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STUDY DESIGN

The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics

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Background The aims of this study were to: (i) report the baseline characteristics of patients enrolled in the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial, (ii) compare DAPA-HF patients to participants in contemporary heart failure (HF) registries and in other recent HF trials, and (iii) compare individuals with diabetes, pre-diabetes and a normal glycated haemoglobin (HbA1c) in DAPA-HF.

Methods and results Adults with HF in New York Heart Association functional class ≥ II, a left ventricular ejection fraction ≤ 40%, an elevated N-terminal pro-B-type natriuretic peptide concentration and receiving standard treatment were eligible for DAPA-HF, which is comparing dapagliflozin 10 mg once daily to matching placebo. In patients without a history of diabetes, previously undiagnosed diabetes was defined as a confirmed HbA1c ≥ 6.5%. Among patients without known or undiagnosed diabetes, pre-diabetes was defined as a HbA1c ≥ 5.7% The remainder of patients, with a HbA1c < 5.7%, were defined as normoglycaemic. Of the 4744 patients[†] (mean age 66 years; 23% women) randomized, 42% had known diabetes and 3% undiagnosed diabetes. Of the remainder, 67% had pre-diabetes and 33% normal HbA1c. Overall, DAPA-HF patients were generally similar to those in recent registries and in relevant trials and had high levels of background therapy: 94% angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor, 96% beta-blocker, and 71% mineralocorticoid receptor antagonist; 26% had a defibrillator. Patients with diabetes had worse HF status, more co-morbidity, and greater renal impairment but received similar HF therapy. Patients with diabetes received non-insulin hypoglycaemic therapy alone in 49%, insulin alone in 11%, both in 14%, and none in 26%.

Conclusions Patients randomized in DAPA-HF were similar to those in other contemporary HF with reduced ejection fraction (HFrEF) registries and trials. These patients were receiving recommended HFrEF therapy and those with diabetes were also treated with conventional glucose-lowering therapy. Consequently, DAPA-HF will test the incremental efficacy and safety of dapagliflozin in HFrEF patients with and without diabetes.
Clinical Trial Registration: ClinicalTrials.gov Identifier NCT03036124

Keywords Heart failure • Diabetes • Pre-diabetes • SGLT2 inhibitor • Natriuretic peptides

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[†]Correction added on 17 October 2019, after first online publication, the number of patients in trial is written as 4774 whereas the correct number is 4744.

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Introduction

In large clinical trials in patients with type 2 diabetes at high cardiovascular risk, three different sodium–glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce the risk of heart failure (HF) hospitalization.[1–3] This beneficial effect was observed soon after randomization, suggesting a mechanism or mechanisms of action different from those usually considered with conventional glucose-lowering therapies.[4–8] In addition to a diuretic-haemodynamic action, effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid have also been proposed. Many of these actions could also be beneficial in HF patients without diabetes. The renal protection afforded by SGLT2 inhibitors is also clearly relevant in all patients with HF.[9] Consequently, several trials have been designed to prospectively evaluate the efficacy and safety of SGLT2 inhibitors in patients with established HF, both with and without diabetes.[10] Here we describe the baseline characteristics of participants in the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial.

Methods

DAPA-HF is a randomized, double-blind, controlled trial in patients with chronic HF with reduced ejection fraction (HFrEF), evaluating the effect of dapagliflozin 10 mg once daily, compared with placebo, in addition to standard care, on the risk of worsening HF and cardiovascular death. The trial is registered as ClinicalTrials.gov Identifier: NCT03036124 and the design has been published in full.[10]

Summary of DAPA-HF design

Patients

Men and women aged ≥ 18 years with HF are eligible if they are in New York Heart Association (NYHA) functional class ≥ II, have a left ventricular ejection fraction (LVEF) ≤ 40%, are optimally treated with pharmacological and device therapy for HF, and willing to provide written informed consent. In addition, patients must have a N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥ 600 pg/mL if not hospitalized for HF within the previous 12 months or ≥ 400 pg/mL if hospitalized for HF within the previous 12 months. Patients with atrial fibrillation or atrial flutter must have a level ≥ 900 pg/mL, irrespective of history of HF hospitalization.

Key exclusion criteria include: type 1 diabetes mellitus, symptoms of hypotension or systolic blood pressure < 95 mmHg, recent worsening HF or other cardiovascular events or procedures (or planned procedures), estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (or rapidly declining renal function), and other conditions likely to prevent patient participation in the trial or greatly limit life expectancy. A full list of exclusion criteria is provided in the design paper.[10]

Treatment of heart failure

Patients were required to receive standard drug and device therapy for HFrEF, in accordance with recognized guidelines, including: (i) an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or sacubitril/valsartan, and (ii) a beta-blocker, unless contraindicated or not tolerated, as well as (iii) a mineralocorticoid receptor antagonist (MRA), if considered appropriate.

Study visits and follow-up

After provision of informed consent, visit 1 started a 14 ± 7 day enrolment period during which the trial inclusion and exclusion criteria were checked, and baseline information was collected (including from clinical examination and laboratory measurements). Visit 2 was the randomization visit at which further assessments were conducted and study drug was dispensed. After randomization, follow-up visits took place at 14 and 60 days, with a particular focus on assessment of HF and volume status, adverse events, and checking blood chemistry, and then at 120, 240, and 360 days and 4 monthly thereafter, as detailed in the design paper.[10]

Outcomes

The primary objective is to determine whether dapagliflozin is superior to placebo, when added to standard care, in reducing the incidence of a worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death, analysed as time-to-first event. The first of the secondary outcomes is the composite of HF hospitalization or cardiovascular death. The additional secondary outcomes are described in the design paper.[10]

Statistical considerations

The underlying statistical assumptions in DAPA-HF are described in the design paper and details of the statistical approach to the analysis of subgroups, including patients with and without diabetes, are given in the online supplementary *Methods S1*.[10]

Definition of diabetes and pre-diabetes in DAPA-HF

History of diabetes was provided by investigators. In patients without a history of diabetes, previously undiagnosed diabetes was defined as a glycated haemoglobin (HbA1c), measured in a central laboratory, of ≥ 6.5% at both visit 1 and visit 2. Among patients without known or undiagnosed diabetes, pre-diabetes was defined as a HbA1c ≥ 5.7% at visit 1 or visit 2. The remainder of patients, with a HbA1c < 5.7% at both visit 1 and visit 2, were defined as normoglycaemic (euglycaemic).

Comparator registries

Three recent registries encompassing Europe, Asia and the United States of America (USA) were used for comparison of patients in DAPA-HF with the so-called 'real-world' cohorts.[11–17]

Comparator trials: summary of inclusion/exclusion criteria

We compared the baseline characteristics of patients in DAPA-HF with a number of recent randomized controlled trials.[18–21] Two of these had broad inclusion criteria and are shown in the Results section; two more had restricted inclusion criteria (e.g. both included only patients in sinus rhythm and one only those with an ischaemic aetiology) and are shown in the online supplementary *Methods S1*.

PARADIGM-HF and ATMOSPHERE

The inclusion and exclusion criteria for the Prospective comparison of Angiotensin Receptor neprilysin inhibitors with Angiotensin

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Table 1 Baseline characteristics of patients with heart failure and reduced ejection fraction in contemporary registries and in DAPA-HF

	ESC Long-Term Registry (n = 5460)	ASIAN-HF (n = 5276)	CHAMP-HF (n = 3494)	DAPA-HF (n = 4744)
Mean age, years	64	60	66	66
Female sex, *n* (%)	22	22	29	23
Median BMI, kg/m^2	28	25	30	27
Mean systolic BP, mmHg	122	118	121	122
Mean heart rate, b.p.m.	73	80	74	72
Mean LVEF, %	29	28	30	31
NYHA class III/IV, %	31	33	32	32
Ischaemic aetiology, %	49	47	40	56
Diabetes, %	32	40	41	42
Arial fibrillation, %	37	18	36	40
Diuretic, %	84	82	61[a]	93
ACEi/ARB, %	92	75	73[b]	94[b]
Beta-blocker, %	93	79	83	96
MRA, %	68	59	33	71
Digoxin, %	24	31	14	19
Ivabradine, %	10	NR	1	5
ARNI, %	0	0	13	11

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NR, not reported; NYHA, New York Heart Association.
[a]Loop diuretic only.
[b]Includes sacubitril/valsartan.

converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial and the Aliskiren Trial of Minimizing OutcomeS in Patients with HEart failuRE (ATMOSPHERE) were almost identical.[18,19] Patients were eligible at screening if: ≥18 years, NYHA class II–IV, LVEF ≤35% (changed from ≤40% in PARADIGM-HF by amendment), elevated natriuretic peptide level, taking an ACE inhibitor or ARB, beta-blocker (unless contraindicated or not tolerated) and MRA, if indicated. The natriuretic peptide eligibility criteria were: BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL; patients hospitalized in the preceding 12 months were eligible with a lower level: BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL. Exclusion criteria included symptomatic hypotension or systolic blood pressure <95 mmHg (<90 mmHg in ATMOSPHERE), and eGFR <30 mL/min/1.73 m^2 (<35 mL/min/1.73 m^2 in ATMOSPHERE).

Results

The first patient enrolment visit took place 8 February 2017 and the first randomization occurred 15 February 2017. Subsequent recruitment in DAPA-HF was rapid, and randomization was completed 17 August 2018, with 4744 patients† randomized at 410 sites in 20 countries.

DAPA-HF compared with contemporary heart failure with reduced ejection fraction registries

Table 1 shows a comparison of key patient characteristics in three contemporary HF registries, compared with DAPA-HF. Other than a somewhat higher percentage of patients with an ischaemic aetiology, patients in DAPA-HF were very similar to those in the registries, with the exception of the low prevalence of atrial fibrillation/flutter in Asian patients, as identified in other studies in that region of the world. The fraction of patients ≥75 years in the European Society of Cardiology (ESC) Long-Term Registry was 22%, compared with 24% in DAPA-HF. The proportion of patients ≥65 years in the Change the Management of Patients with Heart Failure (CHAMP-HF) registry was 59%, compared with 60% in DAPA-HF. The mean eGFR in CHAMP-HF was 60 mL/min/1.73 m^2, which was lower than in DAPA-HF (66 mL/min/1.73 m^2) but the fraction of patients with an eGFR <60 mL/min/1.73 m^2 was lower in CHAMP-HF than in DAPA-HF (26% vs. 41%). The use of conventional, evidence-based, disease-modifying therapy was greater, overall, in DAPA-HF than in the registries (*Table 1* and *Figure 1*). The newer treatments, ivabradine and sacubitril/valsartan, were each used in a small minority of patients, both in the registries and in DAPA-HF (*Table 1*). However, the use of sacubitril/valsartan in DAPA-HF varied greatly by geographical region: 32.3% in North America, 24.5% in Western Europe, 6.9% in Latin America, 5.4% in Asia, and 2.7% in Central/Eastern Europe.

DAPA-HF compared with other recent heart failure with reduced ejection fraction trials

Table 2 shows a comparison of key patient characteristics in two recent HFrEF trials (PARADIGM-HF and ATMOSPHERE) with DAPA-HF. Patients in DAPA-HF were, on average, somewhat older

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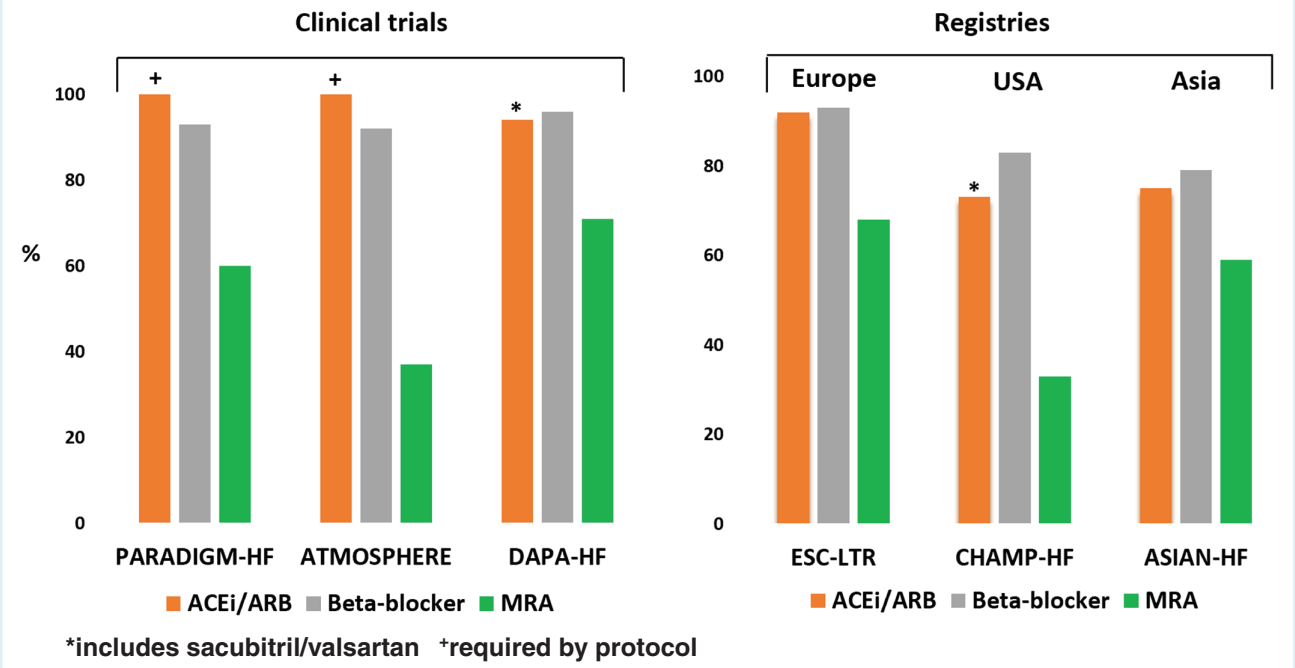

Figure 1 Comparison of use of disease-modifying therapy for heart failure with reduced ejection fraction in recent registries, trials and in DAPA-HF. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist. *Includes sacubitril/valsartan; +required by protocol.

(mean 66 years) than in the other two trials. The percentage of females was similarly small in all trials. DAPA-HF and ATMOSPHERE enrolled more Asians than PARADIGM-HF.

Heart failure characteristics

A larger proportion of patients in DAPA-HF were in NYHA functional class III/IV (32%) than in PARADIGM-HF or ATMOSPHERE (24% and 28%, respectively). The average Kansas City Cardiomyopathy Questionnaire (KCCQ) overall and clinical summary scores were lower in DAPA-HF, reflecting the NYHA class distributions in the trials.

Left ventricular ejection fraction was slightly higher in DAPA-HF than in the other two trials whereas NT-proBNP levels were broadly similar in all three trials. Heart rate and blood pressure were similar in each of the trials.

The percentage of patients with prior HF hospitalization was substantially smaller in DAPA-HF (47%) than in the other two trials (63% PARADIGM-HF and 60% ATMOSPHERE). In DAPA-HF, 16.4% of patients had been hospitalized for HF in the previous 6 months and 27.3% in the previous year.

The fraction of patients with an ischaemic aetiology was similar across the three trials.

Past history and co-morbidity

Median body mass index was similar across all three trials. Overall, around 30% of patients were obese, with this proportion somewhat higher in DAPA-HF than in the other trials. The percentage of patients with a history of diabetes was higher in DAPA-HF (42%) than in PARADIGM-HF (34%); the fraction in ATMOSPHERE was lower because of the exclusion of patients with diabetes part-way through enrolment.[19]

The proportion of patients with previous myocardial infarction and prior coronary revascularization was similar in the three trials and reflected the prevalence of ischaemic aetiology. The percentage of patients with a history of hypertension and prior stroke was slightly higher in DAPA-HF, compared with the other trials. The proportion of participants with atrial fibrillation/flutter on their electrocardiogram was similar across trials. Mean eGFR was lowest, and the fraction of patients with an eGFR < 60 mL/min/1.73m^2 was highest, in DAPA-HF (see Discussion section). Overall, 28% of men and 26% of women in DAPA-HF had anaemia, a slightly higher proportion than in the other two trials.

Baseline drug and device therapy

Beta-blocker use was higher in DAPA-HF than in any prior trial (*Figure 1*), whereas digoxin use was less than in the other trials. The rate of use of an MRA was very high in DAPA-HF (71%) compared with PARADIGM-HF (60%) and ATMOSPHERE (37%). Overall, 10.8% of patients in DAPA-HF were treated with sacubitril/valsartan at baseline and 4.8% with ivabradine. The percentage treated with ivabradine was 1.0% in ATMOSPHERE and 1.5% in PARADIGM-HF.

The proportion of patients in DAPA-HF with an implantable cardioverter-defibrillator (ICD) was larger than in either of the previous trials.

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Table 2 Baseline characteristics in recent randomized clinical trials in patients with heart failure and reduced ejection fraction

	PARADIGM-HF (n = 8442)	ATMOSPHERE (n = 7063)	DAPA-HF (n = 4744)
Mean age, years	64	63	66
Female sex, *n* (%)	22	22	23
Race (%)			
White	66	66	70
Black	5	2	5
Asian	18	25	24
Other	11	7	1
Region (%)			
Western Europe	24.4	26.4	11.6
Eastern Europe/Russia	33.6	27.7	33.8
North America	7.2	2.5	14.3
Latin America	17.0	16.0	17.2
Asia Pacific	17.7	27.4	23.1
HF characteristics			
NYHA class, %			
I	5	2	0
II	70	69	68
III	24	28	32
IV	1	1	1
Mean KCCQ score			
OSS	73	75	68
CSS	73	78	71
Mean LVEF, %	29	28	31
Median NT-proBNP, pg/mL			
All	1615	1198	1437
No AF/F, *n*	1444	1014	1291
AF/F, *n*	1955	1652	1945
History of HF hospitalization, %	63	60	47
Ischaemic aetiology, %	60	56	56
Mean blood pressure, mmHg			
Systolic	121	124	122
Diastolic	74	75	74
Mean heart rate, b.p.m.	72	72	72
Medical history and co-morbidity			
Median BMI, kg/m^2	28	27	27
Obese, %	32	27	35
Diabetes, %	34	28	42
Hypertension, %	71	62	74
MI, %	43	41	44
PCI, %	21	20	34
CABG, %	15	14	17
Stroke, %	9	7	10
Atrial fibrillation/flutter, %			
History	37	34	40
ECG	25	23	24
Mean eGFR, mL/min/1.73 m^2	68	74	66
eGFR < 60 mL/min/1.73 m^2, %	37	27	41
Mean haemoglobin, g/L	140	138	136
Anaemia, %			
Men	21	22	28
Women	18	24	26
Treatment (%)			
Diuretic	80	80	93
ACEi	78	100	56
ARB	23	0	28
ACEi or ARB	100	100	94[a]
β-blocker	93	92	96
MRA	60	37	71
Digitalis glycoside	30	32	19
Ivabradine	2	1	5
CRT	7	6	7
ICD	15	15	26

ACEi, angiotensin-converting enzyme inhibitor; AF/F, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; CSS, clinical summary score; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; PCI, percutaneous coronary intervention.
[a]Includes 10.8% taking sacubitril/valsartan.

A comparison of DAPA-HF with the Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial (SHIFT) and the Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER-HF) is shown in the online supplementary *Table S1*.

Comparison of patients with and without diabetes

Of all patients randomized, 1983 (42%) had a pre-existing diagnosis of diabetes and 154 a HbA1c in the diabetes range at visit 1 and visit 2, i.e. the total number with known or undiagnosed diabetes was 2137 (45%). The baseline characteristics of these two groups are shown in *Table 3* and discussed further below.

Of the 2607 patients without diabetes, 1750 had pre-diabetes (67% of those without diabetes and 37% of all randomized participants) and 857 a normal HbA1c (33% and 18%, respectively). The baseline characteristics of these two groups, as well as patients with diabetes, are shown in the online supplementary *Table S2*.

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Table 3 Baseline characteristics of patients in DAPA-HF according to glycaemic status

	No diabetes (n = 2607)	Diabetes (n = 2137)
Mean age, years	66.2	66.6
> 65 years, %	58	57
> 75 years, %	23	19
Female sex, *n* (%)	24	22
Race (%)		
White	71	70
Black	3.8	6.0
Asian	24	23
Other	1.5	1.5
HF characteristics		
NYHA class, %		
II	71	64
III	29	35
IV	0.8	1.0
Mean KCCQ score		
OSS	69.7	66.4
CSS	72.7	69.2
Mean LVEF, %	31	31
LVEF range 36–40, %	28	31
Median NT-proBNP, pg/mL		
All	1413	1484
No AF/F	1265	1325
AF/F	1876	2046
History of HF hospitalization, %	46	49
≤ 6 months	15	18
≤ 12 months	27	28
Ischaemic aetiology, %	51	62
Mean blood pressure, mmHg		
Systolic	121	123
Diastolic	73	74
Systolic blood pressure		
≥130 mmHg, %	26	34
≥140 mmHg, %	10.9	15.1
Mean ECG QRS duration, ms	123	121
≥ 130 ms,%	36	33
≥ 150 ms, %	24	20
Mean heart rate, b.p.m.	71	72
No AF/F, b.p.m.	69	71
AF/F, b.p.m.	76	76
Medical history and co-morbidity		
Median BMI, kg/m^2	26	29
Obese, %	28	44
Hypertension, %	68	82
MI, %	40	49
PCI, %	30	39
CABG, %	14	20
Stroke, %	9	11
Atrial fibrillation/flutter, %		
History	41	38
ECG	24	24
Sleep apnoea, %	4.4	7.2
Foot ulcer, %	0.5	2.1
Amputation, %	0.7	1.9
Neuropathy, %	1.5	9.3
Mean eGFR, mL/min/1.73 m^2	67.8	63.3
eGFR < 60 mL/min/1.73 m^2, %	36.2	46.0
Mean HbA1c, %	5.8	7.4
Mean BUN, mmol/L	7.8	9.0
Serum potassium, mmol/L	4.5	4.6
Haemoglobin, g/L	137	134
Anaemia, %		
Men	23.4	33.6
Women	25.2	28.0
HF treatment (%)		
Diuretic	92	95
ACEi	57	55
ARB	26	29
ARNI	10.7	10.9
β-blocker	95	97
MRA	70	71
Digitalis glycoside	17.5	19.8
CRT	7.8	7.1
ICD	25.5	27.0
Diabetes treatment (%)		
Biguanide[a]	0.4	47
Sulfonylurea	0	20
DPP-4 inhibitor	0	14
α-glucosidase inhibitor	0	4.2
GLP-1 receptor agonist	0	1.0
Insulin	0	25
Insulin only	0	11
Insulin with other therapy	0	14

ACEi, angiotensin-converting enzyme inhibitor; AF/F, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; CSS, clinical summary score; DPP, dipeptidyl peptidase; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; HbA1c, glycated haemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; PCI, percutaneous coronary intervention.
[a]Metformin in all cases.

Patients with pre-diabetes were older than individuals with a normal HbA1c but were otherwise more similar to euglycaemic patients than patients with type 2 diabetes.

Heart failure characteristics

Patients with pre-diabetes and diabetes had worse KCCQ scores than those without diabetes and the NYHA class distribution was worse in patients with diabetes.

The proportion of patients with an ischaemic aetiology was higher in those with diabetes (62%) than in those without. Mean

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LVEF was similar in both groups but NT-proBNP was higher in patients with diabetes. Heart rate was similar in the two groups but blood pressure (and the percentage with an elevated blood pressure) was highest in patients with diabetes.

The proportion of patients with a prior HF hospitalization did not differ greatly between the groups.

Past history and co-morbidity

Median body mass index and the fraction of obese patients increased significantly between those with and without diabetes (44% and 28%, respectively).

The proportion of patients with a history of myocardial infarction and coronary revascularization was higher in patients with diabetes, in keeping with the fraction of patients with an ischaemic aetiology. The percentage of participants with a history of hypertension differed in a similar way, consistent with baseline blood pressure. Investigator-reported co-morbidities collected in DAPA-HF, additional to those collected in the other trials, were foot ulcer, amputation, neuropathy and sleep apnoea. Each of those was uncommon but more frequent in patients with a history of diabetes, although were also reported in a few patients without diabetes.

Mean eGFR was lower, and the proportion of patients with an eGFR < 60 mL/min/1.73 m^2 higher, in those with diabetes compared to no diabetes, with 46% of patients in the former group categorized as having chronic kidney disease. The percentage of patients with anaemia was also highest among those with diabetes (33.6% of men and 28.0% of women).

Baseline drug and device therapy for heart failure

A similar fraction of patients in each group was treated with a renin–angiotensin system blocker, beta-blocker, a MRA and devices [ICD and cardiac resynchronization therapy (CRT)]. The highest rate of use of digoxin was in the diabetes group.

Baseline therapy for diabetes

In patients with a pre-existing diagnosis of diabetes ($n = 1983$), 27.0% were treated with insulin (11.8% with only insulin), 50.8% with a biguanide, 21.7% with a sulfonylurea, 15.4% with a dipeptidyl peptidase-4 (DPP-4) inhibitor, 4.5% with an alpha glucosidase inhibitor, 1.1% with a glucagon-like peptide 1 receptor agonist, and 0.6% with a thiazolidinedione. The proportion of patients with known diabetes receiving no glucose-lowering treatment was 20.3%. These percentages were slightly different when the total of patients with known or unknown diabetes ($n = 2137$) was used as the denominator (*Table 3*).

Discussion

DAPA-HF is one of the two large mortality/morbidity trials evaluating the effects of a SGLT2 inhibitor in outpatients with HFrEF.[10,22] Both DAPA-HF and the EMPagliflozin outcomE tRial in patients with chrOnic heaRt Failure with Reduced ejection fraction (EMPEROR-Reduced) trial allow inclusion of patients without as well as with a history of diabetes.[10,22] Consistent with this, the majority (58%) of patients enrolled in DAPA-HF did not have known diabetes. The proportion with an existing diagnosis of diabetes (42%) was similar to that in contemporary registries but somewhat larger than in the comparator HFrEF trials.[11–17,21] The patients randomized in DAPA-HF were also broadly similar, in other respects, to those in the recent registries, although, as has been recognized previously, atrial fibrillation was less frequent in Asian patients.[11–17] Patients in DAPA-HF were also generally similar to those in the comparator trials with globally diverse enrolment (particularly PARADIGM-HF and ATMOSPHERE), taking account of specific inclusion and exclusion criteria and other issues such as the cessation of randomization of patients with diabetes part-way through recruitment in ATMOSPHERE.[23] One of the few exceptions included the fraction obese, which was larger in DAPA-HF, in keeping with higher prevalence of diabetes and hypertension in DAPA-HF. The worse kidney function in DAPA-HF probably also reflects the slightly older age and high prevalence of diabetes and hypertension in the current trial, as well as the very high rate of use of renin–angiotensin–aldosterone system blockers, including an MRA in 71% of patients (see below). The high frequency of renal dysfunction in COMMANDER-HF is also consistent with this interpretation.[21]

Three other differences of note include: (i) the low rate of use of digoxin, (ii) the higher use of devices, especially an ICD than in the other trials, and (iii) the lower proportion (47%) of patients with a prior HF hospitalization. The low use of digoxin probably reflects a historical decline related to the availability of alternative therapeutic options, as well as safety concerns about digoxin; digoxin use was also low in the CHAMP-HF registry.[13,14,24] The higher rate of ICD/CRT-D use in DAPA-HF, compared with PARADIGM-HF, however seems to be wholly accounted for by the regional distribution of patients in the two trials, and reflects the higher rate of implantation of these devices in North America and Europe, compared with other geographical areas. This variation likely reflects economic restrictions and is similar to that seen for new (and more costly) pharmacological therapies (see below).

The percentage of patients in the ESC Long-Term Registry with a history of HF hospitalization was also 47%. The fraction with such an admission in the prior 12 months was 27% in DAPA-HF and 38% in CHAMP-HF. These lower rates than historically reported may reflect changing practice aimed at avoiding admission and, also, the effectiveness of modern HF therapies used in combination.[25]

Our finding that approximately 70% of patients without a prior diagnosis of diabetes had previously undiagnosed diabetes or pre-diabetes is in keeping with the only other analyses of this type we know of from PARADIGM-HF and GISSI-HF, although in these other reports only a single baseline HbA1c was available.[26,27] Part of the hypothesis for using SGLT2 inhibitors in HFrEF patients not known to have diabetes is that glucose lowering may also be beneficial in patients with pre-diabetes and may delay or prevent the development of diabetes, and the present findings show that we will be able to test this theory in DAPA-HF.[10]

Comparison of patients with a normal HbA1c, pre-diabetes and any diabetes (existing diagnosis and undiagnosed combined) is therefore of some interest. Patients with diabetes were older

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than those with a normal HbA1c and had worse symptoms and quality of life, despite a similar LVEF and proportion with a history of HF hospitalization. Patients with diabetes did, however, have a higher NT-proBNP level and more often had an ischaemic aetiology (and other manifestations of coronary artery disease) than participants with a normal HbA1c. Patients with pre-diabetes generally exhibited findings intermediate between these two ends of the spectrum, illustrating that 'non-diabetic' patients in prior trials are a heterogeneous group, with clearly worse HF status in patients with dysglycaemia compared to those who are euglycaemic.

Certain co-morbidities, however, were distinctly more common just in those with diabetes, particular obesity, hypertension (whether as history or as determined by measurement of blood pressure), sleep apnoea (which might relate to obesity, if predominantly obstructive in type), renal impairment, anaemia and neuropathy. The triad of diabetes, chronic kidney disease and anaemia (sometimes referred to as the 'cardiorenal–anaemia syndrome') is associated with particularly poor outcomes in HF.[28]

A particularly important consideration in any trial evaluating a new, incremental, therapy is the adequacy of background treatment. In DAPA-HF, rates of use of conventional therapy were high, comparing favourably with other trials and, especially, 'real-world' cohorts. The ESC Long-Term Registry reported use of an ACE inhibitor or ARB in 92%, a beta-blocker in 93% and an MRA in 68% of 4792 patients with HFrEF.[11,12] However, in the recent CHAMP-HF registry from the USA, these rates were much lower: 73%, 83% and 33%, respectively, despite the patients having a similar mean age and LVEF, and lower percentage of patients with chronic kidney disease, than those in DAPA-HF.[13,14,28] This may explain the higher median baseline NT-proBNP level in CHAMP-HF (2013 vs. 1437 pg/mL), lower KCCQ overall summary score (62 vs. 68) and smaller fraction with an eGFR < 60 mL/min/1.73 m^2 (26% vs. 41%), compared with DAPA-HF. In CHAMP-HF, more comprehensive therapy was associated with much lower NT-proBNP levels and lower eGFR.[13,14,28]

Looking at novel HFrEF therapies, only 11% of patients in DAPA-HF were treated with the angiotensin receptor–neprilysin inhibitor combination, sacubitril/valsartan, a finding consistent with the 13% receiving this therapy in the recent CHAMP-HF registry mentioned above.[13,14,29] However, the percentage treated with sacubitril/valsartan varied widely in DAPA-HF, from 32% in North America and 25% in Western Europe to 7% or less in other regions, perhaps reflecting different economic circumstances and health service provision. Ivabradine was also little used in recent trials and registries. Sacubitril/valsartan is of particular interest in patients with dysglycaemia as neprilysin is reported to metabolise glucagon-like peptide-1 and neprilysin inhibition to reduce HbA1c and need for insulin in HFrEF patients with diabetes.[30]

We found identical rates of use of all key HFrEF therapies in patients with and without diabetes. Indeed, although the proportion of diabetes patients in DAPA-HF with chronic kidney disease was striking (46% of patients with diabetes), the use of ACE inhibitors, ARBs and MRAs was as high in the other patient subgroups in the trial. These findings are consistent with reports from PARADIGM-HF, SHIFT and the ESC Long-Term Registry and encouraging, given prior observations of underuse of these life-saving treatments because of misplaced concerns about their use in patients with renal dysfunction.[26,31,32] Another interesting comparison is a very large registry which included US ($n = 28\,877$) and Asian ($n = 2235$) patients with both HFrEF and diabetes.[33] There was a gradient in use of treatment from low-income Asian countries, through high-income Asian countries to the USA: ACE inhibitor or ARB use 68.5% to 76.6% and beta-blocker use 68.3% to 90.5%; MRA use was not reported.

Regarding anti-hyperglycaemic therapy, most patients with a history of type 2 diabetes in DAPA-HF were treated with oral glucose-lowering therapy (oral therapy only in 53%), insulin (insulin alone in 12%) or both (15%), with 20% of patients receiving no glucose-lowering therapy, findings consistent with other studies. Specifically, in the ESC Long-Term Registry, 28% of patients were not receiving glucose-lowering therapy and in the US/Asian cohort study mentioned earlier, 30–40% of patients with HFrEF were not receiving glucose-lowering treatment, similar to the percentage in PARADIGM-HF.[26,32] About a fifth of patients with type 2 diabetes were not treated with pharmacological glucose-lowering therapy in other registries, diabetes trials and HF studies.[34–36] There are few detailed descriptions of the classes of oral glucose-lowering therapies prescribed for patients with HFrEF but in the reports available, the pattern is similar to what we observed in DAPA-HF – with metformin, sulfonylureas and DPP-4 inhibitors accounting for the large majority of these. However, what was different among the studies was the fraction of patients treated with insulin, which varied in the prior reports from 44% in the USA to 24% in Asia; in PARADIGM-HF the proportion was 25% and in SHIFT 32%. This pattern of greater use of insulin in North America, to treat type 2 diabetes, has been reported previously.[26,30–33,37]

Consequently, DAPA-HF will test the potential incremental efficacy (and safety) of dapagliflozin, not only in addition to comprehensive disease-modifying pharmacotherapy for HFrEF but also in addition to insulin, conventional non-insulin anti-hyperglycaemic therapies and dietary management of type 2 diabetes.[38]

In summary, DAPA-HF has enrolled patients with and without diabetes who have persisting symptoms, a reduced LVEF and an elevated NT-proBNP level, who are similar to those enrolled in contemporary HFrEF registries and randomized in other recent HFrEF trials. The high prevalence of obesity, type 2 diabetes and pre-diabetes, and chronic kidney disease in these patients emphasises the 'cardiometabolic' profile of HFrEF and the potential for SGLT2 inhibition to improve outcomes through glycaemic, renal and other mechanisms.

Supplementary Information

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

Methods S1. Statistical analysis.

Table S1. Baseline characteristics in recent randomized clinical trials in patients with heart failure and reduced ejection fraction.

Table S2. Baseline characteristics of patients in DAPA-HF according to glycaemic status (normal glycated haemoglobin, pre-diabetes and diabetes).

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