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▶ **To cite this version:**

Alice M Jackson, Rasmus Rørth, Jiankang Liu, Søren Lund Kristensen, Inder S Anand, et al.. Diabetes and pre-diabetes in patients with heart failure and preserved ejection fraction. European Journal of Heart Failure, 2022, 24 (3), pp.497-509. 10.1002/ejhf.2403 . hal-03716757

HAL Id: hal-03716757

https://hal.univ-lorraine.fr/hal-03716757

Submitted on 7 Jul 2022

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European Journal of Heart Failure (2022) **24**, 497–509
doi:10.1002/ejhf.2403

RESEARCH ARTICLE

Diabetes and pre-diabetes in patients with heart failure and preserved ejection fraction

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Received 8 August 2021; revised 5 December 2021; accepted 8 December 2021; online publish-ahead-of-print 4 January 2022

Aim

There is an association between heart failure with preserved ejection fraction (HFpEF) and insulin resistance, but less is known about the diabetic continuum, and in particular about pre-diabetes, in HFpEF. We examined characteristics and outcomes of participants with diabetes or pre-diabetes in PARAGON-HF.

Methods and results

Patients aged ≥50 years with left ventricular ejection fraction ≥45%, structural heart disease and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) were eligible. Patients were classified according to glycated haemoglobin (HbA1c): (i) normal HbA1c, <6.0%; (ii) pre-diabetes, 6.0%–6.4%; (iii) diabetes, ≥6.5% or history of diabetes. The primary outcome was a composite of cardiovascular (CV) death and total heart failure hospitalizations (HFH). Of 4796 patients, 50% had diabetes and 18% had pre-diabetes. Compared to patients with normal HbA1c, patients with pre-diabetes and diabetes more often were obese, had a history of myocardial infarction and had lower Kansas City Cardiomyopathy Questionnaire scores, while patients with diabetes had more clinical evidence of congestion, but similar NT-proBNP concentrations. The risks of the primary composite outcome (rate ratio [RR] 1.59, 95% confidence interval [CI] 1.35–1.88), total HFH (RR 1.67, 95% CI 1.39–2.02) and CV death (hazard ratio [HR] 1.35, 95% CI 1.07–1.71) were higher among patients with diabetes, compared to those with normal HbA1c. Patients with pre-diabetes had a higher risk (which was intermediate between that of patients with diabetes and those with normal HbA1c) of the primary outcome (HR 1.27, 95% CI 1.00–1.60) and HFH (HR 1.35, 95% CI 1.03–1.77), but not of CV death (HR 1.02, 95%

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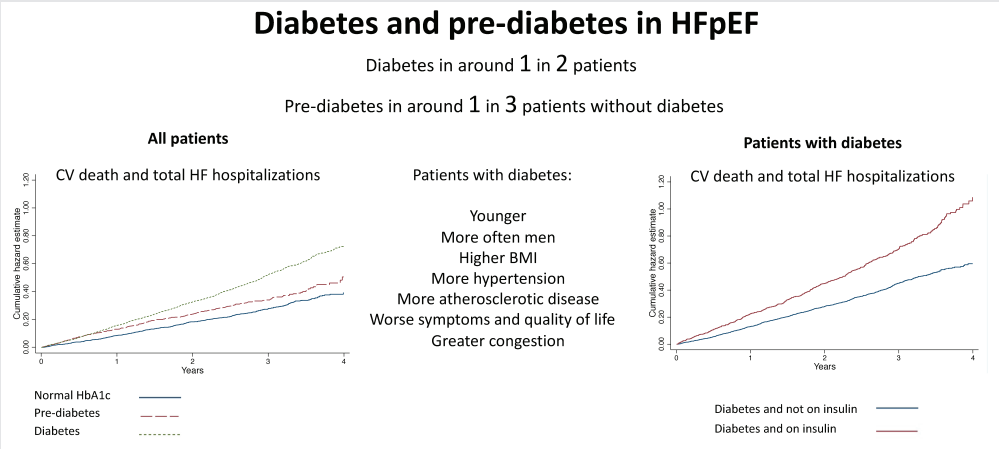
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CI 0.75–1.40). Patients with diabetes treated with insulin had worse outcomes than those not, and those with 'lean diabetes' had similar mortality rates to those with a higher body mass index, but lower rates of HFH.

Conclusion Pre-diabetes is common in patients with HFpEF and is associated with worse clinical status and greater risk of HFH. Clinical Trial Registration: ClinicalTrials.gov Identifier NCT01920711.

Graphical Abstract



Patient characteristics and outcomes, according to diabetes status, and according to whether patients with diabetes were treated with insulin or not, in PARAGON-HF. BMI, body mass index; CV, cardiovascular; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction.

Keywords Heart failure • Diabetes • Obesity • Insulin

Introduction

Diabetes is common in patients with heart failure (HF), whether left ventricular ejection fraction (LVEF) is reduced or preserved.[1–4] Recently, regional and racial variations in the prevalence of diabetes in patients with HF and reduced ejection fraction (HFrEF) have been highlighted, as have geographic differences in management of diabetes in these patients.[5–7] Similarly, a high prevalence of pre-diabetic dysglycaemia ('pre-diabetes') has been described in patients with HFrEF, which has also been shown to be associated with worse outcomes, compared with normoglycaemia.[7,8] Much less is known about this group of patients with HF and preserved ejection fraction (HFpEF). The PARAGON-HF (Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction) trial offers a unique opportunity to study the prevalence of diabetes and pre-diabetes and associated outcomes in a large multinational cohort of patients with HFpEF.[9–11] In this *post hoc* analysis, we report the prevalence of pre-diabetes and diabetes in patients with HFpEF and their characteristics, treatment, rates of hospitalization and mortality. In addition, among individuals with diabetes, we looked at those with 'lean diabetes' and people treated with insulin, as both these subgroups have been reported to be at higher risk of adverse clinical outcomes.[12–14]

Methods

The trial sponsor, Novartis, is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel, based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

Study design and patients

The design, baseline characteristics and primary outcomes of PARAGON-HF are published.[9–11] In brief, 4796 patients in New York Heart Association (NYHA) functional class II–IV with a LVEF ≥45%, elevated N-terminal pro-B-type natriuretic peptide

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(NT-proBNP) level and structural heart disease were enrolled. Key exclusion criteria included body mass index (BMI) >40 kg/m^2, known intolerance of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, a history of angioedema, systolic blood pressure <100 mmHg, estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2, or serum potassium >5.4 mmol/L. Patients were randomly assigned to treatment with sacubitril-valsartan or valsartan. Enrolment in the trial took place from 2014 to 2016, before the routine use of sodium–glucose cotransporter 2 (SGLT2) inhibitors in HF. The trial was approved by Ethics Committees at all participating sites and all patients provided written informed consent.

Definition of glycaemic status

Investigators were asked to state on the trial case report form whether patients had a known diagnosis of diabetes. All patients also had a measurement of glycated haemoglobin (HbA1c) at baseline. Patients were categorized into three groups based on their history of diabetes and baseline HbA1c level using the International Diabetes Expert Committee (World Health Organization criteria): (i) normal HbA1c, <6.0%; (ii) pre-diabetes, 6.0%–6.4%; and (iii) diabetes, ≥6.5% or a known prior diagnosis of diabetes.[15]

Outcomes

The primary outcome for this analysis was that used in PARAGON-HF, i.e. total HF hospitalizations and cardiovascular death. All-cause mortality, first HF hospitalization, decline in renal function (eGFR decrease of 50% or more, end-stage kidney disease, or death due to kidney failure), change from baseline to 8 months in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and in NYHA class were evaluated as secondary outcomes.

Statistical analyses

Baseline characteristics according to diabetes status were described by use of proportions for categorical variables and means with standard deviations, or medians with quartiles for continuous variables. We also examined two subgroups of patients among those with diabetes: patients with 'lean diabetes' (defined as BMI <25 kg/m^2) and those treated with insulin. Differences in baseline characteristics according to diabetes status were tested by use of χ^2 tests, Wilcoxon rank-sum tests, *t*-tests, or tests for trends where appropriate. The primary composite outcome and total HF hospitalizations were analysed by use of the semiparametric proportional rates method of Lin et al.[16] stratified by geographic region. Cox proportional hazard models stratified by region were used to compare the risk of first events according to diabetes status. Nelson–Aalen and Kaplan–Meier curves were used to illustrate the cumulative recurrent and first events, respectively. Adjusted models included age, sex, race, prior HF hospitalization, HF duration, NYHA class, NT-proBNP, smoking status (current), LVEF, systolic blood pressure, heart rate, serum creatinine level and history of myocardial infarction, stroke, chronic obstructive pulmonary disease, atrial fibrillation, hypertension, randomly assigned treatment and region (where model not stratified). Treatment effect across the spectrum of HbA1c was modelled using a fractional polynomial and the results were displayed graphically using the mfpi command in STATA. A restricted cubic spline was used to model the rate ratio for the primary composite outcome across the spectrum of HbA1c, referent to HbA1c 5.6%. Change from baseline in KCCQ-CSS to 8 months was analysed using a multilevel mixed-effects linear regression model, together with a multilevel mixed-effects logistic regression model for a 5-point deterioration. Change from baseline in NYHA class to 8 months was analysed using a multilevel mixed-effects logistic regression model. All mixed-effects models included baseline value, randomized treatment and treatment–visit interaction. Analyses were conducted using STATA version 16 (StataCorp LLC, College Station, TX, USA). A *p*-value of <0.05 was considered statistically significant.

Results

Of the 4796 patients studied, 2388 (49.8%) had diabetes; 2062 with a prior diagnosis, and 326 without a prior diagnosis, but with a HbA1c ≥6.5% (i.e. with undiagnosed diabetes). Those with undiagnosed diabetes accounted for 7% of all patients, and for 12% of patients without a prior diagnosis of diabetes. A further 874 participants (18% of all patients/36% of those without diabetes [diagnosed or undiagnosed]) had a HbA1c between 6.0% and 6.4% (i.e. pre-diabetes). Only 1534 participants (32%) had a HbA1c <6.0% (i.e. normal HbA1c) (*Table 1*). The distribution of HbA1c is shown in online supplementary *Figure S1*.

Baseline characteristics

Patients with diabetes were younger and were more often men and from Central/Eastern Europe, compared to those with normal HbA1c (*Table 1*). Individuals with diabetes had a higher BMI, waist circumference and waist hip-ratio than those with normal HbA1c. Patients with diabetes more commonly had a history of hypertension (and a higher systolic blood pressure) and evidence of atherosclerotic/atherothrombotic disease (e.g. myocardial infarction, stroke, peripheral artery disease), anaemia and sleep apnoea. Patients with diabetes had a worse NYHA class distribution and a worse mean KCCQ-CSS, compared to those with normal HbA1c. Patients with diabetes had more congestion (reflected in peripheral oedema and orthopnoea) but a similar plasma NT-proBNP, compared to those with normal HbA1c. In general, participants with pre-diabetes had a phenotypic picture intermediate between those with normal HbA1c and diabetes (*Table 1*). Some notable exceptions were the proportion of women (54%, 55% and 49% among those with normal HbA1c, pre-diabetes and diabetes, respectively), and the proportion with anemia (12%, 11%, and 18%, respectively). The KCCQ-CSS was similarly reduced (i.e. worse) in patients with pre-diabetes and those with diabetes, compared to patients with normal HbA1c.

Patients with 'lean diabetes'

Among participants with diabetes, 270 patients (11%) had a BMI <25 kg/m^2 ('lean diabetes'). Patients with a lower BMI were older, had a different racial composition (39% vs. 10% Asian; 58% vs. 83% White) and geographic distribution than patients with BMI ≥25 kg/m^2, had a higher (better) mean KCCQ-CSS but a higher median NT-proBNP than those with a higher BMI (*Table 2*).

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Table 1 Baseline characteristics according to diabetes status: diabetes (prior diagnosis or glycated haemoglobin [HbA1c] ≥6.5%), pre-diabetes (HbA1c 6.0%–6.4%) or normal HbA1c (<6.0%)

	Normal HbA1c (<6.0%)	Pre-diabetes (HbA1c 6.0%–6.4%)	Diabetes (prior diagnosis or HbA1c ≥6.5%)	*p*-value for trend (all)	*p*-value (pre-diabetes vs. normal HbA1c)	*p*-value (diabetes vs. normal HbA1c)
Patients, *n* (%)	1534 (32.0)	874 (18.2)	2388 (49.8)			
Age, years, mean (±SD)	73.2 ± 8.7	73.9 ± 8.1	72.0 ± 8.3	<0.001	0.057	<0.001
Women, *n* (%)	822 (53.6)	479 (54.8)	1178 (49.3)	0.01	0.56	0.009
Race, *n* (%)				0.18	0.54	0.34
Asian	196 (12.8)	95 (10.9)	316 (13.2)			
Black	27 (1.8)	14 (1.6)	61 (2.6)			
Other	54 (3.5)	34 (3.9)	92 (3.9)			
White	1257 (81.9)	731 (83.6)	1919 (80.4)			
Region, *n* (%)				0.002	0.012	<0.001
Asia-Pacific/other	247 (16.1)	117 (13.4)	398 (16.7)			
Central Europe	489 (31.9)	339 (38.8)	887 (37.1)			
Latin America	136 (8.9)	77 (8.8)	157 (6.6)			
North America	170 (11.1)	86 (9.8)	303 (12.7)			
Western Europe	492 (32.1)	255 (29.2)	643 (26.9)			
HbA1c, %, median (Q1–Q3)	5.6 (5.4–5.8)	6.1 (6.0–6.3)	7.0 (6.5–7.9)	<0.001	<0.001	<0.001
Non-ischaemic aetiology, *n* (%)	1089 (71.0)	576 (65.9)	1407 (58.9)	<0.001	0.009	<0.001
Prior HF hospitalization, *n* (%)	675 (44.0)	383 (43.8)	1248 (52.3)	<0.001	0.93	<0.001
HF duration, *n* (%)				0.001	0.40	0.026
0–3 months	256 (16.7)	155 (17.8)	362 (15.2)			
3–6 months	206 (13.5)	122 (14.0)	258 (10.8)			
6–12 months	209 (13.7)	109 (12.5)	298 (12.5)			
1–2 years	210 (13.7)	129 (14.8)	340 (14.3)			
2–5 years	313 (20.5)	151 (17.3)	529 (22.2)			
>5 years	336 (22.0)	207 (23.7)	594 (24.9)			
NYHA class, *n* (%)				0.049	0.67	0.031
I	40 (2.6)	18 (2.1)	79 (3.3)			
II	1216 (79.3)	694 (79.5)	1796 (75.2)			
III	271 (17.7)	159 (18.2)	502 (21.0)			
IV	7 (0.5)	2 (0.2)	10 (0.4)			
LVEF, %, mean (±SD)	58.1 ± 8.0	57.4 ± 7.7	57.2 ± 7.9	<0.001	0.050	0.001
Heart rate, bpm, mean (±SD)	69.0 ± 11.9	70.3 ± 12.5	71.4 ± 12.3	<0.001	0.012	<0.001
SBP, mmHg, mean (±SD)	130.1 ± 15.6	128.3 ± 15.0	131.7 ± 15.5	<0.001	0.005	0.003
BMI, kg/m^2, median (Q1–Q3)	28.7 (25.6–32.5)	29.2 (25.8–33.2)	31.1 (27.4–34.8)	<0.001	0.034	<0.001
BMI, kg/m^2, *n* (%)				<0.001	0.073	<0.001
<18	7 (0.5)	0 (0.0)	2 (0.1)			
18–24.99	315 (20.5)	164 (18.8)	268 (11.2)			
25–29.99	597 (38.9)	327 (37.5)	758 (31.7)			
≥30	615 (40.1)	382 (43.8)	1360 (57.0)			
Waist circumference, cm, median (Q1–Q3)	101 (92–110)	103 (93–112)	107 (97–116)	<0.001	0.009	<0.001
Waist-hip ratio, mean (±SD)	0.95 ± 0.12	0.96 ± 0.13	0.98 ± 0.12	<0.001	0.26	<0.001
Current smoker, *n* (%)	120 (7.9)	66 (7.6)	167 (7.0)	0.31	0.82	0.32
eGFR, ml/min/1.73 m^2, mean (±SD)	63.4 ± 18.4	62.3 ± 18.1	62.2 ± 19.9	0.008	0.16	0.066
Serum creatinine, mg/dl, mean (±SD)	1.06 ± 0.28	1.07 ± 0.29	1.11 ± 0.33	<0.001	0.33	<0.001
Potassium, mmol/l, median (Q1–Q3)	4.5 (4.2–4.7)	4.5 (4.2–4.8)	4.5 (4.2–4.8)	<0.001	0.096	<0.001
NT-proBNP, pg/ml, median (Q1–Q3) without AF	590 (371–1024)	618 (393–1058)	596 (382–1074)	0.73	0.27	0.66
NT-proBNP, pg/ml, median (Q1–Q3) with AF	1572 (1162–2358)	1620 (1171–2330)	1577 (1174–2197)	0.66	0.68	0.74
KCCQ-CSS, mean (±SD)	74.4 ± 18.1	71.7 ± 19.8	71.2 ± 19.2	<0.001	<0.001	<0.001
Signs or symptoms, *n* (%)						
Paroxysmal nocturnal dyspnoea	57 (3.7)	27 (3.1)	107 (4.5)	0.18	0.43	0.24
Dyspnoea at rest	41 (2.7)	22 (2.5)	76 (3.2)	0.32	0.83	0.36
Dyspnoea on effort	1414 (92.2)	811 (93.1)	2199 (92.2)	0.90	0.43	0.97
Fatigue	770 (50.2)	441 (50.7)	1226 (51.4)	0.47	0.83	0.47
Orthopnoea	251 (16.4)	144 (16.5)	491 (20.6)	0.001	0.92	0.001
Third heart sound	30 (2.0)	20 (2.3)	61 (2.6)	0.22	0.58	0.22
Jugular venous distention	210 (13.8)	110 (12.8)	335 (14.2)	0.67	0.49	0.74
Oedema	560 (36.5)	297 (34.1)	969 (40.6)	0.005	0.24	0.010
Rales	108 (7.0)	64 (7.3)	173 (7.3)	0.82	0.78	0.80
Medical history, *n* (%)						
Myocardial infarction	262 (17.1)	184 (21.1)	637 (26.7)	<0.001	0.016	<0.001
Atrial flutter/fibrillation[a]	455 (29.8)	329 (37.7)	768 (32.3)	0.19	<0.001	0.095
Hypertension	1452 (94.7)	823 (94.2)	2309 (96.7)	0.001	0.61	0.002
Stroke	157 (10.2)	79 (9.1)	272 (11.4)	0.19	0.36	0.26
COPD	195 (12.7)	125 (14.3)	350 (14.7)	0.09	0.27	0.087

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Table 1 (Continued)

	Normal HbA1c (<6.0%)	Pre-diabetes (HbA1c 6.0%–6.4%)	Diabetes (prior diagnosis or HbA1c ≥6.5%)	*p*-value for trend (all)	*p*-value (pre-diabetes vs. normal HbA1c)	*p*-value (diabetes vs. normal HbA1c)
Anaemia	183 (11.9)	97 (11.1)	427 (17.9)	<0.001	0.54	<0.001
Lower limb artery stenosis	18 (1.2)	16 (1.8)	72 (3.0)	<0.001	0.19	<0.001
Sleep apnoea	97 (6.3)	46 (5.3)	221 (9.3)	<0.001	0.30	<0.001
Medications, *n* (%)						
Diuretics	1464 (95.4)	831 (95.1)	2290 (95.9)	0.45	0.69	0.49
ACE-inhibitor/ARB	1317 (85.9)	753 (86.2)	2069 (86.6)	0.48	0.84	0.48
Beta-blocker	1159 (75.6)	701 (80.2)	1961 (82.1)	<0.001	0.009	<0.001
MRA	396 (25.8)	222 (25.4)	621 (26.0)	0.87	0.82	0.89
Antiplatelets	170 (11.1)	87 (10.0)	378 (15.8)	<0.001	0.39	<0.001
Insulin	0 (0.0)	1 (0.1)	656 (27.5)	–	–	–
Oral hypoglycaemic agent	3 (0.2)	3 (0.3)	1476 (61.8)	–	–	–
Sulfonylurea	0 (0.0)	0 (0.0)	463 (19.4)	–	–	–
Thiazolidinedione	0 (0.0)	0 (0.0)	17 (0.7)	–	–	–
Biguanide	3 (0.2)	2 (0.2)	1045 (43.8)	–	–	–
GLP-1 receptor agonist	0 (0.0)	0 (0.0)	20 (0.8)	–	–	–

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.
[a]On electrocardiogram at baseline.

Diabetes patients treated with insulin

Amongst participants with diabetes, 656 patients (27%) were treated with insulin, alone or in combination with other glucose-lowering therapy. Patients treated with insulin were younger, more obese, and a had a higher median HbA1c level, compared to those not treated with insulin (*Table 2*). Insulin-treated patients had a worse mean KCCQ-CSS, worse NYHA class distribution, more peripheral oedema and orthopnoea, a higher prevalence of coronary artery disease, anaemia and sleep apnoea, but less atrial fibrillation. Despite this overall worse HF profile, more evidence of congestion and lower eGFR, insulin-treated patients had similar plasma concentrations of NT-proBNP compared to those not treated with insulin.

Clinical outcomes according to glycated haemoglobin categories and diabetes status

The risks of the primary composite outcome, its components and all-cause mortality were highest among those with diabetes, compared to patients with pre-diabetes and those with normal HbA1c (*Table 3*; *Figures 1* and *2*; online supplementary *Figure S2*). Patients with pre-diabetes had a higher risk of the primary composite outcome and HF hospitalization, but similar risk of cardiovascular death and all-cause mortality, compared to patients with normal HbA1c.

At 8-month follow-up, there was no difference in worsening of NYHA class or change in KCCQ-CSS amongst groups (online supplementary *Table S1*).

The risk of the composite renal outcome was also greater amongst patients with diabetes compared to other groups (*Table 2*).

Clinical outcomes in patients with 'lean diabetes'

Patients with a BMI <25 kg/m^2 had slightly, but not significantly, higher risk of cardiovascular and all-cause mortality than those with BMI ≥25 kg/m^2 (*Table 4*). The rate of first HF hospitalization was similar for patients with BMI <25 or ≥25 kg/m^2 but patients with BMI <25 kg/m^2 had a lower rate of total HF hospitalizations, compared with patients with a BMI ≥25 kg/m^2 (*Table 4* and online supplementary *Figures S3* and *S4*).

Clinical outcomes in patients with diabetes according to insulin treatment

Patients treated with insulin had a higher risk of the primary composite outcome, its components and all-cause mortality (*Table 4* and online supplementary *Figures S5* and *S6*).

Effect of sacubitril-valsartan according to diabetes status and glycated haemoglobin level

For the primary composite outcome, we found no significant interaction between the effects of treatment (sacubitril-valsartan compared to valsartan), and glycaemic subgroup (p interaction = 0.96) (online supplementary *Table S2*) or using HbA1c as a continuous variable (p interaction = 0.32) (*Figure 3*). The same was true for the effect of treatment on the components of the primary outcome across the glycaemic subgroups (online supplementary *Table S2*).

Discussion

In this *post-hoc* analysis of the PARAGON-HF trial, we found that diabetes and pre-diabetes together affect around two thirds of

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Table 2 Baseline characteristics according to 'lean diabetes' phenotype (versus non-lean) and insulin use (versus no insulin use) in patients with diabetes

	BMI ≥25 kg/m²	BMI <25 kg/m²	*p*-value	No insulin	Insulin	*p*-value
Patients, *n* (%)	2118 (88.7)	270 (11.3)		1732 (72.5)	656 (27.5)	
Age, years, mean (± SD)	71.8 ± 8.1	74.0 ± 9.2	<0.001	72.7 ± 8.3	70.4 ± 8.1	<0.001
Women, *n* (%)	1042 (49.2)	136 (50.4)	0.72	864 (49.9)	314 (47.9)	0.38
Race, *n* (%)			<0.001			<0.001
Asian	211 (10.0)	105 (38.9)		235 (13.6)	81 (12.3)	
Black	60 (2.8)	1 (0.4)		30 (1.7)	31 (4.7)	
Other	84 (4.0)	8 (3.0)		64 (3.7)	28 (4.3)	
White	1763 (83.2)	156 (57.8)		1403 (81.0)	516 (78.7)	
Region, *n* (%)			<0.001			<0.001
Asia-Pacific/other	289 (13.6)	109 (40.4)		296 (17.1)	102 (15.5)	
Central Europe	826 (39.0)	61 (22.6)		691 (39.9)	196 (29.9)	
Latin America	145 (6.8)	12 (4.4)		113 (6.5)	44 (6.7)	
North America	288 (13.6)	15 (5.6)		169 (9.8)	134 (20.4)	
Western Europe	570 (26.9)	73 (27.0)		463 (26.7)	180 (27.4)	
HbA1c, %, median (Q1–Q3)	7.0 (6.5–7.9)	6.9 (6.5–7.7)	0.26	6.7 (6.3–7.4)	7.9 (7.1–9.2)	<0.001
Non-ischaemic aetiology, *n* (%)	1272 (60.1)	135 (50.0)	0.002	1044 (60.3)	363 (55.3)	0.03
Prior HF hospitalization, *n* (%)	1112 (52.5)	136 (50.4)	0.50	860 (49.7)	388 (59.1)	<0.001
HF duration, *n* (%)			0.06			0.12
0–3 months	315 (14.9)	47 (17.4)		270 (15.6)	92 (14.1)	
3–6 months	222 (10.5)	36 (13.3)		182 (10.5)	76 (11.6)	
6–12 months	254 (12.0)	44 (16.3)		230 (13.3)	68 (10.4)	
1–2 years	311 (14.7)	29 (10.7)		256 (14.8)	84 (12.8)	
2–5 years	475 (22.5)	54 (20.0)		374 (21.7)	155 (23.7)	
>5 years	534 (25.3)	60 (22.2)		415 (24.0)	179 (27.4)	
NYHA class, *n* (%)			0.17			0.048
I	68 (3.2)	11 (4.1)		58 (3.4)	21 (3.2)	
II	1583 (74.8)	213 (78.9)		1324 (76.5)	472 (72.0)	
III	458 (21.6)	44 (16.3)		344 (19.9)	158 (24.1)	
IV	8 (0.4)	2 (0.7)		5 (0.3)	5 (0.8)	
LVEF, %, mean (± SD)	57.2 ± 7.9	57.1 ± 7.9	0.77	57.1 ± 7.9	57.6 ± 7.9	0.20
Heart rate, bpm, mean (± SD)	71.2 ± 12.1	72.7 ± 13.5	0.067	71.5 ± 12.3	71.1 ± 12.3	0.50
SBP, mmHg, mean (± SD)	131.8 ± 15.4	130.2 ± 15.6	0.11	131.1 ± 15.1	133.2 ± 16.3	0.002
BMI, kg/m², median (Q1–Q3)	31.8 (28.6–35.3)	23.4 (21.9–24.3)	<0.001	30.4 (27.3–34.2)	32.4 (28.6–35.9)	<0.001
Waist circumference, cm, median (Q1–Q3)	109 (100–118)	90 (84–96)	<0.001	105 (96–115)	110 (100–119)	<0.001
Waist-hip ratio, mean (± SD)	0.99 ± 0.12	0.93 ± 0.08	<0.001	0.97 ± 0.11	0.99 ± 0.14	0.011
Current smoker, *n* (%)	142 (6.7)	25 (9.4)	0.11	122 (7.1)	45 (6.9)	0.85
eGFR, ml/min/1.73 m², mean (± SD)	62.0 ± 19.8	64.0 ± 20.2	0.11	63.2 ± 19.5	59.6 ± 20.5	<0.001
Serum creatinine, mg/dl, mean (± SD)	1.12 ± 0.33	1.07 ± 0.31	0.013	1.09 ± 0.32	1.18 ± 0.36	<0.001
Potassium, mmol/l, median (Q1–Q3)	4.5 (4.2–4.8)	4.5 (4.2–4.8)	0.57	4.5 (4.2–4.8)	4.5 (4.2–4.9)	0.22
NT-proBNP, pg/ml, median (Q1–Q3) without AF	572 (375–992)	879 (483–1584)	<0.001	587 (382–1091)	620 (379–1059)	0.49
NT-proBNP, pg/ml, median (Q1–Q3) with AF	1557 (1159–2168)	1793 [1370–2465]	0.009	1576 (1192–2204)	1595 (1136–2178)	0.62
KCCQ-CSS, mean (± SD)	70.5 ± 19.2	76.5 ± 18.5	<0.001	71.9 ± 18.8	69.2 ± 20.1	0.002
Signs or symptoms, *n* (%)						
Paroxysmal nocturnal dyspnoea	99 (4.7)	8 (3.0)	0.20	74 (4.3)	33 (5.0)	0.42
Dyspnoea at rest	70 (3.3)	6 (2.2)	0.34	56 (3.2)	20 (3.1)	0.82
Dyspnoea on effort	1958 (92.6)	241 (89.3)	0.05	1598 (92.4)	601 (91.8)	0.62
Fatigue	1088 (51.4)	138 (51.1)	0.92	901 (52.1)	325 (49.6)	0.28
Orthopnoea	453 (21.4)	38 (14.1)	0.005	314 (18.2)	177 (27.0)	<0.001
Third heart sound	55 (2.6)	6 (2.2)	0.75	51 (3.0)	10 (1.5)	0.048
Jugular venous distention	306 (14.6)	29 (10.8)	0.095	229 (13.3)	106 (16.4)	0.054
Oedema	889 (42.0)	80 (29.6)	<0.001	672 (38.8)	297 (45.3)	0.004
Rales	157 (7.4)	16 (5.9)	0.37	127 (7.3)	46 (7.0)	0.79
Medical history, *n* (%)						
Myocardial infarction	556 (26.3)	81 (30.0)	0.19	429 (24.8)	208 (31.7)	<0.001
Atrial flutter/fibrillation[a]	690 (32.7)	78 (28.9)	0.20	615 (35.6)	153 (23.5)	<0.001
Hypertension	2063 (97.4)	246 (91.1)	<0.001	1671 (96.5)	638 (97.3)	0.34
Stroke	240 (11.3)	32 (11.9)	0.79	183 (10.6)	89 (13.6)	0.04
COPD	315 (14.9)	35 (13.0)	0.40	246 (14.2)	104 (15.9)	0.30
Anaemia	381 (18.0)	46 (17.0)	0.70	265 (15.3)	162 (24.7)	<0.001
Lower limb artery stenosis	56 (2.7)	16 (5.9)	0.003	44 (2.5)	28 (4.3)	0.03
Sleep apnoea	215 (10.2)	6 (2.2)	<0.001	130 (7.5)	91 (14.0)	<0.001

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Table 2 (Continued)

	BMI ≥25 kg/m²	BMI <25 kg/m²	*p*-value	No insulin	Insulin	*p*-value
Medications, *n* (%)						
Diuretics	2044 (96.5)	246 (91.1)	<0.001	1650 (95.3)	640 (97.6)	0.01
ACE-inhibitor/ARB	1842 (87.0)	227 (84.1)	0.18	1506 (87.0)	563 (85.8)	0.47
Beta-blocker	1757 (83.0)	204 (75.6)	0.003	1418 (81.9)	543 (82.8)	0.61
MRA	546 (25.8)	75 (27.8)	0.48	454 (26.2)	167 (25.5)	0.71
Antiplatelets	318 (15.0)	60 (22.2)	0.002	241 (13.9)	137 (20.9)	<0.001
Insulin	591 (27.9)	65 (24.1)	0.18	0 (0.0)	656 (100.0)	<0.001
Oral hypoglycaemic agents	1332 (62.9)	144 (53.3)	0.002	1096 (63.3)	380 (57.9)	0.02
GLP-1 receptor agonist	20 (0.9)	0 (0.0)	0.11	11 (0.6)	9 (1.4)	0.08

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.
[a]On electrocardiogram at baseline.

Table 3 Event rates and hazard/rate ratios for all outcomes, according to diabetes status

	No. of events	Crude rate per 100 py	Adjusted HR/RR (95% CI)	*p*-value
Primary composite outcome				
Normal HbA1c	427	9.4 (8.6–10.4)	1.00 (ref.)	
Pre-diabetes	295	11.8 (10.5–13.2)	1.27 (1.00–1.60)	0.05
Diabetes	1181	17.3 (16.3–18.3)	1.59 (1.35–1.88)	<0.001
Total hospitalizations for HF				
Normal HbA1c	320	7.1 (6.3–7.9)	1.00 (ref.)	
Pre-diabetes	230	9.2 (8.1–10.5)	1.35 (1.03–1.77)	0.03
Diabetes	937	13.7 (12.9–14.6)	1.67 (1.39–2.02)	<0.001
CV death				
Normal HbA1c	107	2.4 (2.0–2.9)	1.00 (ref.)	
Pre-diabetes	65	2.6 (2.0–3.3)	1.02 (0.75–1.40)	0.88
Diabetes	244	3.6 (3.1–4.0)	1.35 (1.07–1.71)	0.01
First hospitalization for HF or CV death				
Normal HbA1c	278	6.6 (5.8–7.4)	1.00 (ref.)	
Pre-diabetes	178	7.8 (6.7–9.0)	1.17 (0.96–1.42)	0.11
Diabetes	627	10.3 (9.5–11.1)	1.38 (1.19–1.60)	<0.001
First hospitalization for HF				
Normal HbA1c	209	4.9 (4.3–5.6)	1.00 (ref.)	
Pre-diabetes	138	6.0 (5.1–7.1)	1.25 (1.00–1.55)	0.047
Diabetes	491	8.0 (7.4–8.8)	1.44 (1.22–1.70)	<0.001
Death from any cause				
Normal HbA1c	180	4.0 (3.4–4.6)	1.00 (ref.)	
Pre-diabetes	106	4.2 (3.5–5.1)	0.98 (0.77–1.25)	0.87
Diabetes	405	5.9 (5.4–6.5)	1.40 (1.17–1.68)	<0.001
Renal composite outcome				
Normal HbA1c	20	0.4 (0.3–0.7)	1.00 (ref.)	
Pre-diabetes	10	0.4 (0.2–0.7)	1.01 (0.47–2.17)	0.97
Diabetes	67	1.0 (0.8–1.3)	2.28 (1.37–3.79)	0.002

CI, confidence interval; CV, cardiovascular; HbA1c, glycated haemoglobin; HF, heart failure; HR, hazard ratio; py, person-years; RR, rate ratio.
Adjusted for age, sex, race, New York Heart Association class, smoking status (current), prior HF hospitalization, HF duration, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide (log), systolic blood pressure, heart rate, serum creatinine level, history of myocardial infarction, stroke, chronic obstructive pulmonary disease, atrial fibrillation, hypertension, and randomly assigned treatment.
Renal composite outcome = Estimated glomerular filtration rate decrease of 50% or more, end-stage kidney disease, or death due to kidney failure.

patients with HFpEF, highlighting the highly dysglycaemic character of this HF phenotype, globally. Patients with each of pre-diabetes and diabetes had higher rates of HF hospitalization than patients with normal HbA1c, with the risk of patients with pre-diabetes intermediate between that of patients with diabetes and those with normal HbA1c. The risk of all-cause mortality and cardiovascular death were significantly higher in patients with diabetes but similar in patients with pre-diabetes and those with normal HbA1c. Glycaemic status had no significant influence on the effect of sacubitril-valsartan on outcomes.

In patients with HF and diabetes, with a HFpEF phenotype, there is the development of myocardial hypertrophy, collagen deposition and fibrosis. Such pathological changes are driven by several factors, including hyperglycaemia, hyperinsulinaemia, lipotoxicity and altered cardiac metabolism.[17] These changes can be seen in patients not only with diabetes, but also in those with insulin resistance,

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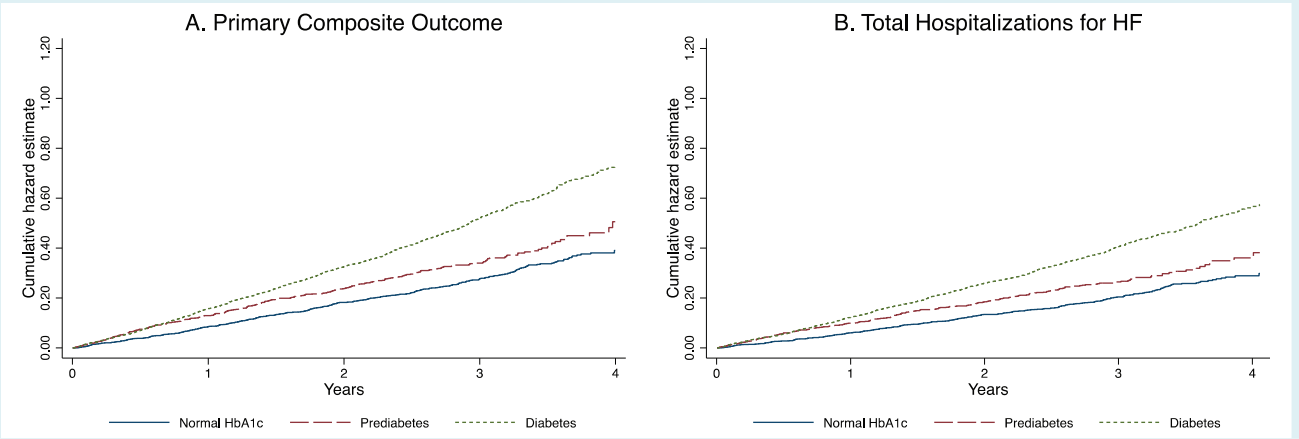


Figure 1 (*A*) Primary composite outcome of cardiovascular death and total heart failure (HF) hospitalizations (both first and recurrent) and (*B*) total HF hospitalizations (both first and recurrent), according to diabetes status. HbA1c, glycated haemoglobin.

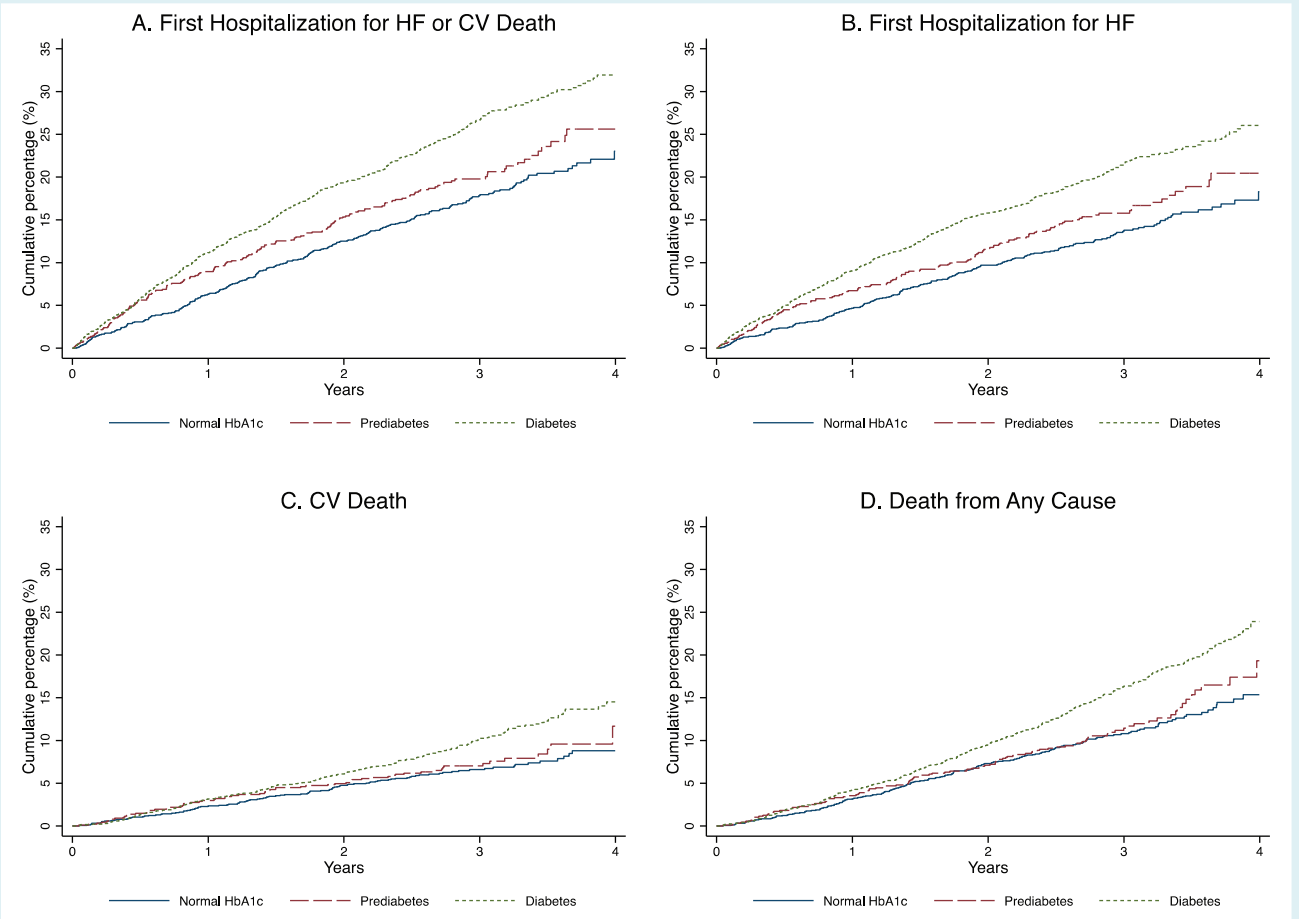


Figure 2 Composite outcome of cardiovascular (CV) death or first heart failure (HF) hospitalization (*A*), the components of the composite (*B*, *C*) and death from any cause (all analysed as time-to-first event) (*D*), according to diabetes status. HbA1c, glycated haemoglobin.

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Table 4 Event rates and hazard/rate ratios for all outcomes according to 'lean diabetes' phenotype (versus non-lean) and insulin use (versus no insulin use) in patients with diabetes

	No. of events	Crude rate per 100 py	Adjusted HR/RR (95% CI)	*p*-value
Primary composite outcome				
BMI ≥25 kg/m^2	1063	17.4 (16.4–18.5)	1.00 (ref.)	
BMI <25 kg/m^2	118	16.3 (13.6–19.5)	0.86 (0.65–1.14)	0.29
No insulin	731	14.7 (13.7–15.8)	1.00 (ref.)	
Insulin	450	24.3 (22.1–26.6)	1.30 (1.06–1.60)	0.01
Total hospitalizations for HF				
BMI ≥25 kg/m^2	858	14.1 (13.2–15.0)	1.00 (ref.)	
BMI <25 kg/m^2	79	10.9 (8.7–13.6)	0.75 (0.55–1.03)	0.08
No insulin	564	11.3 (10.4–12.3)	1.00 (ref.)	
Insulin	373	20.1 (18.2–22.3)	1.32 (1.05–1.67)	0.02
CV death				
BMI ≥25 kg/m^2	205	3.6 (2.9–3.8)	1.00 (ref.)	
BMI <25 kg/m^2	39	5.4 (3.9–7.4)	1.25 (0.85–1.84)	0.25
No insulin	167	3.4 (2.9–3.9)	1.00 (ref.)	
Insulin	77	4.2 (3.3–5.2)	1.20 (0.90–1.61)	0.22
First hospitalization for HF or CV death				
BMI ≥25 kg/m^2	552	10.1 (9.3–11.0)	1.00 (ref.)	
BMI <25 kg/m^2	75	11.3 (9.0–14.2)	0.98 (0.75–1.27)	0.87
No insulin	411	9.1 (8.2–10.0)	1.00 (ref.)	
Insulin	216	13.7 (12.0–15.7)	1.31 (1.10–1.57)	0.003
First hospitalization for HF				
BMI ≥25 kg/m^2	437	8.0 (7.3–8.8)	1.00 (ref.)	
BMI <25 kg/m^2	54	8.1 (6.2–10.6)	0.94 (0.69–1.27)	0.68
No insulin	321	7.1 (6.4–7.9)	1.00 (ref.)	
Insulin	170	10.8 (9.3–12.6)	1.27 (1.04–1.56)	0.02
Death from any cause				
BMI ≥25 kg/m^2	349	5.7 (5.1–6.3)	1.00 (ref.)	
BMI <25 kg/m^2	56	7.7 (5.9–10.0)	1.08 (0.79–1.47)	0.62
No insulin	274	5.5 (4.9–6.2)	1.00 (ref.)	
Insulin	131	7.1 (6.0–8.4)	1.40 (1.12–1.75)	0.003
Renal composite outcome				
BMI ≥25 kg/m^2	59	1.0 (0.8–1.3)	1.00 (ref.)	
BMI <25 kg/m^2	8	1.1 (0.6–2.2)	0.84 (0.37–1.90)	0.67
No insulin	42	0.9 (0.6–1.2)	1.00 (ref.)	
Insulin	25	1.4 (0.9–2.0)	1.30 (0.76–2.22)	0.34

BMI, body mass index; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; py, person-years; RR, rate ratio.
Adjusted for age, sex, race, New York Heart Association class, smoking status (current), prior HF hospitalization, HF duration, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide (log), systolic blood pressure, heart rate, serum creatinine level, history of myocardial infarction, stroke, chronic obstructive pulmonary disease, atrial fibrillation, hypertension and randomly assigned treatment.
Renal composite outcome = Estimated glomerular filtration rate decrease of 50% or more, end-stage kidney disease, or death due to kidney failure.

dyslipidaemia or obesity, either independently, or when there is an overlap of conditions. While it is well known that diabetes is associated with worse outcomes in patients with HFpEF, especially if treated with insulin, much less is known about the prevalence of pre-diabetes and risk associated with pre-diabetes.[18] Indeed, the few prior analyses of pre-diabetes in HF either only described patients with HFrEF or did not provide outcome data by LVEF phenotype.[19–21]

In PARAGON-HF, a high proportion (36%) of participants without diabetes had pre-diabetes. Many of the phenotypic characteristics of these patients were intermediate between those of participants with normal HbA1c and those with diabetes. This is consistent with the view that pre-diabetes represents an earlier stage of a dysglycaemic continuum. However, there are already metabolic cardiac consequences at this stage. For example, myocardial glucose uptake is depressed in HF patients with pre-diabetes, compared to HF patients with a normal oral glucose tolerance test.[22] It was striking that patient-reported wellbeing, as reflected in the KCCQ-CSS, was as impaired in patients with pre-diabetes as in those with diabetes in PARAGON-HF. There was also an elevated

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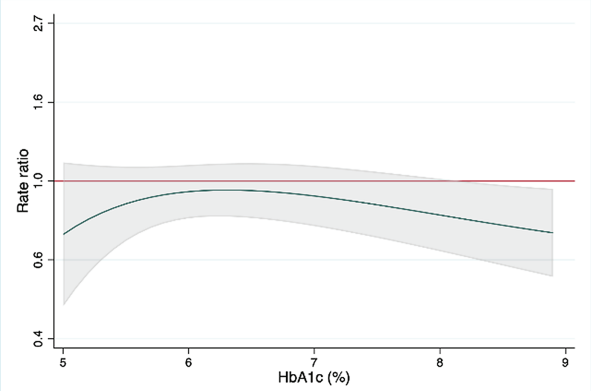


Figure 3 Effect of sacubitril-valsartan, compared with valsartan, on the primary composite outcome (cardiovascular death and total heart failure hospitalizations) across the range of glycated haemoglobin (HbA1c) 5% to 9%. The green line is the rate ratio; the red line is the line of unity; the grey shaded area represents the 95% confidence interval.

incidence of both first and repeat HF hospitalizations in patients with pre-diabetes (compared to those with normal HbA1c), which persisted despite adjustment for other predictive variables, including NT-proBNP. However, the excess risk of hospitalization in pre-diabetes was not as great as seen in patients with diabetes (compared to those with normal HbA1c). By contrast, mortality did not appear to be elevated in people with pre-diabetes (compared to those with normal HbA1c), whereas mortality was clearly higher in participants with diabetes. It is possible that the association between elevated glucose and mortality may be related to duration, as well as degree, of hyperglycaemia. However, diagnosis of diabetes also leads to commencement of glucose-lowering therapy and the safety of many types of antihyperglycaemic treatment, including insulin, is unknown in patients with HF.[23] The risk of the worsening renal function endpoint was elevated only in patients with diabetes, and not in pre-diabetes. Although here there is some uncertainty about this difference, because of the very small number of events, it too may reflect the duration of hyperglycaemia.

We also report novel findings in relation to established diabetes. Its prevalence varied considerably across geographic regions, being most common in North America and Asia. The high prevalence of diabetes in Asia (particularly East Asia) is of interest given the lower average BMI in individuals from this region, with a 'lean diabetes' phenotype being common there.[6,24] Greater deposition of adipose tissue in the visceral space and more beta-cell dysfunction are possible explanations for this phenomenon.[25] Others have noted that Asian patients with 'lean diabetes' were more likely to have HFpEF than HFrEF.[24] Although some have reported patients with 'lean diabetes' to be at higher risk of death than patients with diabetes with a higher BMI, we did not confirm this. Moreover, we observed that there were fewer HF hospitalizations in patients with 'lean diabetes', compared to diabetes patients with a BMI $\geq$25 kg/m^2. By contrast, we were able to confirm the well-known association between insulin and poor outcomes in HF, even after comprehensive adjustment for other prognostic variables.[12,13,26] Indeed, patients with diabetes treated with insulin were 1.3-times more likely to experience the primary composite outcome in the trial.

We made other new observations in relation to diabetes; in addition to the expected comorbidities (e.g. a greater prevalence of obesity, hypertension, coronary heart disease), anaemia and sleep apnoea were also more common than in participants with normal HbA1c. Both comorbidities were even more common among those taking insulin, and each is clearly relevant to the symptom profile of patients with HFpEF.[27] Although sleep apnoea is likely to be associated with obesity, the higher prevalence of anaemia is harder to explain, especially as mean eGFR was similar across patient subgroups. However, an increased risk of anaemia has been described in patients with type 2 diabetes without chronic kidney disease previously and may be related to iron deficiency, among other factors.[28] A further explanation might be that plasma volume is greater in patients with diabetes, who had more signs of congestion and worse symptoms of HF than in patients without.[29]

The documentation of symptoms and signs at baseline, along with an accompanying natriuretic peptide measurement in PARAGON-HF, suggests a discrepancy between greater congestion in patients with diabetes, compared to those without, despite similar NT-proBNP levels. This raises the possibility of a relative natriuretic peptide deficiency in patients with diabetes, which contributes to their greater sodium and water overload. If correct, the deficiency might be related to obesity.[30–32] It is therefore of interest that patients with 'lean diabetes' had higher concentrations of NT-proBNP and less evidence of congestion, compared to non-lean diabetics. Another possibility is that the worse symptoms in patients with diabetes (and in the group treated with insulin versus those not) might be related to a greater degree of obesity or larger waist circumference. Unfavourable haemodynamic findings, including increased left ventricular filling pressure, have been described in women with HFpEF with greater visceral adiposity.[33]

Another important finding in the present study was the relatively high proportion of patients with HFpEF with undiagnosed diabetes (7% of all participants, 12% of participants without an existing diagnosis of diabetes), raising the question of awareness among cardiologists about the possibility of comorbid diabetes in their patients and, perhaps, the difficulty in diagnosing diabetes in individuals who may already be fatigued and experience urinary frequency and thirst because of diuretic therapy.

This leaves individuals with normal HbA1c, who represented just under one third of the overall trial cohort. These patients are at high risk developing dysglycaemia and diabetes. Therefore, prevention, as well as treatment, of diabetes in these patients may be a therapeutic goal, along with reduction in weight. Although there have been important developments in some of these therapeutic areas, including a benefit of SGLT2 inhibitors in HFpEF, detailed discussion is beyond the scope of this paper.[34–36]

Finally, the effect of sacubitril-valsartan on the primary outcome in PARAGON-HF, which was of borderline statistical significance, did not differ according to baseline HbA1c level.

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Limitations

As with any study of this type there are limitations. This was not a pre-planned analysis. The protocol had specific inclusion and exclusion criteria and patients self-selected by agreeing to participate. Consequently, they only partially reflect the entire spectrum of patients with HFpEF, although they do share many of the typical characteristics described in epidemiologic cohorts and registries. Of relevance to this study is the BMI threshold used for exclusion of patients in PARAGON-HF (BMI >40 kg/m^2), which may impact the prevalence of diabetes and pre-diabetes in this particular cohort. The definitions of pre-diabetes and undiagnosed diabetes were based on single HbA1c measurements and not on fasting plasma glucose measurements or a 2-h plasma glucose value during a 75-g oral glucose tolerance test; the latter approaches are known to give a different prevalence of pre-diabetes. Duration of diabetes and data on diabetic complications, such as retinopathy and neuropathy, were not available. We did not report longitudinal changes in HbA1c. The PARAGON-HF trial enrolled patients before the use of SGLT2 inhibitors had become common.

Conclusion

In summary, diabetes and pre-diabetes together affect around two thirds of HFpEF patients, highlighting the highly dysglycaemic character of this HF phenotype, globally. Diabetes, and to a lesser extent pre-diabetes, was associated with worse clinical status and higher risk of adverse cardiovascular outcomes. Although a focus on developing safe and effective glucose-lowering therapies for patients with HF is clearly important, attempts to prevent the development of, and even to reverse, diabetes (and, perhaps, even pre-diabetes) should not be neglected.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

PARAGON-HF was funded by Novartis Pharmaceuticals. J.J.V.McM is supported by British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217. A.M.J. is supported by a British Heart Foundation Clinical Research Training Fellowship (FS/18/14/33330).

Conflict of interest: I.S.A. has received consulting fees from Amgen, ARCA Biopharma, AstraZeneca, Boston Scientific Corporation, Boehringer Ingelheim, LivaNova, Novartis, and Zensun. B.L.C. has been a consultant for Amgen, AO Biome, Biogen, Boehringer Ingelheim, Corvia, Gilead, Myokardia, and Novartis. J.G.F.C. has received research grants from Bayer, Bristol-Myers Squibb, Pharmacosmos and Vifor and has received honoraria for advisory boards, lectures and or trial committees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, HeartFelt Technologies, Idorsia, Johnson & Johnson, Medtronic, Myokardia, Novartis, Pharmacosmos, Respicardia, Servier, Torrent, Vifor and Viscardia. A.S.D. reported receiving personal fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, Merck, Regeneron, and Relypsa and grants and personal fees from AstraZeneca, Alnylam, and Novartis, outside the submitted work. C.S.P.L. has received grant support and fees for serving on an advisory board from Boston Scientific and Roche Diagnostics; grant support, fees for serving on an advisory board, and fees for serving on steering committees from Bayer; grant support from Medtronic; grant support and fees for serving on a steering committee from Vifor pharma; fees for serving on an advisory board and for serving on steering committees from AstraZeneca and Novartis; fees for serving on an advisory board from Amgen, Boehringer Ingelheim, and Abbott Diagnostics; consulting fees from Merck and Stealth BioTherapeutics; fees for serving on a steering committee from Janssen Research and Development; lecture fees and consulting fees from Menarini; and fees for serving on a scientific committee from Corvia Medical. J.G., M.P.L. and A.R.R. are employees of Novartis and A.R.R. owns Novartis stock. A.P.M. reports receiving fees for serving on a study committee from Bayer and Fresenius. F.M. has received personal fees from Novartis. M.P. has received consulting fees from AbbVie, Akcea, Actavis, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. M.A.P. has received grants paid to his institution for serving on the Steering Committee of PARAGON-HF, and for serving as Study Chair of Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) from Novartis and personal fees for consulting from AstraZeneca, CinCor, Corvidia, DalCor, GlaxoSmithKline, Novartis, NovoNordisk, Pharmascience and Sanofi, and also owns Stock Options of DalCor. B.P. reports receiving fees for serving on a steering committee, fees for serving on an advisory board, and lecture fees from Bayer HealthCare Pharmaceuticals and MSD; lecture fees from AstraZeneca; fees for serving on an advisory board and lecture fees from Bristol-Myers Squibb; fees for serving on an advisory board from Daiichi Sankyo; and lecture fees and honoraria from Medscape. M.M.R. reports being an unpaid consultant for Novartis. J.L.R. has received grants and consulting fees from Novartis and consulting fees from Abbott, AstraZeneca, MyoKardia, and Sanofi. P.M.S. has received honoraria for lectures from Medtronic, Abbott, Servier, AstraZeneca, Respicardia; consultancy agreement and honoraria for lecturer from Boehringer Ingelheim, Novartis; and consultancy agreement from Vifor Pharma. J.T. has received personal fees from Roche Diagnostics, Olink Proteomics, and Us2.ai, outside the submitted work, and has a patent 16/216929 licensed. D.J.vV. reports receiving fees for serving on a steering committee and travel support from ARCA biopharma and Corvia Medical. M.B.Y. reports grants from Amgen, Inc., Novartis, Bayer and Dalcor Pharmaceuticals. F.Z. has received personal fees from Novartis, Janssen, Bayer, Boston Scientific, Amgen, CVRx, Boehringer, Cardiorenal, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck and CardioVascular Clinical Trialists (CVCT).

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M.R.Z. has received research funding from Novartis and has been a consultant for Novartis, Abbott, Boston Scientific, CVRx, EBR, Endotronics, Ironwood, Merck, Medtronic, and Myokardia V Wave. L.K. has received honoraria from Novartis, Boehringer, Novo, and AstraZeneca. M.C.P. has received lecture fees from AstraZeneca and Eli Lilly, personal fees from NovoNordisk, AstraZeneca, NAPP Pharmaceuticals, Takeda Pharmaceutical, Alnylam, Bayer, Resverlogix, and Cardiorentis and grants and personal fees from Boehringer Ingelheim and Novartis. P.S.J. has received consulting fees, advisory board fees, and lecture fees from Novartis; advisory board fees from Cytokinetics; and grant support from Boehringer Ingelheim. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and has consulted for Abbott, Action Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Lilly, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent. J.J.V.McM. has received grants and his employer paid by AstraZeneca, Theracos, and GlaxoSmithKline during the conduct of the study and grants and his employer being paid by Novartis, Amgen, Bristol-Myers Squibb, Bayer, Abbvie, Dal-Cor, Kidney Research UK, and Cardurion and grants from British Heart Foundation. All other authors have nothing to disclose.

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