with normal HbA1c was 26 months and it was 27 months in both patients with pre-diabetes and diabetes.

Baseline Characteristics: Patients with pre-diabetes and diabetes were older, more often Caucasian, had longer heart failure duration, a higher body mass index (and more obesity), as well as evidence of overall worse heart failure status (Table 1). Manifestations of worse heart failure status included higher NYHA class and B-type natriuretic peptide levels, lower KCCQ score and eGFR, more edema and greater use of diuretics (Table 1). The exception to this was ejection fraction, which was marginally although insignificantly higher in patients with pre-diabetes and diabetes compared to those with a normal HbA1c. Patients with pre-diabetes and diabetes also more commonly had a history of myocardial infarction and atrial fibrillation. Generally, the trends identified were most marked in patients with diabetes, and intermediate between diabetes and normoglycemia in individuals with pre-diabetes. Patients in Latin America had the lowest prevalence of pre-diabetes/diabetes and the highest proportion of normoglycemic patients. The prevalence of diabetes was most prevalent in North America and the Asia-Pacific region. However, when both diabetes and pre-diabetes were taken into account, the rate of dysglycemia was similar in Western/Central Europe and the Asia-Pacific region and less in North America, compared with these other regions.

Clinical outcomes according to HbA1c category and diabetes status: The clinical outcomes of interest according to the predefined glycemia categories are summarized in Table 2 and illustrated in Figure 1. The rates of both the primary composite outcome and all-cause death were lowest in the normal HbA1c group, significantly higher in the pre-diabetes category and highest in individuals with undiagnosed and known diabetes (Table 2, Figure 1). Patients with a history of diabetes were at higher risk of the primary composite outcome of heart failure hospitalization and cardiovascular mortality compared to those with normal HbA1c: adjusted hazard ratio [HR], 1.64, 95% confidence interval 1.43-1.87; $P < 0.001$. The HR for patients with undiagnosed diabetes ($\text{HbA1C} > 6.5\%$) compared to those with $\text{HbA1c} < 6.0\%$ was 1.39 (1.17-1.64); $P < 0.001$. The elevation in risk related to dysglycemia appeared more marked for heart failure hospitalization than for cardiovascular death or all-cause death. These differences in risk persisted after adjusting for other prognostic variables. In particular, the elevated risk related to pre-diabetes as well as diabetes was apparent across the spectrum of ejection fraction, although non-significantly so in patients with $\text{EF} > 35\%$ and tended to be accentuated at lower ejection fraction (Figure 2). A similar pattern was observed when we assessed the risk related to diabetes and pre-diabetes according to kidney function (Figure 3). In a cubic spline analysis restricted to patients not on glucose-lowering drugs ($n=6069$) we found a correlation between increasing HbA1c and elevated risk of the primary outcome (Figure 4).

At 8 months after randomization, more patients with diabetes (31%) had a decline of ≥ 5 points in KCCQ score, compared to patients with pre-diabetes (28%), and those with a normal HbA1c (26%); p -value for difference 0.0002. Compared to the group with normal HbA1c, the odds ratios for a 5-point reduction were 1.24 (1.10-1.39) for patients with diabetes and 1.08 (0.94-1.23) for patients with pre-diabetes (Table 2).

Effect of LCZ696 (sacubitril/valsartan) according to diabetes status: The effect of LCZ696 on the different outcomes is shown in Table 3. In each of the three pre-defined glycemia categories LCZ696 reduced the occurrence of the primary composite outcome compared with enalapril. Fewer patients treated with LCZ696 considered themselves worse 8 months into the study (defined by a reduction in KCCQ score of ≥ 5 points) in all three pre-defined glycemia categories, with no significant interaction between glycemia category and treatment ($p=0.12$).

Pre-specified safety assessments: Adverse events causing drug discontinuation were overall rare, although more prevalent in patients with diabetes, compared to patients with normal HbA1c, and intermediate in the pre-diabetes group (Table 4). Renal impairment and hyperkalemia were more prevalent adverse events in patients with diabetes. We found no interaction with LCZ696 treatment, except for a higher likelihood of increase in serum creatinine $3.0 \geq$ mg/dl, but importantly this did not lead to more study-drug-discontinuation. Angioedema was very rare, regardless of diabetic status and assigned treatment.

Patients with previously known diabetes versus undiagnosed diabetes: Notable differences between these two groups included older age, longer duration of heart failure, lower eGFR, and more frequent ischemic etiology (and prior MI), in patients with known diabetes (Table 1). In terms of medication, patients with known diabetes were more likely to be treated with antiplatelet agents and statins. The risk of the primary outcome was higher in patients with known diabetes ($p=0.025$), primarily due to a higher risk of heart failure hospitalization ($p=0.032$), whereas risk of cardiovascular death was similar in those with known and undiagnosed diabetes ($p=0.205$). Finally, risk of all-cause mortality appeared higher in patients with known diabetes, compared to patients with HbA1c $\geq 6.5\%$, and more so in adjusted analyses (HR 1.46 [1.26-1.70] vs. HR 1.25 [1.03-1.51]; $p=0.07$).

DISCUSSION

This study has three key findings. Firstly, while it is known that the prevalence of diabetes is high in patients with HF-REF, it appears that both pre-diabetes and undiagnosed diabetes are also common in these patients. Secondly, non-diabetic dysglycemia (pre-diabetes) is associated with a substantially increased risk of adverse outcomes in HF-REF. Lastly, LCZ696 (**sacubitril/valsartan**) is superior to enalapril, irrespective of glycemic status.

The first of our findings shows that a HF-REF patient without a history of diabetes has approximately a one in five chance of actually having the condition (but not yet diagnosed), and a greater than one in three chance of having pre-diabetes, based on HbA1c testing. Few prior studies have reported the prevalence of non-diabetic dysglycemia in HF-REF. In one seminal report, describing a substudy of 663 patients in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study¹⁶, 27% had known diabetes. Of the remainder, 11% had undiagnosed diabetes (fasting plasma glucose ≥ 7.1 mmol/l) and 12% a fasting glucose between 6.1 and 7.1 mmol/l diagnostic of the pre-diabetic condition impaired fasting glycemia. Egstrup and colleagues used the more sensitive approach of oral glucose tolerance testing to explore the same question in 227 ambulatory patients with HF-REF without known diabetes attending a heart failure clinic in Denmark.¹⁷ Of these, 60% had normal glucose tolerance, 22% impaired glucose tolerance and 18% undiagnosed diabetes (an additional 20% of the study cohort had known diabetes). Among patients without diabetes in our much larger and geographically diverse population, the proportion of patients with pre-diabetes (38%) and undiagnosed diabetes (20%) were both higher. The overall prevalence of diabetes and pre-diabetes was, therefore, remarkable 74%. We found some geographic variation in prevalence, with patients from Latin America having the lowest prevalence of dysglycemia and patients in the Asia-Pacific region and Europe the highest. This contrasts strikingly with the prevalence of diabetes in the general population.

For example, using similar HbA1c diagnostic thresholds, the prevalence of diagnosed diabetes, undiagnosed diabetes and pre-diabetes in USA residents aged ≥ 65 years was 17.7 (95% CI 15.6-19.8)%, 3.5 (2.6-4.4)% and 8.1 (6.6-9.6)%, respectively, giving a total of 29.3% individuals with diabetes or pre-diabetes, an overall prevalence considerably less than half of that observed in our HF-REF patients.¹⁸

The significance of this finding relates to the worse clinical status and substantially elevated risk of adverse clinical outcomes conferred by both pre-diabetes and diabetes. In one study, pre-diabetes and insulin resistance were correlated with worse symptom status, reduced exercise tolerance and neurohumoral activation, and another study showed that elevated HbA1c was associated with increased mortality in non-diabetic patients referred for suspected heart failure.^{19, 20} Our findings confirm and extend these prior observations from RESOLVD, particularly with the demonstration of a worse KCCQ score, more edema and higher natriuretic peptide levels in patients with pre-diabetes compared to those with a normal HbA1c.¹⁶ The finding that lower HbA1c in patients without known diabetes corresponded to a better prognosis is in contrast with the observed U-shaped relation between HbA1c and adverse outcomes in patients with known and treated diabetes.²¹ We also found, as previously, that these manifestations of worse clinical status were apparent despite a similar or even higher ejection fraction than in the group with a normal HbA1c, which is an unexplained and perhaps paradoxical finding.

Although the heightened risk related to diabetes is well known, the risk associated with pre-diabetes is not. This new finding is important for a number of reasons. Most significantly, it shows that dysglycemia itself, rather than use of hypoglycemic drugs, is a risk factor for adverse outcomes. Recently there has been concern that the agents used to lower blood glucose may be harmful in patients with heart failure.^{3, 22, 23} As our patients with pre-diabetes

were not receiving these treatments, hypoglycemic agents cannot account for the worse outcomes in this group compared to subjects with a normal HbA1c. However, patients with diabetes also did worse than patients with pre-diabetes (and those with known diabetes did worse than those with undiagnosed diabetes), still leaving open the possibility of harm related to hypoglycemic drugs (although there are other reasons why the more severe and probably longer duration of hyperglycemia in diabetes might be associated with worse outcomes than pre-diabetes).

Secondly, these findings are important as they emphasize the need to better understand the effect of treatments for dysglycemia on outcomes in patients with heart failure. If hypoglycemic treatments were shown to improve outcomes across the range of dysglycemia including both pre-diabetes and diabetes, potentially a very large proportion of patients would be eligible for such treatment. However, although the relationship between dysglycemia and adverse events in heart failure is clear and strong, it is only an association and a clear cause-and-effect mechanistic pathway has not been confirmed. Moreover, as alluded to above, there has been concern that at least some hypoglycemic agents may increase rather than decrease the risk of heart failure-related events.²³

As anticipated, renal dysfunction and hyperkalemia were more common among patients with diabetes (compared to those with normoglycemia) in the enalapril group; however, both these adverse effects were numerically (but statistically insignificantly) less common in the LCZ696 group, compared with the enalapril group, across all glycemia categories. Renal dysfunction was also more frequent in ACE inhibitor treated patients with diabetes than in those without diabetes.²⁴ Marked renal dysfunction (serum creatinine ≥ 3.0 mg/dl) was less frequent with LCZ696 than with enalapril, irrespective of glycemia status. Hypotension was

more common overall with LCZ696 compared with enalapril; the increment in hypotension with LCZ696 was smaller in patients with diabetes than in the other glycemia groups.

The current study has a number of limitations. It is a retrospective analysis. Our dysglycemia categorization is based on one set of criteria and other slightly different criteria exist.^{25, 26}

Our patients had only one measurement of HbA1c, and not at least two measurements and/or supplementary analyses of fasting glucose and oral glucose tolerance, as recommended in guidelines.^{14, 15}

In summary, we have shown that in patients with chronic HF-REF dysglycemia is very common and pre-diabetes, as well as diabetes, is associated with worse clinical status and a significantly increased risk of adverse cardiovascular outcomes compared to normoglycemic patients. LCZ696 was beneficial, irrespective of HbA1c concentration and diabetes status.

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DISCLOSURES

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Table legends

Table 1	Baseline Characteristics according to presence of diabetes, defined by prior diagnosis, undiagnosed diabetes ($HbA1c \geq 6.5$), pre-diabetes ($HbA1c$ 6.0-6.4) or normoglycemia ($HbA1c < 6.0$)
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Table 1 Baseline Characteristics according to presence of diabetes, defined by prior diagnosis, undiagnosed diabetes (HbA1c \geq 6.5), pre-diabetes (HbA1c 6.0-6.4) or normoglycemia (HbA1c<6.0)

	No prior diagnosis of diabetes			Prior diabetes	p-value
	HbA1c < 6.0	HbA1c 6.0-6.4	HbA1c > 6.4	Any HbA1c	
Patients, no (%)	2158 (26%)	2103 (26%)	1106 (13%)	2907 (35%)	
Age, mean	62 \pm 12	64 \pm 12	63 \pm 12	65 \pm 10	<0.0001
Female, n (%)	474 (22%)	470 (22%)	258 (23%)	613 (21%)	0.4429
Caucasian, n (%)	1333 (62%)	1424 (68%)	688 (62%)	2010 (69%)	<0.0001
LCZ696 treatment, n(%)	1087 (50%)	1040 (50%)	549 (50%)	1451 (50%)	0.9426
HbA1c, median(Q1-Q3)	5.6 (5.4-5.7)	6.1 (6.0-6.2)	6.6 (6.5-6.9)	7.2 (6.5-8.4)	<0.0001
HF duration, n (%)					<0.0001
0-1 years	707 (33%)	629 (30%)	379 (34%)	765 (26%)	
>1-5 years	841 (39%)	834 (40%)	414 (38%)	1106 (38%)	
>5 years	610 (28%)	640 (30%)	313 (28%)	1036 (36%)	
NYHA class, n (%)					<0.0001
I	109 (5%)	102 (5%)	56 (5%)	115 (4%)	
II	1614 (75%)	1474 (70%)	750 (68%)	1996 (69%)	
III	420 (19%)	502 (24%)	294 (27%)	770 (26%)	
IV	10 (1%)	22 (1%)	4 (0%)	24 (1%)	
Geographical region					<0.0001
North America	185 (30%)	102 (17%)	27 (4%)	299 (49%)	
Latin America	512 (37%)	345 (25%)	154 (11%)	385 (28%)	
Western Europe	431 (23%)	529 (28%)	260 (14%)	678 (36%)	
Central Europe	670 (24%)	758 (27%)	397 (14%)	962 (35%)	
Asia-Pacific	360 (23%)	369 (23%)	268 (17%)	583 (37%)	
Jugular venous distension, n (%)	199 (9%)	199 (10%)	120 (11%)	289 (10%)	0.4738
Edema, n (%)	363 (17%)	444 (21%)	234 (21%)	688 (24%)	<0.0001
Rales, n (%)	139 (6%)	170 (8%)	92 (8%)	252 (9%)	0.0287
Third heart sound, n (%)	199 (9%)	176 (8%)	121 (11%)	290 (10%)	0.0810
Ejection fraction	0.29 \pm 0.06	0.30 \pm 0.06	0.29 \pm 0.06	0.30 \pm 0.06	0.0338
Heart rate/bpm	71 \pm 12	72 \pm 12	73 \pm 13	74 \pm 12	<0.0001
SBP, mm Hg	121 \pm 15	120 \pm 15	120 \pm 14	123 \pm 16	<0.0001
KCCQ score	76 \pm 18	73 \pm 19	72 \pm 19	71 \pm 20	<0.0001
BMI, Kg/m ²					<0.0001
<18	36 (2%)	40 (2%)	17 (2%)	13 (0%)	
18-24.9	790 (37%)	654 (31%)	294 (27%)	604 (21%)	
25-29.9	842 (39%)	792 (38%)	452 (41%)	1082 (37%)	
30-	490 (23%)	617 (29%)	343 (31%)	1208 (42%)	
eGFR, ml/min/1.73m ²	69 [57, 83]	66 [55, 79]	67 [54, 79]	65 [51, 79]	<0.0001
CKD (eGFR<60)	646 (30%)	734 (35%)	400 (36%)	1138 (39%)	<0.0001
BNP, pg/ml	585 [351, 1083]	614 [383, 1213]	712 [421, 1423]	604 [376, 1098]	<0.0001
NTproBNP, pg/ml	187 [104, 358]	196 [107, 393]	217 [113, 443]	183 [101, 366]	<0.0001
ICD/CRT-D, n (%)	321 (15%)	292 (14%)	113 (10%)	501 (17%)	<0.0001

CRT-P+D, n (%)	152 (7%)	129 (6%)	54 (5%)	232 (8%)	0.0025
Medical history, n (%)					
Ischemic etiology	1117 (52%)	1207 (57%)	659 (60%)	1980 (68%)	<0.0001
Prior MI	814 (38%)	848 (40%)	454 (41%)	1459 (50%)	<0.0001
Prior stroke	180 (8%)	178 (9%)	69 (6%)	286 (10%)	0.0033
prior AF	697 (32%)	827 (39%)	436 (39%)	1072 (37%)	<0.0001
Medication, n (%)					
Loop diuretic	1628 (75%)	1644 (78%)	933 (84%)	2434 (84%)	<0.0001
Digoxin	610 (28%)	645 (31%)	370 (34%)	882 (30%)	0.0214
β-blocker	2014 (93%)	1958 (93%)	1021 (92%)	2704 (93%)	0.7566
MRA	1224 (57%)	1175 (56%)	643 (58%)	1562 (54%)	0.0431
Statin	1041 (48%)	1106 (53%)	589 (53%)	1916 (66%)	<0.0001
Antiplatelets, any	1151 (53%)	1124 (53%)	582 (53%)	1797 (62%)	<0.0001
Insulin	0	0	0	722 (25%)	<0.0001
Hypoglycemic agent	3 (0.1%)	5 (0.2%)	4 (0.4%)	1779 (61%)	<0.0001

*data for those with a history of diabetes (n=2907) and with HbA1c 6.5% (n=1106) respectively are presented in Supplementary Table 1

Table 2 Event rates, and risks of the primary endpoint (CV death or heart failure hospitalization), CV death, HF hospitalization, all-cause mortality, and worsening KCCQ score, according to history of diabetes and glycemic status

	No. patients	No. events	Crude rate per 100py	Unadjusted hazard ratio	Adjusted* hazard ratio	P-value
Primary composite endpoint						
No DM & HbA1c < 6.0	2160	388	8.52 (7.72-9.43)	1.00 (ref.)	1.00 (ref.)	
No DM & HbA1c 6.0-6.4	2103	478	10.88 (9.94-11.90)	1.27 (1.12-1.46)	1.27 (1.10-1.47)	0.001
No DM & HbA1c ≥6.5	1106	289	12.87 (11.47-14.45)	1.51 (1.30-1.76)	1.39 (1.17-1.64)	<0.001
DM & any HbA1c	2907	851	14.84 (13.88-15.88)	1.73 (1.54-1.95)	1.64 (1.43-1.87)	<0.001
CV death						
No DM & HbA1c < 6.0	2160	249	5.25 (4.64-5.94)	1.00 (ref.)	1.00 (ref.)	
No DM & HbA1c 6.0-6.4	2103	302	6.46 (5.77-7.23)	1.23 (1.04-1.45)	1.29 (1.07-1.54)	0.006
No DM & HbA1c ≥6.5	1106	189	7.80 (6.76-8.99)	1.49 (1.23-1.79)	1.37 (1.06-1.69)	0.009
DM & any HbA1c	2907	496	7.76 (7.11-8.47)	1.48 (1.27-1.72)	1.54 (1.30-1.83)	<0.001
Heart failure hospitalization						
No DM & HbA1c < 6.0	2160	201	4.42 (3.85-5.07)	1.00 (ref.)	1.00 (ref.)	
No DM & HbA1c 6.0-6.4	2103	265	6.03 (5.35-6.80)	1.37 (1.14-1.64)	1.31 (1.08-1.60)	0.006
No DM & HbA1c ≥6.5	1106	170	7.57 (6.52-8.80)	1.72 (1.40-2.11)	1.54 (1.23-1.92)	<0.001
DM & any HbA1c	2907	543	9.47 (8.71-10.30)	2.13 (1.81-2.51)	1.89 (1.58-2.25)	<0.001
All-cause mortality						
No DM & HbA1c < 6.0	2160	321	6.77 (6.07-7.55)	1.00 (ref.)	1.00 (ref.)	
No DM & HbA1c 6.0-6.4	2103	373	7.97 (7.20-8.82)	1.18 (1.01-1.36)	1.22 (1.03-1.51)	0.016
No DM & HbA1c ≥6.5	1106	218	9.00 (7.88-10.27)	1.33 (1.12-1.58)	1.25 (1.03-1.51)	0.023
DM & any HbA1c	2907	613	9.59 (8.86-10.38)	1.42 (1.24-1.62)	1.46 (1.26-1.70)	<0.001
Significant worsening in KCCQ clinical score (≥5) at 8 months						
No DM & HbA1c < 6.0	2158	559		1.00 (ref.)	1.00 (ref.)	
No DM & HbA1c 6.0-6.4	2103	582		1.10 (0.96-1.26)	1.04 (0.91-1.20)	0.557
No DM & HbA1c ≥6.5	1106	312		1.12 (0.96-1.32)	1.13 (0.95-1.34)	0.176
DM & any HbA1c	2907	917		1.32 (1.17-1.50)	1.22 (1.07-1.40)	0.003

*Adjusted for: age, sex, race (white vs. all other), geographical region, heart failure duration, NYHA class, LVEF, heart rate, KCCQ score, BMI, eGFR, NTproBNP, ischemic etiology, prior MI, prior stroke, prior AF.

†Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100 (higher scores indicating fewer symptoms). Effect of diabetes/dysglycemia is estimated by logistic regression and shown as odds ratios.

Table 3 Treatment effects of LCZ696 (sacubitril/valsartan) according to history of diabetes and glycemic status

	Overall	Normoglycemia	Pre-diabetes	Undiagnosed diabetes	Diabetes	P-value for interaction
HF hospitalization or cardiovascular death	0.80 (0.73-0.87)	0.68 (0.56-0.83)	0.76 (0.63-0.91)	0.97 (0.77-1.22)	0.87 (0.77-0.98)	0.13
Cardiovascular death	0.80 (0.71-0.89)	0.62 (0.48-0.80)	0.76 (0.61-0.96)	0.86 (0.65-1.15)	0.92 (0.77-1.09)	0.09
HF hospitalization	0.80 (0.71-0.89)	0.85 (0.65-1.12)	0.73 (0.57-0.93)	0.88 (0.65-1.20)	0.79 (0.67-0.94)	0.78
All-cause mortality	0.84 (0.76-0.93)	0.68 (0.55-0.85)	0.77 (0.63-0.95)	0.91 (0.69-1.18)	0.97 (0.83-1.14)	0.06
Significant worsening in KCCQ clinical score (≥5) at 8 months	0.83(0.76-0.92)	0.73 (0.60-0.89)	0.86 (0.71-1.04)	0.93 (0.71-1.21)	0.86 (0.74-1.01)	0.14

Table 4 Pre-specified safety assessments according history of diabetes and glycemic status

	Normal HbA1c (n=2158)		Pre-Diabetes (n=2103)		Undiagnosed diabetes (n=1106)		Diabetes (n=2907)		Inter-action P
	Enalapril	LCZ696	Enalapril	LCZ696	Enalapril	LCZ696	Enalapril	LCZ696	
Hypotension									
Symptomatic hypotension	98 (9%)	160 (15%)	88 (8%)	173 (17%)	46 (8%)	57 (10%)	149 (10%)	191 (13%)	0.051
Symptomatic hypotension with SBP < 90 mm Hg	15 (1%)	28 (3%)	12 (1%)	37 (4%)	8 (1%)	11 (2%)	23 (2%)	34 (2%)	0.296
Leading to study-drug discontinuation*	5 (1%)	10 (1%)	7 (1%)	9 (1%)	5 (1%)	5 (1%)	11 (1%)	11 (1%)	0.336
Renal impairment N (%)									
Serum creatinine ≥ 2.5 mg/dl	29 (3%)	28 (3%)	35 (3%)	29 (3%)	21 (4%)	16 (3%)	102 (7%)	65 (5%)	0.126
Serum creatinine ≥ 3.0 mg/dl	13 (1%)	15 (1%)	8 (1%)	15 (1%)	8 (1%)	8 (2%)	53 (4%)	25 (2%)	0.029
Leading to study-drug discontinuation	9 (1%)	5 (1%)	12 (1%)	2 (0%)	8 (1%)	6 (1%)	30 (2%)	16 (1%)	0.594
Hyperkalemia N (%)									
Serum potassium > 5.5 mmol/l	149 (14%)	151 (14%)	167 (16%)	143 (14%)	83 (15%)	94 (17%)	319 (22%)	281 (19%)	0.488
Serum potassium > 6.0 mmol/l	54 (5%)	40 (4%)	54 (5%)	38 (4%)	26 (5%)	25 (5%)	100 (7%)	77 (5%)	0.738
Leading to study-drug discontinuation*	2 (0%)	1 (0%)	2 (0%)	1 (0%)	3 (1%)	3 (1%)	8 (1%)	6 (0%)	0.744
Cough N (%)									
Any cough	143 (13%)	116 (11%)	150 (14%)	121 (12%)	82 (15%)	70 (13%)	220 (15%)	160 (11%)	0.697
Leading to study-drug discontinuation*	5 (1%)	1 (0%)	9 (1%)	3 (0%)	1 (0%)	2 (0%)	15 (1%)	2 (0%)	0.737

Angioedema (adjudicated)									
No treatment or antihistamines only	4 (0%)	4 (0%)	2 (0%)	3 (0%)	1 (1%)	2 (0%)	0 (0%)	2 (0%)	0.360
Catecholamines or corticosteroids without hospitalization	0 (0%)	1 (0%)	3(0%)	3 (0%)	1 (1%)	0 (0%)	0 (0%)	2 (0%)	0.741
Hospitalized without airway compromise	0 (0%)	1 (0%)	1 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.779
Airway compromise	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Any adverse event leading to study-drug discontinuation N (%)	21 (2%)	15(1%)	30 (3%)	15 (1%)	16 (3%)	14 (3%)	61 (4%)	34 (3%)	0.905

Figure 1 Cumulative event curves for the primary composite endpoint of cardiovascular death or heart failure hospitalization, each of the components separately, and all-cause mortality according to history of diabetes and glycemic status

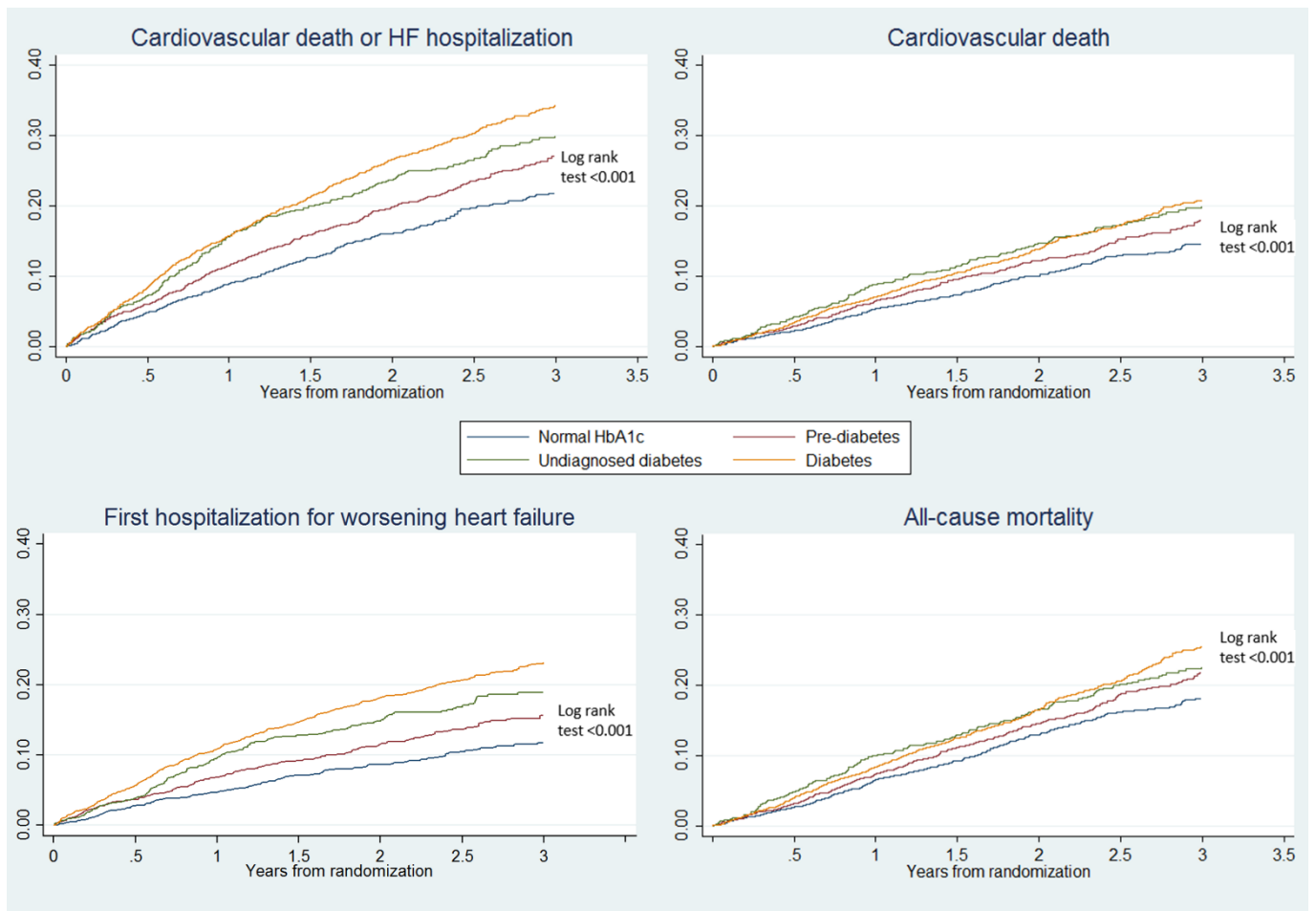
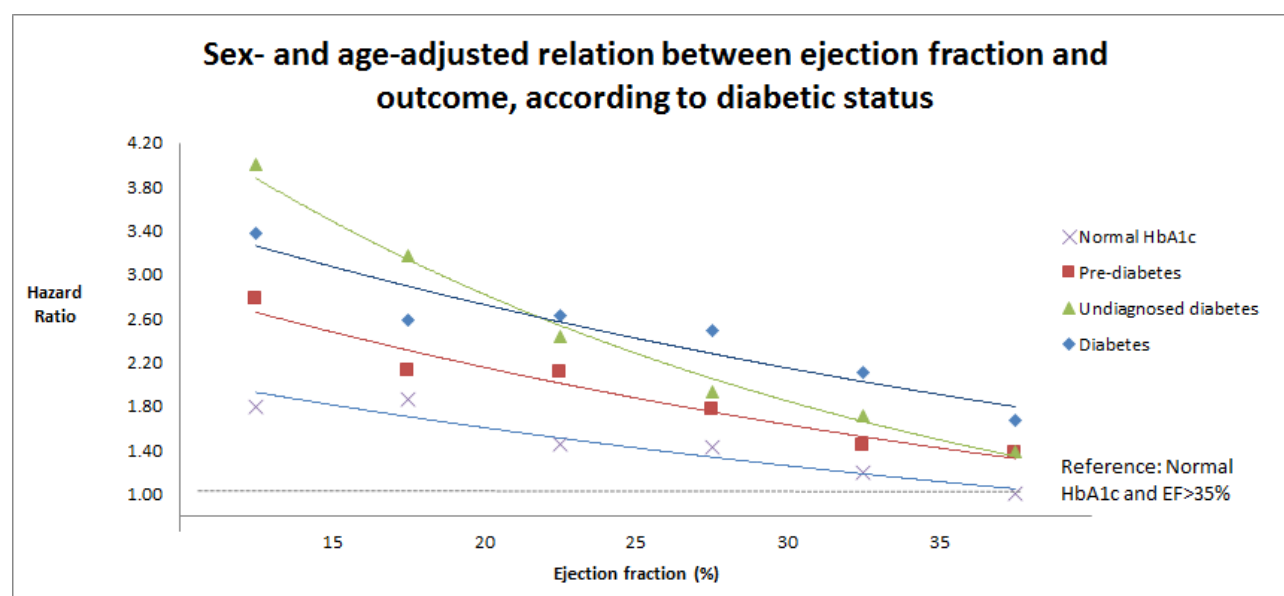
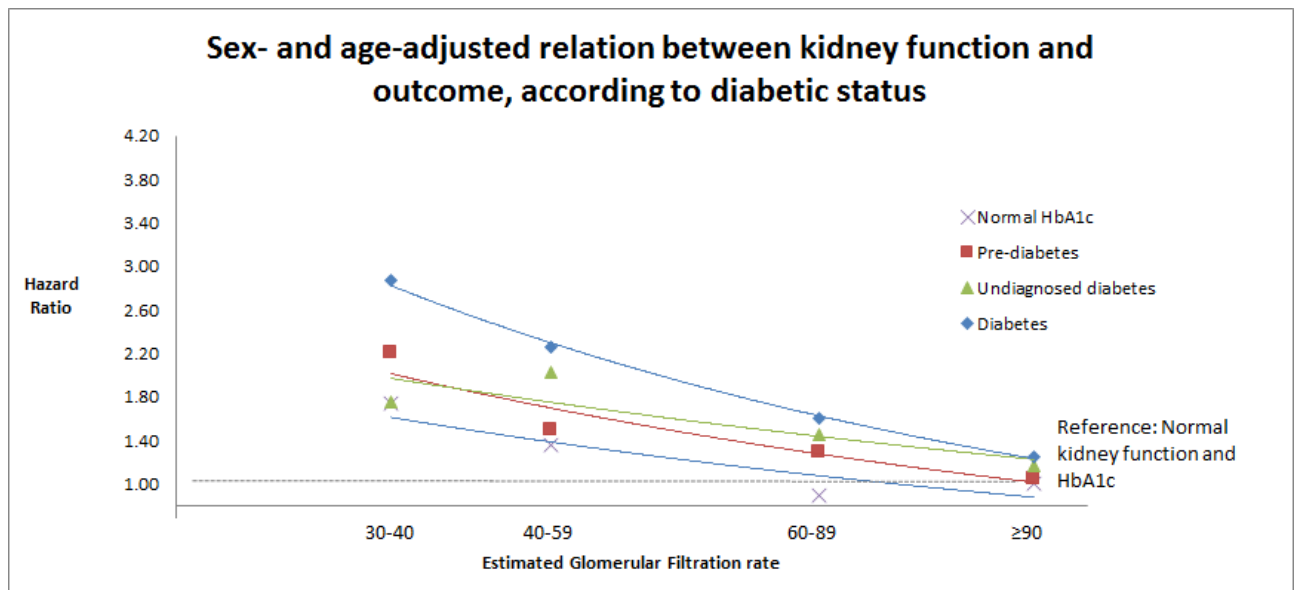


Figure 2 Relation between ejection fraction and the primary outcome stratified by history of diabetes and glycemic status



DM status	EF	<15% HR (95% CI)	15-20% HR (95% CI)	20-25% HR (95% CI)	25-30% HR (95% CI)	30-35% HR (95% CI)	>35% HR (95% CI)
Normoglycemia		1.79 (0.95-3.35)	1.86 (1.22-2.86)	1.45 (0.98-2.15)	1.43 (0.99-2.05)	1.19 (0.83-1.72)	1.00 (reference)
Prediabetes		2.78 (1.63-4.73)	2.12 (1.39-3.24)	2.11 (1.44-3.08)	1.77 (1.23-2.54)	1.44 (1.01-2.06)	1.37 (0.92-2.05)
Undiagnosed diabetes		4.01 (2.29-7.01)	3.17 (2.00-5.00)	2.44 (1.63-3.67)	1.93 (1.30-2.86)	1.71 (1.17-2.50)	1.38 (0.85-2.24)
Diabetes		3.37 (2.11-5.39)	2.59 (1.77-3.79)	2.66 (1.87-3.80)	2.49 (1.77-3.50)	2.11 (1.51-2.96)	1.67 (1.15-2.44)

Figure 3 Relation between diabetic status and the primary outcome stratified by kidney function



eGFR	30-40	40-59	60-89	≥90
DM status				
Normoglycemia	1.74 (1.08-2.81)	1.36 (0.99-1.86)	0.89 (0.66-1.19)	1.00 (Reference)
Prediabetes	2.21 (1.41-3.45)	1.49 (1.10-2.02)	1.29 (0.97-1.71)	1.04 (0.71-1.53)
Undiagnosed diabetes	1.76 (0.98-3.17)	2.02 (1.47-2.78)	1.46 (1.08-1.98)	1.17 (0.75-1.82)
Diabetes	2.87 (2.04-4.06)	2.26 (1.71-3.00)	1.60 (1.22-2.11)	1.25 (0.88-1.76)

*Patients with severe CKD (eGFR<30) were excluded from the PARADIGM-HF trial

Figure 4 Risk of the primary composite outcome according to HbA1c in patients not receiving glucose-lowering drugs.

