Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON45523

Source
ToetsingOnline

Brief title
DAPA HF

Condition

- Heart failures

Synonym
Hartfailure, reduced ejection fraction

Research involving

Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca BV

Intervention

Keyword: Chronic Heart Failure, Dapagliflozin, Prevention, Reduced Ejection Fraction

Outcome measures

Primary outcome

The main objective of the study is to investigate whether dapagliflozin, compared with placebo, reduces the incidence of CV death or hospitalization for HF or equivalent event (ie an urgent HF visit) when added to background standard of care treatment.

Secondary outcome

The rationale for including CV death or hospitalization for HF, but excluding non-hospitalized urgent HF visits, is that this is the more conventional composite HF endpoint, may be regarded as including *harder* outcomes and will allow direct comparison with other HF trials.

The rationale for including total number of hospitalizations (including re-hospitalizations) for HF is to capture the impact of recurrent non-fatal HF hospitalizations. Taken together with CV death, these events give a better estimate of the full burden of HF on patients and healthcare systems than time-to-first event analysis.

The rationale for the secondary renal composite EP is that renal dysfunction is very common in heart failure, may lead to discontinuation of disease-modifying therapies and is associated with poor outcomes.

All-cause mortality will be assessed as a secondary endpoint because it is important to evaluate the effect of dapagliflozin on non-cardiovascular, as well as cardiovascular, mortality and hence overall mortality.

Study description

Background summary

Despite advances in management and treatment of chronic heart failure (HF) with reduced ejection fraction (HFrEF), HF continues to be a major cause of mortality, initial and recurrent hospitalizations, and suboptimal quality of life.
The prevalence and incidence of HF continues to increase globally. An estimated 38 million people are affected by HF worldwide with over 1 million hospitalizations annually in the United States and Europe. The annual global economic burden in 2012 was estimated to be $108 billion and is projected to increase dramatically as the population ages.
The current treatment paradigm for HF involves the simultaneous targeting of multiple pathways including the renin-angiotensin-aldosterone axis (RAA), the autonomic system, and symptomatic treatment with diuretics.

Recently, in patients with type 2 diabetes (T2D) and high cardiovascular (CV) risk, the sodium glucose co-transporter 2 (SGLT2) inhibitor, empagliflozin (JARDIANCE*), demonstrated a marked reduction in CV mortality (38% relative risk reduction [RRR]), allcause mortality (32% RRR) as well as 35% RRR in hospitalization from HF compared with placebo when added to background standard of care treatment.
In a secondary analysis of HF outcomes, empagliflozin reduced the risk of hospitalization for HF or cardiovascular death by 28 % in patients with HF at baseline.

Dapagliflozin (Forxiga*/Farxiga*) is a highly selective and reversible inhibitor of human renal SGLT2, the major transporter responsible for glucose reabsorption in the kidney. Dapagliflozin*s mechanism of action results in a

direct and insulin-independent elimination of glucose by the kidneys. In addition to the improved glycaemic control, the persistent loss of glucose with associated calories in the urine, results in a consistent and maintained reduction of the total body weight. Further, dapagliflozin induces a diuresis, natriuresis and a decrease in blood pressure without a concomitant increase in heart rate.
Possible mechanisms for SGLT2 inhibitor benefit in patients with heart failure could include osmotic diuresis and reductions in arterial stiffness, weight, blood pressure, serum uric acid and albuminuria.
Data on the effect of SGLT2 inhibition in patients without diabetes is limited. However, dapagliflozin has safely been administered in healthy volunteers over a broad dose range.
Dapagliflozin has been investigated in a thorough T2D clinical development program. In addition, the trial DECLARE-TIMI58 (D1693C00001) is ongoing and includes >17,000 T2D patients with elevated CV risk to evaluate dapagliflozin 10 mg on CV outcome.

The aim of the proposed study is to investigate the efficacy and safety of dapagliflozin in patients with an established diagnosis of HFrEF (with or without T2D) where the prevalence and unmet needs for reducing CV mortality and heart failure events as well as improving symptoms remain high.

Study objective

The aim of the proposed study is to investigate the efficacy and safety of dapagliflozin in patients with an established diagnosis of HFrEF (with or without T2D) where the prevalence and unmet needs for reducing CV mortality and heart failure events as well as improving symptoms remain high.

Study design

This is a randomized, double-blind, parallel-group, multicentre phase 3 study.

Intervention

Patients will use either dapagliflozin 10 mg or placebo once daily in addition to their standard of care hart failure medication.

Study burden and risks

The subjects visit the hospital at least 11 times over 15 months (depending on when the subject is enrolled in the study). Median duration of the study is 33 months. The subjects are asked to keep in touch throughout the duration of the study with the study doctor.
During the study several times a physical examination will be done, and blood samples will be taken. Blood sampling may cause some discomfort. In women of

childbearing potential a pregnancy test is performed. The use of study medication can cause side effects. The research is carried out in the expectation that dapagliflozin may prevent the occurrence of cardiovascular death and hospitalization for heart failure. In the future, the information collected in this study will ensure that patients are better treated for chronic heart failure with reduced ejectionfraction.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of signed informed consent prior to any study specific procedures
2. Male or female, aged *18 years at the time of consent
3. Established documented diagnosis of symptomatic HFrEF
4. LVEF*40% within the last 12 months prior to enrolment (Visit 1)

5. NT-proBNP >600 pg/ml
6. Patients should receive background standard of care for HFrEF
7. eGFR *30 ml/min/1.73 m2 at visit 1

Exclusion criteria

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 (T1D)
3. Symptomatic hypotension or systolic BP <95 mmHg on 2 consecutive measurements
4. Current acute decompensated HF or hospitalization due to decompensated HF <4 weeks prior to enrolment
5. MI, unstable angina, stroke or transient ischemic attack (TIA) within 12 weeks prior to enrolment
6. Coronary revascularization 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 cardiac CRT within 12 weeks prior to enrolment or intent to implant a CRT device
8. Previous cardiac transplantation or implantation of a ventricular assistance device (VAD) or similar device, or implantation expected after randomization

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2017

Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Farxiga
Generic name:	dapagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-12-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-02-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003897-41-NL
CCMO	NL59837.091.16

Study results