In-hospital initiation of empagliflozin for the treatment of new-onset acute heart failure regardless of ejection fraction: A Pilot Study

Draft Protocol v.1.2

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Protocol Summary	
Design:	Prospective, single-centre, non-randomized, open-label
Target Enrolment:	100 subjects
Study drug:	Empagliflozin 10mg oral tablet daily
Study location	The Chinese University of Hong Kong/ Prince of Wales Hospital.
Study duration	90 days
Inclusion Criteria	1. Subject age >18 hospitalized for primary diagnosis of acute HF 2. Dyspnoea (exertional or at rest) and 2 of the following signs: - Congestion on chest X-ray - Rales on chest auscultation - Clinically relevant oedema (e.g. ≥1+ on a 0 to 3+ scale) - Elevated jugular venous pressure 3. Stabilization criteria (while in the hospital): - SBP ≥100mmHg and no symptoms of hypotension in preceding 24 hours - No increase in i.v. diuretic dose for 24 h prior - No i.v. vasodilators including nitrates within the last 6 h prior - No i.v. inotropic drugs for 24 h prior 4. NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL. Patients with AF: NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL. Measured during index hospitalization 5. Heart failure hospitalization that requires the treatment of a minimum single dose of 40 mg of i.v. furosemide (or equivalent i.v loop diurectics defined as 20 mg of torsemind or 1mg of bumetanide)
Exclusion Criteria	1. Cardiogenic shock 2. Documented history of HF with previous HF admission 3. Current hospitalization for acute HF primarily triggered by pulmonary embolism, cerebrovascular accident, or acute MI 4. Interventions in past 30 days prior or planned during the study: - Major cardiac surgery, or Tran Aortic Valve Implantation, or Percutaneous Coronary Intervention, or MitraClip - Implantation of cardiac resynchronization therapy device - Cardiac mechanical support implantation newn 4. Current or expected heart transplant, LVAD, IABP, or patients with planned inotropic support in an outpatient setting 5. Haemodynamically severe uncorrected primary cardiac valvular disease planned for surgery or intervention during the course of the study. 6. eGFR <20 mL/min/1.73m2 as measured during index hospitalization (latest measurement before randomization) or patients requiring dialysis 7. Type 1 diabetes mellitus 8. History of ketoacidosis, including diabetic ketoacidosis

	9. Current or prior treatment with SGLT2 inhibitors in 90 days prior to enrolment
Primary Clinical Outcome	Clinical benefit, a composite of all cause mortality, number of heart failure events (including hospitalization for HFs, urgent heart failure visits and unplanned outpatient visits), time to first heart failure event,change from baseline in 6-minute walk distance (6MWD) and change from baseline in KCCQ-TSS after 90 days of treatment.
Secondary Outcomes	• Change from baseline in KCCQ-TSS after 90 days of treatment. • Change from baseline in log-transformed NT-proBNP level over 90 days of treatment. • Change in NYHA class • Days alive and out of hospital from study drug initiation until 90 days after initial hospital discharge. • Days alive and out of hospital from study drug initiation until 90 days after randomization. • Time to first occurrence of cardiovascular death or heart failure event until end of trial visit. • Occurrence of HHF until 90 days after initial hospital discharge. • Occurrence of chronic dialysis or renal transplant or sustained reduction of ≥40% eGFR, or - Sustained eGFR <15mL/min/1.73m2 for patients with baseline eGFR ≥30 mL/min/1.73m2 - Sustained eGFR <10mL/min/1.73m2 for patients with baseline eGFR <30 mL/min/1.73m2. • Weight loss per mean daily loop diuretic dose after 15, 30, 60 and 90 days of treatment. • Change from baseline in 6MWD at 90 days. • Cost effectiveness of early initiation of empagliflozin for heart failure events avoided and quality-of-life years (QALY) gained.

1. Introduction

Heart failure (HF) is one of the most important reasons for hospital admission and is associated with high mortality and morbidity (1). After discharge, up to 40% of patients are readmitted within 6 months and 1-year post-discharge mortality is high (2-4). The cost burden of treating patients with HF is high and ~80% of healthcare costs are related to hospital admissions (5).

Sodium-glucose cotransporter-2 (SGLT2) inhibitor is considered one of the four foundational therapies (ACE-I or ARNI, beta-blockers, MRA, and SGLT2 inhibitors) for HFrEF (6) However, guidelines do not specify the sequence and the timing of which therapy to be commenced. In particular, empagliflozin has been shown in randomized controlled trials to reduce the combined risk of cardiovascular death or HF hospitalization in HF patients with both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), respectively, regardless of the presence or absence of diabetes in the EMPEROR-Reduced and EMPEROR-Preserved trials (7, 8). Empagliflozin is the first medical therapy with proven benefits for patients with HFpEF which accounts for approximately 50% of heart failure cases in Hong Kong (9). In September 2021, the FDA granted breakthrough therapy designation for empagliflozin as an investigational treatment for adults with HFpEF. Furthermore,

the benefits of empagliflozin are seen early in the treatment course, and is maintained during subsequent follow-ups.

The EMPULSE study which was recently presented at the 2021 American Heart Association Annual scientific session, demonstrated in-hospital initiation of empagliflozin in patients with acute heart failure regardless of left ventricular ejection fraction (LVEF) to be safe and effective (10). In this trial, 530 patients with acute HF were randomized 1:1 to 10 mg of empagliflozin or placebo once stabilized in the hospital (median 3 days) and followed-up for 90 days for the primary composite endpoint of time to death, frequency of HF events, time to first HF event, and change in quality of life score from baseline. About one-third (33%) patients randomized had new-onset acute HF, two-thirds (69.1%) of patients had LVEFs <40%, and29% randomized to empagliflozin and 35% of those randomized to placebo had LVEF >40%. In terms of safety, rates of serious adverse events and any adverse events were both higher in the placebo arm. Acute renal failure, occurred in 7.7% of patients in the SGLT2 inhibitor arm compared with 12.1% of placebo-treated patients. For the primary composite endpoint, patients treated with empagliflozin were 36% more likely to experience a clinical benefit in the first 90 days (stratified win ratio 1.36; 95% CI 1.09-1.68). all-cause mortality (4.2% vs 8.3%) and heart failure events (10.6% vs 14.7%) were numerically lower in the empagliflozin arm. Improvement in quality of life was a key driver of difference in the primary endpoint: placebo-adjusted mean difference at 90 days was 4.5 points favouring empagliflozin. Other larger trials of treatment with SGLT2 inhibitor in acute heart HF are underway, including the DICTATE-AHF and DAPA ACT HF-TIMI 68 trials, both with dapagliflozin.

Current guidelines recommend in-hospital echocardiogram in the clinical setting of new-onset or decompensated (6). However, echocardiogram is often delayed months after discharge or not performed at all under Hong Kong public hospital setting. As a result, initiation of guideline recommended therapies like ARB/ARNI/MRA/BB may be delayed for HFrEF patients awaiting echocardiogram or unnecessary for HFpEF patients. Out of the 4 guidelines recommended treatment for HF, only empagliflozin has proven benefits for the treatment of both HFrEF and HFpEF. Given that empagliflozin is well tolerated and its benefits are seen early, it may be reasonable to initiate empagliflozin early during index hospitalization even before the assessment of LVEF is available. However, costs remains a major barrier for early initiation of SGLT2-inhibitor.

The timing of SGLT inhibitors initiation in the treatment of acute HF is not established. In particular, new-onset acute HF is a group which is understudied in the major trials to date. This study aims to evaluate the efficacy and safety of in-hospital initiation of empagliflozin in patients hospitalized for new onset acute HF, regardless of LVEF for up to 90 days of follow-up.

2. Methods

Study design: This is an investigator-initiated, prospective, single-centre, non-randomized open label study that evaluates the efficacy and safety of initiating empagliflozin during index hospitalization for acute heart failure regardless of LVEF.

Patient population: The study will recruit up to 200 patients.

Inclusion criteria:

1. Subject age >18 hospitalized for primary diagnosis of acute HF

2. Dyspnoea (exertional or at rest) and 2 of the following signs:

- Congestion on chest X-ray

- Rales on chest auscultation

- Clinically relevant oedema (e.g. ≥1+ on a 0 to 3+ scale)

- Elevated jugular venous pressure

3. Stabilization criteria (while in the hospital):

- SBP ≥100mmHg and no symptoms of hypotension in the preceding 24 hours

- No increase in i.v. diuretic dose for 24 h prior

- No i.v. vasodilators including nitrates within the last 24 h prior

- No i.v. inotropic drugs for 24 h prior

4. NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL. (Patients with AF: NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL. Measured during index hospitalization

5. Heart failure hospitalization that requires the treatment of a minimum single dose of 40 mg of i.v. furosemide(or Equivalent i.v loop diurectics defined as 20 mg of torsemind or 1mg of bumetanide)

Exclusion criteria:

1. Cardiogenic shock

2. Documented history of HF with previous HF admission

2. Current hospitalization for acute HF primarily triggered by pulmonary embolism, cerebrovascular accident, or acute MI

3. Interventions in the past 30 days prior or planned during the study:

- Major cardiac surgery, or TAVI, or PCI, or MitraClip

- Implantation of cardiac resynchronization therapy device

- Cardiac mechanical support implantation

4. Current or expected heart transplant, LVAD, IABP, or patients with planned inotropic support in an outpatient setting

5. Haemodynamically severe uncorrected primary cardiac valvular disease planned for surgery or intervention during the course of the study

6. eGFR <20 mL/min/1.73m2 as measured during index hospitalization (latest measurement before randomization) or patients requiring dialysis

7. Type 1 diabetes mellitus

8. History of ketoacidosis, including diabetic ketoacidosis

9. Current or prior treatment with SGLT2 inhibitors in the 90 days prior to enrolment.

Study locations: This study will be primarily conducted at The Chinese University of Hong Kong/ Prince of Wales Hospital.

The study drug:

Empagliflozin 10mg daily (open label)

Study procedure:

Patients who meet inclusion and none of the exclusion criteria will be enrolled during hospitalization after stabilization. Patients should receive usual care per current relevant local and regional guidelines, as defined by their clinicians. Patients can be enrolled regardless of T2D status or ejection fraction. Enrolment is stratified according to patients with new-onset HF and worsening chronic HF. Informed consent will be is signed before study enrolment. Baseline KCCQ-TSS and baseline 6MWT will performed prior to study drug initiation and repeated at 30 and 90 days. Echocardiogram is not mandatory but permitted before subjects enrolment. Follow-up will be at 30 days, 60 days and 90 days.

Study drug will be dispensed by the research pharmacy provided by the study team (free of charge to the patient) as an open-label treatment.

Patients who meet inclusion and none of the exclusion criteria but declined study medication will be invited to be followed-up in a registry as reference group. These patients will follow the same baseline and follow-up assessment protocol (minus the study drug).

Study Endpoints:

The primary outcome is clinical benefit at 90 days defined as a composite of all course mortality, number of heart failure events (including hospitalization for HFs, urgent heart failure visits and unplanned outpatient visits), time to first heart failure event and change in KCCQ-TSS from baseline.

Secondary outcomes include improvement in KCCQ-TSS of ≥10 points after 90 days of treatment, change from baseline in log-transformed NT-proBNP levels over 90 days, days alive and out of hospital until 90 days, time to first occurrence of CV death or HFE until end of trial period, and change in 6-minute walk test and change in KCCQ-TSS between baseline and 90 days. Secondary safety endpoints include Occurrence of chronic dialysis or renal transplant or sustained reduction of ≥40% eGFR, or Sustained eGFR <15mL/min/1.73m2 for patients with baseline eGFR ≥30 mL/min/1.73m2, or Sustained eGFR <10mL/min/1.73m2 for patients with baseline eGFR <30 mL/min/1.73m2.

Statistical analysis: Categorical variables will be reported as percentages and counts, and continuous variables will be reported as means ± standard deviations. Data analysis will be performed using STATA version 15 software (College Station, TX, USA).

Cost-effectiveness analysis will be performed to calculate incremental-cost effective ratio (ICER) for HFE avoided and QALY gained. Events of patients enrolled in the registry will be used as reference comparator. Costs will be based on Hospital Authority gazette prices for hospital admissions and visits.

Table 1. Data to be collected in this study

	Enrollment	30 days	60 days	90 days
Patient Informed Consent	x			
History including baseline characteristics	x			
Baseline co-morbidities:	x			

Baseline and in-hospital medications	x			
Physical examination include body weight	x	x	x	x
Laboratory test including NT-proBNP or BNP within 72hr of index admission, eGFR	x	x	x	x
Clinical events: all cause mortality, cardiovascular-associated death, A&E visit for acute heart failure, unplanned outpatient clinic visit, re-admission for heart failure	x	x	x	x
6MWD	x			x
Symptoms QOL assessment: NYHA class, KCCQ-TSS	x			x
Prescription records of SGLT2 inhibitors	x	x	x	x
Adverse drug effects	x	x	x	x

3. CONFIDENTIALITY OF DATA

Paper and electronic dataset that contain patient's identity and confidential information will be stored in locked cabinets or password protected computers only accessible by the appointed research staff to prevent unauthorized access to data. The Investigator/Site will archive and retain all documents pertaining to the Study as per the applicable regulatory record retention requirements for a period of three (3) years after completion or early termination of the Study. The data can be destroyed after completion of storage period as agreed by principal investigator.

4. Potential Harm

The EMPULSE study has shown overall safety of emplagliflozin was consistent with previous findings, confirming the established safety profile of empagliflozin in patients with heart failure. Empagliflozin was well tolerated with fewer serious adverse events than was placebo (32.3% vs 43.6%). The incidences of worsening renal function and volume depletion were not common and were balanced between treatment groups. No ketoacidosis occurred in the empagliflozin groups.

5. ETHICS

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan. The application for research ethics will be submitted to the Joint CUHK-NTEC Clinical Research Ethics Committee. This study will be conducted in accordance with the principles of the Declaration of Helsinki.

Study drug will be provided by the study team (free of charge to the patient) as an open-label treatment for 90 days.

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