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STUDY DESIGN

A trial to evaluate the effect of the sodium–glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF)

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Background Sodium–glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce the risk of incident heart failure hospitalization in individuals with type 2 diabetes who have, or are at high risk of, cardiovascular disease. Most patients in these trials did not have heart failure at baseline and the effect of SGLT2 inhibitors on outcomes in individuals with established heart failure (with or without diabetes) is unknown.

Design and methods The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF) is an international, multicentre, parallel group, randomized, double-blind, study in patients with chronic heart failure, evaluating the effect of dapagliflozin 10 mg, compared with placebo, given once daily, in addition to standard care, on the primary composite outcome of a worsening heart failure event (hospitalization or equivalent event, i.e. an urgent heart failure visit) or cardiovascular death. Patients with and without diabetes are eligible and must have a left ventricular ejection fraction $\leq 40\%$, a moderately elevated N-terminal pro B-type natriuretic peptide level, and an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2. The trial is event-driven, with a target of 844 primary outcomes. Secondary outcomes include the composite of total heart failure hospitalizations (including repeat episodes), and cardiovascular death and patient-reported outcomes. A total of 4744 patients have been randomized.

Conclusions DAPA-HF will determine the efficacy and safety of the SGLT2 inhibitor dapagliflozin, added to conventional therapy, in a broad spectrum of patients with heart failure and reduced ejection fraction.

Keywords Clinical trial • Heart failure • Sodium–glucose co-transporter 2 inhibitor • Type 2 diabetes mellitus

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Introduction

Although being one of the most common, disabling and deadly complications of diabetes, heart failure has not been the focus of cardiovascular outcome trials evaluating glucose-lowering therapies.[1,2] Despite this, evidence has accrued that different diabetes medications have distinct effects on the risk of developing heart failure.[1,2] Specifically, thiazolidinediones and saxagliptin (and possibly alogliptin) increase the risk of heart failure hospitalization, whereas in three recent trials there were nominally statistically significant reductions in heart failure hospitalization with sodium–glucose co-transporter 2 (SGLT2) inhibitors.[3–9] In the EMPA-REG OUTCOME trial, the relative risk reduction in heart failure hospitalization among patients with type 2 diabetes treated with empagliflozin was 35%,[7] in the Canagliflozin Cardiovascular Assessment Study Program (CANVAS), the reduction was 33%,[8] and in the Dapagliflozin Effect on CardiovascuLAR Events trial (DECLARE–TIMI 58) the reduction was 27%.[9] These exciting findings have raised many questions, including what type (or types) of heart failure occurred in these patients (i.e. with reduced or preserved ejection fraction), through which mechanism(s) SGLT2 inhibitors exert these salutary effects and whether they may even be independent of glucose-lowering, and if they might extend to patients without type 2 diabetes?[3–12] Additional mechanisms proposed include diuretic and haemodynamic actions, improved myocardial metabolism, effects on cardiac ion channels and others.[3–12] The beneficial effects of SGLT2 inhibitors on kidney function may also be relevant.[3–12]

An even bigger question is whether SGLT2 inhibitors might also be of benefit in patients with established heart failure. Few patients in EMPA-REG OUTCOME, CANVAS and DECLARE–TIMI 58 had a diagnosis of heart failure at baseline and the heart failure phenotype of those that did has not been reported.[7,8] Yet diabetes and pre-diabetic dysglycaemia are extremely common in individuals with heart failure, and heart failure patients with diabetes or pre-diabetes are at especially high risk of cardiovascular death and heart failure hospitalization.[13,14] Consequently, a treatment that both lowers glucose and improves heart failure outcomes is greatly needed, particularly if not accompanied by weight gain and the risk of hypoglycaemia, as is the case with some conventional therapies (insulin and insulin secretagogues). Moreover, it is possible that the favourable mechanisms of action of SGLT2 inhibitors might even extend to heart failure patients without manifest dysglycaemia.[3–12]

To further explore these possibilities, we have designed a prospective randomized, placebo-controlled trial examining the effect of dapagliflozin on morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF) — the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF).

Methods

DAPA-HF is an international, multicentre, parallel group, event-driven, randomized, double-blind, trial in patients with chronic HFrEF, evaluating the effect of dapagliflozin 10 mg, compared with placebo, given once daily, in addition to standard of care, on the risk of worsening heart failure and cardiovascular death. The trial is registered as ClinicalTrials.gov Identifier: NCT03036124.

Study design and conduct

Patients

Men and women aged 18 years or older with a diagnosis of heart failure for at least 2 months are eligible if they are in New York Heart Association functional class II or above, have a left ventricular ejection fraction documented to be $\leq$ 40% within the last 12 months, are optimally treated with pharmacological and device therapy for heart failure, and willing to provide written informed consent. In addition, patients must have a N-terminal pro B-type natriuretic peptide concentration $\geq$ 600 pg/mL or, if hospitalised for heart failure within the previous 12 months, $\geq$ 400 pg/mL. Patients with atrial fibrillation or atrial flutter must have a level $\geq$ 900 pg/mL, irrespective of history of heart failure hospitalization. Full details are provided in the online supplementary *Appendix S1*.

Key exclusion criteria include: recent treatment with or intolerance of a SGLT2 inhibitor, type 1 diabetes mellitus, symptoms of hypotension or systolic blood pressure < 95 mmHg, recent worsening heart failure 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 *Table 1*.

Treatment of heart failure

Patients should receive background standard drug and device therapy for HFrEF, in accordance with recognized guidelines. Guideline-recommended medications should be used at the target doses specified, unless contraindicated or not tolerated. Therapy should have been individually optimized and stable for $\geq$ 4 weeks (with the exception of diuretics which can be dosed flexibly – see below). Unless contraindicated or not tolerated, treatment should include: (i) an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or sacubitril/valsartan; (ii) a beta-blocker and, if considered appropriate; (iii) a mineralocorticoid receptor antagonist (MRA); further details are provided in the online supplementary *Appendix S1*.

It is recognized that diuretic dosing may be titrated according to symptoms, signs, weight and other information and may thus vary. Each patient should, however, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual.

Treatment of diabetes

Patients with type 2 diabetes at randomization will continue to take their glucose-lowering therapies but these can be adjusted at the discretion of their diabetes health care provider. The dose of insulin and/or sulfonylurea therapy may be reduced to minimize the risk of hypoglycaemia, for example in patients with a baseline glycated haemoglobin (HbA1c) < 7%.

Randomization

Once a patient fulfils the criteria for randomization, investigators use the interactive voice or web response system (IxRS) to obtain treatment assignment. Participants are assigned, double-blind, in balanced blocks to ensure an approximate one-to-one ratio of dapagliflozin or

Table 1 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor
2. Type 1 diabetes mellitus
3. Symptomatic hypotension or systolic blood pressure < 95 mmHg at two out of three measurements either at Visit 1 or Visit 2
4. Current acute decompensated HF or hospitalization due to decompensated HF < 4 weeks prior to enrolment
5. Myocardial infarction, unstable angina, stroke or transient ischemic attack within 12 weeks prior to enrolment
6. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo any of these operations after randomization
7. Implantation of a CRT device within 12 weeks prior to enrolment or intent to implant a CRT device
8. Previous cardiac transplantation or implantation of a ventricular assistance device or similar device, or implantation expected after randomization
9. HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, or uncorrected primary valvular disease
10. Symptomatic bradycardia or second or third-degree heart block without a pacemaker
11. Any condition outside the cardiovascular and renal disease area, such as but not limited to malignancy, with a life expectancy of < 2 years based on investigator's clinical judgement
12. Active malignancy requiring treatment at the time of Visit 1 (with the exception of successfully treated basal cell or treated squamous cell carcinoma)
13. Hepatic impairment (aspartate transaminase or alanine transaminase > 3 × the ULN, or total bilirubin > 2 × ULN at time of enrolment). An isolated increase in bilirubin in patients with known Gilbert's syndrome is not a reason for exclusion
14. Known blood-borne diseases representing a shipping/transportation biohazard
15. Severe (eGFR < 30 mL/min/1.73 m^2 by CKD-EPI equation), unstable or rapidly progressing renal disease at the time of randomization
16. Women of child-bearing potential (i.e. those who are not chemically or surgically sterilised or who are not post-menopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgement of the investigator, from the time of signing the informed consent throughout the study and 4 weeks thereafter, or women who have a positive pregnancy test at enrolment or randomization, or women who are breast-feeding
17. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site)
18. Previous randomization in the present study
19. Participation in another clinical study with an IP during the last month prior to enrolment
20. Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up, or any conditions that, in the opinion of the investigator, may render the patient unable to complete the study

CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT2, sodium–glucose co-transporter 2; IP, investigational product; ULN, upper limit of normal.

matching placebo, in accordance with the sequestered, fixed randomization schedule.

Stratification and capping

Randomization will be stratified based on diagnosis of type 2 diabetes [either an established diagnosis or a central laboratory HbA1c ≥ 6.5% (48 mmol/mol) at enrolment] and at least 30% of the patients enrolled will have type 2 diabetes.

Study visits and follow-up

After provision of informed consent, Visit 1 starts a 14 ± 7 day enrolment period during which the trial inclusion and exclusion criteria are checked and baseline information is collected (including from clinical examination and laboratory measurements). Visit 2 is the randomization visit at which further assessments are conducted (*Figure 1* and online supplementary *Table S1*) and study drug is dispensed. Visit 3 takes place 14 ± 3 days and Visit 4 60 ± 7 days after randomization, with a particular focus on assessment of heart failure and volume status, adverse events, and checking blood chemistry (including renal function and potassium). Further visits take place at 120 ± 7, 240 ± 14, 360 ± 14 days and 4 monthly thereafter. The schedule of assessments is shown in the online supplementary *Table S1*.

Study drug dose reduction/discontinuation

Study drug should be permanently discontinued if pregnancy or diabetic ketoacidosis occur. Dose reduction (to dapagliflozin 5 mg daily or matching placebo) or temporary discontinuation may be considered in cases of acute, unexpected, declines in eGFR (while investigating other causes such as nephrotoxic drugs, urinary tract infection, or obstruction). Similarly, in cases of volume depletion and/or hypotension, alternative causes should be considered (e.g. gastrointestinal fluid loss, use of non-essential blood pressure-lowering drugs) and the dose of concomitant diuretic therapy re-assessed and reduced, if appropriate. Temporary interruption of study drug may also be considered, prophylactically, in patients at potential risk of volume contraction/hypotension, such as patients with an acute medical illness potentially causing volume depletion because of inadequate fluid intake or fluid/blood losses (e.g. gastroenteritis, gastrointestinal haemorrhage), or patients undergoing major surgery.

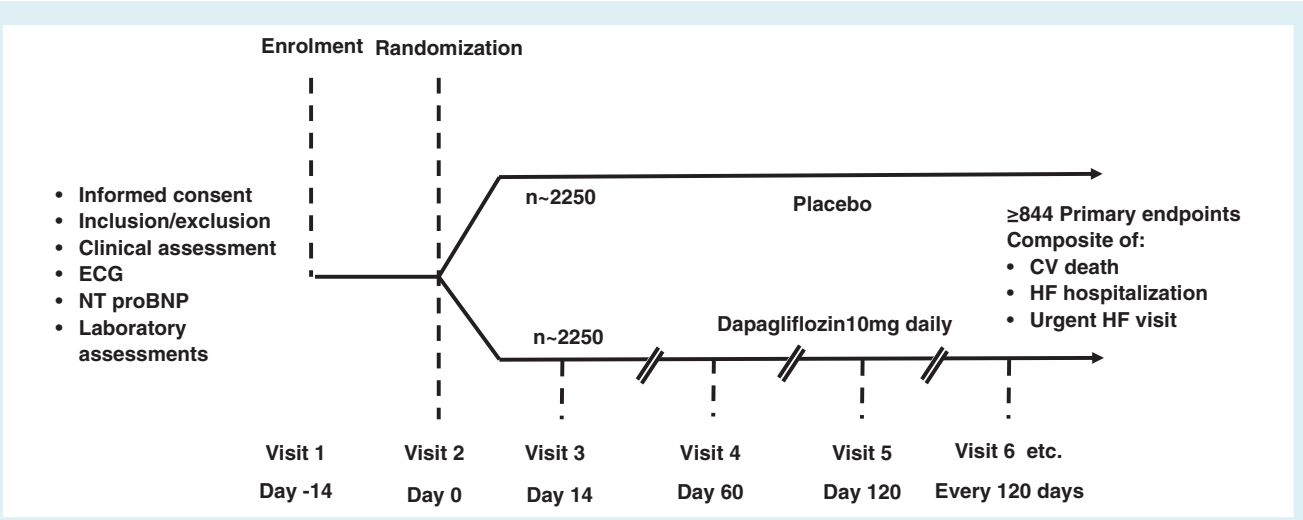

Figure 1 Trial design. CV, cardiovascular; ECG, electrocardiogram; HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide.

The dose of evidence-based, life-saving, heart failure therapies should not be reduced just to maintain treatment with study drug. If possible, the dose of study drug should be increased again if the adverse effect is resolved. Even if study drug is discontinued, investigators are asked to ensure that scheduled study visits, follow-up procedures and data collection continue according to the study protocol until study closure.

Outcomes

Primary and other 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 heart failure episode (hospitalization or the equivalent, i.e. an urgent heart failure visit) or cardiovascular death, analysed as time-to-first event (*Table 2*).

The first of the secondary outcomes is the composite of heart failure hospitalization or cardiovascular death. The additional secondary outcomes are: (i) total number of recurrent heart failure hospitalizations and cardiovascular deaths; (ii) change from baseline to 8 months in the total symptom score using the Kansas City Cardiomyopathy Questionnaire (KCCQ)[15]; patients will complete the KCCQ and other patient-reported outcomes (PROs; *Table 2*) using a handheld electronic device; (iii) the incidence of a composite worsening renal function outcome conisting of (a) $\geq$ 50% sustained decline in eGFR, or ((b) end-stage renal disease (defined as sustained eGFR $<$ 15 mL/min/1.73 m^2, chronic dialysis treatment or renal transplantation) or renal death; and (iv) death from any cause.

There are also a number of exploratory objectives (listed in *Table 2*), including development of new diabetes and new atrial fibrillation, and safety objectives, including documentation of adverse events of interest comprising volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis, amputations, and events potentially placing patients at risk of lower limb amputation.

Endpoint adjudication

An independent Cardiovascular Endpoint Committee (CEC), blinded to treatment allocation, is adjudicating all deaths and non-fatal cardiovascular events submitted by investigators (or otherwise identified) as possible endpoints. The CEC will use a charter reflecting the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials developed by the Standardized Data Collection for Cardiovascular Trials Initiative.[16] Episodes of possible ketoacidosis are also being adjudicated.

Statistical considerations

Sample size assumptions and statistical analysis

Assuming a true hazard ratio (HR) of 0.80 for dapagliflozin vs. placebo, and using a one-sided alpha of 2.5%, 844 primary endpoint events will provide a statistical power of 90% for the test of the primary composite endpoint.

With an annual event rate of 11% in the placebo treatment group, approximately 4500 patients were estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months. The assumed placebo event rate of 11% is based on a review of recently published clinical studies in the HFrEF population, including the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[17] The trial has a group sequential design with one interim analysis (see below) by the Data Monitoring Committee (DMC).

Methods for statistical analyses

We plan to use a closed testing procedure, including a pre-specified hierarchical ordering of the primary and secondary endpoints (as listed above). The Type I error will be controlled at a one-sided 0.02496 level for multiplicity across primary and secondary endpoints and in consideration of planned interim analyses (as described above). Statistical significance of the endpoints will be assessed in the order specified above. The testing procedure will continue down the hierarchy if superiority for the preceding endpoint is demonstrated at a one-sided 0.02496 level and will stop if superiority is not achieved at a one-sided 0.02496 level. Exploratory endpoints will be tested at a one-sided 0.025 level without adjustment for multiplicity.

Table 2 Primary, secondary and exploratory efficacy objectives and safety objectives

	Outcome measure
Primary objective	
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the incidence of CV death or a HF event (hospitalization for HF or equivalent HF event, i.e. an urgent HF visit)	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalization for HF 3. An urgent HF visit
Secondary objectives	
• To compare the effect of dapagliflozin vs. placebo on CV death or hospitalization for HF	Time to the first occurrence of either of the components of this composite: 1. CV death 2. Hospitalization for HF
• To compare the effect of dapagliflozin vs. placebo on total number of recurrent HF hospitalizations and CV death	Total number of (first and recurrent) HF hospitalizations and CV deaths
• To compare the effect of treatment with dapagliflozin vs. placebo on the KCCQ total symptom score for HF symptoms	Change from baseline measured at 8 months in the total symptom score of the KCCQ, a specific HF patient-reported outcome questionnaire
• To determine if dapagliflozin compared with placebo reduces the incidence of a composite endpoint of worsening renal function	Time to the first occurrence of any of the components of this composite: (1) ≥ 50% sustained decline in eGFR (2) Reaching end-stage renal disease • Sustained eGFR < 15 mL/min or, • Chronic dialysis treatment or, • Receiving a renal transplant (3) Renal death
• To determine whether dapagliflozin, compared with placebo, reduces the incidence of all-cause mortality.	Time to death from any cause.
Exploratory objectives	
• To compare the effect of dapagliflozin vs. placebo on an expanded composite outcome reflecting worsening of HF	Time to the first occurrence of any of the components of the expanded composite worsening HF outcome: (1) CV death (2) Hospitalization for HF (3) An urgent HF visit (4) Documented evidence of worsening HF symptoms/signs leading to initiation of a new treatment for HF sustained for at least 4 weeks or augmentation of existing oral therapy for HF (e.g. increase in dose of diuretic) sustained for at least 4 weeks
• To determine whether dapagliflozin compared with placebo will have effect on NYHA class	Change in NYHA class from baseline
• To determine whether dapagliflozin compared with placebo will reduce the incidence of diagnosis of AF in patients without history of AF at baseline	Proportion of patients without history of AF at baseline with a new diagnosis of AF during the study
• To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of hyper- and hypokalaemia	Time to the first occurrence of each of any of the following central lab levels of serum potassium: • > 6.0 mmol/L • > 5.5 mmol/L • < 3.5 mmol/L • < 3.0 mmol/L
• To determine whether dapagliflozin compared with placebo will affect the number of events of doubling of serum creatinine	Number of events with doubling of serum creatinine (compared with the most recent laboratory measurement)

Table 2 Continued

	Outcome measure
• To determine whether dapagliflozin compared with placebo will reduce the incidence of diagnosis of T2DM in patients without diabetes at baseline	Proportion of patients without T2DM at baseline with a new diagnosis of T2DM during the study
• To determine whether dapagliflozin compared with placebo will have effect on HbA1c in the T2DM subgroup	Changes in HbA1c from baseline
• To determine whether dapagliflozin compared with placebo will have an effect on systolic BP	Change in systolic BP from baseline
• To determine whether dapagliflozin compared with placebo will have an effect on body weight	Change in body weight from baseline
• To determine whether dapagliflozin compared with placebo will reduce the incidence of MI	Time to first fatal or non-fatal MI
• To determine whether dapagliflozin compared with placebo will reduce the incidence of any stroke (ischaemic, haemorrhagic, or undetermined)	Time to first fatal or non-fatal stroke of any cause
• To compare the effect of dapagliflozin vs. placebo on health status assessed by PGIC and PGIS questionnaires	Changes in health status measured by PGIC and PGIS
• To compare the effect of dapagliflozin vs. placebo on health status assessed by EQ-5D-5 L to support health economic analysis and health technology assessment	Changes in health status measured by EQ-5D-5 L
• To collect and analyse pharmacokinetic samples for dapagliflozin concentration	Results will be reported separately
• To assess cardiac structure and function with echocardiography at baseline and 8-month follow-up	Results will be reported separately
• To collect and store samples of plasma and serum for future exploratory biomarker research	Results will be reported separately
Safety objectives	
• To evaluate the safety and tolerability of dapagliflozin in this patient population	(1) Serious AEs (2) Discontinuation of IP due to AEs (3) Changes in clinical chemistry/haematology parameters (4) AEs of interest [volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis, AEs leading to amputation and AEs leading to a risk for lower limb amputations ('preceding events')]

AE, adverse event; AF, atrial fibrillation; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EQ-5D-5 L, EuroQol five-dimensional five-level questionnaire; HbA1c, glycated haemoglobin; HF, heart failure; IP, investigational product; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; NYHA, New York Heart Association; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; T2DM, type 2 diabetes mellitus.

The contribution of each component of the primary composite endpoint to the overall treatment effect will also be examined. Total (including recurrent) events will be analysed using a semi-parametric proportional rates model to test the treatment effect and to quantify the treatment difference (and other analytical methods may also be considered).

The primary efficacy endpoint and secondary efficacy endpoints will be examined in subgroups determined by baseline variables reflecting demography, geographical region, heart failure characteristics, diabetes status, kidney function, and additional co-morbidities, concomitant medications, and others.

Full details of all analyses will be provided in a statistical analysis plan completed before the end of the trial and unblinding of the results.

Data Monitoring Committee and interim analysis

A DMC will oversee safety in DAPA-HF and will undertake one planned interim efficacy analysis when 75% of the primary events are adjudicated (the DMC can also conduct an additional interim analysis, if deemed necessary). The significance level for final analysis will be determined by the Haybittle–Peto function based on the actual number and timing of interim analyses. The interim analysis will use a Haybittle–Peto rule with testing of the primary composite endpoint first at a one-sided alpha level of 0.001, and then, if superiority of dapagliflozin over placebo is achieved, testing of cardiovascular death at a one-sided level of 0.001.[18] If this is significant, the DMC will then evaluate the totality of the efficacy data and safety data, to determine whether the benefit is sufficiently

unequivocal and overwhelming to recommend early termination of the trial.

Ancillary studies

Serial echocardiography will be carried out in subset of patients, and baseline and follow-up blood samples are being collected for future measurement of biomarkers of interest.

Trial design and governance

DAPA-HF was designed jointly by AstraZeneca and the Executive Committee with review, refinement and final approval of the protocol by these parties and the country National Lead Investigators. The conduct of the trial is overseen by AstraZeneca and the Executive Committee working in conjunction with the National Lead Investigators. Membership of all committees is listed in the supplementary *Appendix S1*.

Discussion

Several aspects of the design of DAPA-HF merit discussion.

Study drug and dose

Dapagliflozin is a once daily, selective, competitive, reversible inhibitor of SGLT2 with similar *in vitro* potency to canagliflozin and empagliflozin.[19–23] It causes a dose-dependent increase in urinary glucose excretion with a near maximum effect at 10 mg daily and has no clinically important drug interactions. In common with other SGLT2 inhibitors, dapagliflozin causes small reductions in blood pressure and weight, a small initial increase in creatinine (although long-term treatment with SGLT2 inhibitors appears to be reno-protective in type 2 diabetes – see below), as well as an increase in the risk of genital mycotic infection.

Why an SGLT2 inhibitor in patients with heart failure with reduced ejection fraction?

As described in the introduction, canagliflozin, empagliflozin and dapagliflozin reduced the risk of heart failure hospitalization among patients with type 2 diabetes and cardiovascular disease/cardiovascular risk factors, with an apparently similar treatment effect in the small subgroup (~10–15%) of patients in each trial with baseline heart failure of undetermined phenotype, as illustrated in a meta-analysis of EMPA-REG OUTCOME, CANVAS and DECLARE–TIMI 58.[7–9,23] Examination of the event curves in these trials shows a reduction in heart failure hospitalization within weeks to months of randomization. The rapidity of onset of the benefit in the three trials is not consistent with traditional views about the mechanisms and time course of cardiovascular protection accruing with conventional glucose-lowering therapies.[9–12,24–27] Consequently, numerous additional beneficial mechanisms have been proposed, ranging from diuretic–haemodynamic actions, through effects on cardiac metabolism, adipokines, myocardial fibrosis, uric acid, myocyte ion channels and kidney function.[3–12,24–28] A recent mediation analysis suggested that the rise in haematocrit concentration following SGLT2 inhibitor treatment is related to benefit, supporting a diuretic action, and mathematical modelling suggests SGLT2 inhibitors may remove fluid preferentially from the interstitial space and cause less intravascular volume contraction.[27,28] Other data suggest SGLT2 inhibition can lead to ketogenesis and an increase in β-hydroxybutyrate, which provides an alternative and more efficient substrate for myocardial energy generation.

Key inclusion and exclusion criteria

Patients with HFrEF have both a high prevalence of dysglycaemia and high risk of adverse outcomes.[1,2,13,14] Those with persisting symptoms and elevation of natriuretic peptides despite conventional therapy are in particular need of additional treatments to reduce morbidity and mortality. The additional mechanisms of SGLT2 inhibitor action discussed above should be beneficial not only in patients with diabetes and pre-diabetes, but also in the minority who are euglycaemic.[9–12,24–28] Hence DAPA-HF includes patients irrespective of diabetes status and HbA1c concentration.

Because of the known reduction in blood pressure with SGLT2 inhibition and similar action of conventional therapies for HFrEF, entry systolic blood pressure must be 95 mmHg or above. Similarly, because of the small initial reduction in eGFR expected with dapagliflozin (and similar effects from conventional HFrEF therapies), as well as the diminished glycosuric action of SGLT2 inhibitors in patients with severe renal impairment, patients are only eligible for DAPA-HF if their eGFR is ≥ 30 mL/min/1.73 m^2.

Key aspects of trial design

A visit early (14 ± 3 days) after randomization is included to check renal function and blood pressure (as well as for symptoms of hypotension); this visit also allows for adjustment of background diuretic or other non-essential therapies (as reduction of doses of key life-saving HFrEF therapies is discouraged). Dose reduction to 5 mg of dapagliflozin or matching placebo (or discontinuation of study drug) is permitted, as needed at this visit or any subsequent visit; however, dose up-titration (or re-initiation) is encouraged thereafter in all cases, where possible.

Optional biomarker and echocardiography sub-studies are being conducted.

Choice of endpoints

The primary outcome in DAPA-HF is the composite of cardiovascular death, heart failure hospitalization, or an urgent heart failure visit. The third component is an addition to the composite most often used in recent HFrEF trials.[17,29,30] Its

inclusion reflects two key developments. Firstly, in many parts of the world (but particularly in the USA) considerable effort has been made to treat heart failure outside the usual in-patient ward setting.[31] Secondly, and more importantly, there is evidence that even exacerbations of heart failure occurring in the outpatient setting which necessitate treatment are associated with a poor subsequent prognosis — comparable to that of heart failure hospitalization.[32,33] Therefore, we believe that this broader composite endpoint more completely captures prognostically important events in the life course of patients with heart failure. These events are rigorously defined and adjudicated, and the components of the composite will be examined separately for consistency of treatment effect (and the conventional two-part composite will be the first secondary endpoint).[16] Specifically, the outpatient heart failure visits included in the primary outcome will only be those leading to an urgent, unplanned assessment by a physician (e.g. in an emergency department) and requiring treatment for worsening heart failure (other than just an increase in oral diuretics), in accordance with the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials.[16]

Two other key secondary endpoints also reflect new insights into the experience of patients with HFrEF. We will look at recurrent (i.e. first as well as subsequent) heart failure events, again better reflecting the overall burden of HFrEF on patients and health care systems.[34–37] In addition, we will examine the effect of dapagliflozin on a patient-reported outcome, i.e. the KCCQ. Use of the KCCQ has shown that many patients with HFrEF experience important deterioration in symptoms, function and health-related quality of life even in the short term, without experiencing hospital admission or death.[38,39] It has proven to be sensitive to therapeutic interventions and is prognostically important.[38–40]

Given the benefits of SGLT2 inhibitors on renal function in patients with type 2 diabetes and the prevalence and importance of renal impairment in HFrEF, we have also included assessment of progression of kidney disease as another pivotal secondary endpoint.[41,42]

Power calculations and statistical analysis

Key questions in designing DAPA-HF were what rate might be anticipated for the novel primary composite endpoint and what treatment effect size is clinically relevant and realistic? The event rate was estimated based on recent trials, particularly PARADIGM-HF.[32] A treatment effect size of 20% was chosen as clearly clinically relevant and reasonably conservative in light of the ~30% relative risk reduction in heart failure hospitalization observed in EMPA-REG OUTCOME, CANVAS and DECLARE–TIMI 58.[7–9] DAPA-HF is powered for this treatment effect on the primary composite outcome and not the individual components of the composite, particularly cardiovascular death. Furthermore, for nearly all other plausible scenarios, using the treatment effect sizes observed in DECLARE–TIMI 58 and in the SGLT2 inhibitor trial meta-analysis, DAPA-HF has ≥ 80% power to detect a benefit of dapagliflozin.[7–9]

Safety considerations

In view of the safety information collected in prior trials, including DECLARE–TIMI 58, adverse event reporting has been simplified (with agreement of the regulatory authorities) — only serious adverse events, adverse event leading to treatment discontinuation/interruption/dose reduction and adverse event of special interest are collected. Adverse events of interest (in light of the profile of dapagliflozin above and concerns with SGLT2 inhibitors and other diabetes drugs more generally) include volume depletion, renal dysfunction, major hypoglycaemic episodes, fractures, and diabetic ketoacidosis. There is also a regulatory requirement to document amputations as a result of observations in the canagliflozin development programme but not in EMPA-REG OUTCOME or DECLARE–TIMI 58.[43]

Current status

The first enrolment (Visit 1) took place 8 February 2017 and the first randomization (Visit 2) occurred 15 February 2017. Subsequent recruitment in DAPA-HF was rapid, and randomization was completed 17 August 2018.

Conclusions

DAPA-HF will determine the efficacy and safety of the SGLT2 inhibitor dapagliflozin added to conventional therapy in a broad spectrum of patients with HFrEF. A partner morbidity/mortality trial in patients with heart failure and preserved ejection fraction has recently commenced (DELIVER: Dapagliflozin Evaluation to improve the LIVEs of patients with pReserved ejection fraction heart failure; NCT03619213). DAPA-HF and DELIVER will determine whether SGLT2 inhibitors are a safe and effective treatment for patients with established and well characterised heart failure of both major phenotypes, distinct from the trials with these agents to date, which have largely examined the prevention of heart failure. Moreover, DAPA-HF and DELIVER will include a large proportion of patients without type 2 diabetes, also differing from EMPA-REG OUTCOME, CANVAS and DECLARE–TIMI 58, which included only patients with type 2 diabetes. DAPA-HF and DELIVER are complemented by a parallel trial in chronic kidney disease (DAPA-CKD: A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Disease; NCT03036150). Other trials with a different SGLT2 inhibitor, and a SGLT1/2 inhibitor, are also in progress (key features are summarised in *Table 3*).

Supplementary Information

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

Table S1. Study plan and procedures.

Appendix S1. Supplementary details on DAPA-HF.

Table 3 Key features of sodium–glucose co-transporter inhibitor trials in heart failure[a]

	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	DELIVER	SOLOIST-WHF
NCT[a]	03036124	03057977	03057951	03619213	03521934
Patients, *n*	4695	2850	6000	4700	4000
Key inclusion criteria					
NYHA class	II–IV	II–IV	II–IV	II–IV	Hospitalized HF or urgent HF visit
LVEF	≤ 40%	≤ 40%	> 40%	> 40%	Any LVEF
Other	NT-proBNP ≥ 600 pg/mL (≥ 900 pg/mL if AF/F) OR if HF hospitalization ≤ 12 months NT-proBNP ≥ 400 pg/mL (≥ 900 pg/mL)	LVEF ≥ 36 ≤ 40% NT-proBNP ≥ 2500 pg/mL (≥ 5000 if AF/F) LVEF ≥ 31 ≤ 35% NT-proBNP ≥ 1000 pg/mL (≥ 2000 pg/mL) LVEF ≤ 30% NT-proBNP ≥ 600 pg/mL (≥ 1200 pg/mL) OR HF hospitalization ≤ 12 months NT-proBNP ≥ 600 pg/mL (≥ 1200 pg/mL if atrial fibrillation)	Structural heart disease AND NT-proBNP > 300 pg/mL (> 900 pg/mL if AF/F) OR HF hospitalization ≤ 12 months	Structural heart disease AND NT-proBNP ≥ 300 (≥ 600 if AF/F)	BNP ≥ 150 pg/mL (≥ 450 pg/mL if AF/F) OR NT-proBNP ≥ 600 pg/mL (≥ 1800 pg/mL)
Age	≥ 18	≥ 18	≥ 18	≥ 40	18-85
Diabetes status	Diabetes/no diabetes	Diabetes/no diabetes	Diabetes/no diabetes	Diabetes/no diabetes	Diabetes only
In-patient/outpatient	Outpatient	Outpatient	Outpatient	Inpatient/outpatient	Inpatient/outpatient
Key exclusion criteria	SBP < 95 mmHg eGFR < 30 mL/min/1.73 m^2	SBP < 100 mmHg eGFR < 20 mL/min/1.73 m^2	SBP <100 mmHg eGFR <20 mL/min/1.73m^2	SBP < 95 mmHg eGFR < 25 mL/min/1.73 m^2	SBP < 100 mmHg eGFR < 30 mL/min/1.73 m^2
Treatment	Placebo dapagliflozin 10 mg once daily	Placebo empagliflozin 10 mg once daily	Placebo empagliflozin 10 mg once daily	Placebo dapagliflozin 10 mg once daily	Placebo sotagliflozin 400 mg once daily
Primary endpoint(s)	CV death, HF hospitalization or urgent HF visit	CV death or HF hospitalization	CV death or HF hospitalization	CV death, HF hospitalization or urgent HF visit	1. CV death or HF hospitalization (patients with LVEF < 50%) 2. CV death or HF hospitalization (all patients)

AF/F, atrial fibrillation/flutter; BNP, B-type natriuretic peptide; CV, cardiovascular; DAPA-HF, Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to improve the LIVEs of patients with pReserved ejection fraction heart failure; eGFR, estimated glomerular filtration rate; EMPEROR, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt failure; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SOLOIST-WHF, SOtagLiflozin on clinical outcomes in hemOdynamIcally STable patients with type 2 diabetes post Worsening Heart Failure.

[a]Data from ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home, accessed 9 October 2018) and the World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx, accessed 9 October 2018).

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