ISRCTN17064177 https://doi.org/10.1186/ISRCTN17064177

Adding dapagliflozin (SGLT2i) to intravenous loop diuretic therapy for management of acute and residual congestion in hospitalized patients with acute heart failure

Submission date
02/03/2025

Recruitment status
No longer recruiting

Registration date
03/03/2025

Overall study status
Completed

Last Edited
22/07/2025

Condition category
Circulatory System

[_] Prospectively registered
[_] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Congestion is the primary cause of hospitalization and readmission in heart failure patients, strongly correlating with adverse outcomes. Thus, achieving effective decongestion and preventing residual congestion through early administration of intravenous loop diuretics is considered first-line therapy for acute heart failure (AHF). The secondary goal during an AHF episode is the early implementation of optimal guideline-directed medical therapy (GDMT) during hospitalization. While loop diuretics substantially improve symptoms, they have failed to enhance short- and long-term outcomes in AHF.
Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have recently become a cornerstone in treating chronic heart failure, but their mechanisms of action are not entirely understood. One proposed mechanism is their direct effect on the kidneys, promoting natriuresis and water excretion. This has led to studies hypothesizing the potential use of SGLT2i in AHF patients with hypervolemia, aiming to enhance diuresis for decongestion. Despite the clear recommendation of AHF guidelines for early introduction of SGLT2i during hospitalization to optimize GDMT and improve prognosis, concerns remain regarding the risks of acute kidney injury and ketoacidosis during the acute decompensation phase. This uncertainty, combined with insufficient data about the efficacy of SGLT2i in alleviating congestion in AHF, requires further investigation.
We conducted a randomized controlled clinical trial aimed to assess the efficacy of congestion relief, and safety associated with adding SGLT2i (namely, dapagliflozin) to intravenous loop diuretics within 24 hours of hospital presentation in AHF patients.

Who can participate?
Adults (male or female) aged over 18 years, admitted for an episode of acute heart failure, regardless of ejection fraction or diabetes status. Inclusion criteria comprised: NT-proBNP ≥ 400 pg/mL, eGFR > 25 mL/min/1.73 m², and clinical and paraclinical signs of congestion.

What does the study involve?
An open-label randomized controlled clinical trial was conducted. Patients were randomly

assigned to two groups: (A) to receive dapagliflozin 10 mg once daily in addition to a structured intravenous furosemide therapy within 24 hours from admission; (B) to receive structured intravenous furosemide therapy alone.
At baseline (i.e., hospital admission), each patient was assessed for the parameters regarding congestion and medical history; clinical, laboratory and echocardiographic investigations were also performed.
Investigations regarding treatment safety were performed during hospital stay: change in eGFR, change in serum creatinine, change in serum Na, change in serum K, change in systolic blood pressure, fractional excretion of Na, three-day mean diuresis, urinary Na levels.
At hospital discharge, each patient was assessed for the parameters regarding congestion relief (weight change, change in EVEREST score, change in B-lines, change in inferior vena cava diameter, change in N-terminal pro–B-type natriuretic peptide levels), change in CD146 levels (cluster of differentiation 146, an indicator of biomarker associated with congestion and cardiovascular diseases), and total furosemide per episode-of-hospitalization.
One-month post-discharge, echo parameters of heart failure function were registered, and blood samples were taken for CD146 levels determination.

What are the possible benefits and risks of participating?
The benefits of participating in this trial are: all patients receive standard of care and are closely monitored by a highly professional medical team in a tertiary hospital affiliated to a university; half of the participants (randomized) receive a novel treatment which might have benefits in terms of congestion relief. All participants contribute to helping scientists understand the condition and advance treatment for acute heart failure.
There are no foreseen medical risks associated with the intervention.

Where is the study run from?
Vasile Goldis Western University of Arad (Romania)

When is the study starting and how long is it expected to run for?
May 2021 to September 2024

Who is funding the study?
Vasile Goldis Western University of Arad (Romania)

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Arad County Clinical Emergency Hospital, 41/21.08.2021

Study information

Scientific Title
Adding Sodium Glucose Cotransporter-2 inhibitor dapagliflozin to intravenous loop diuretic therapy for management of acute and residual congestion in hospitalized patients with acute heart failure: a single-center, open-label, randomized controlled clinical trial

Acronym
ENDORSE-HF

Study objectives
Adding SGLT2i (namely, dapagliflozin) to intravenous loop diuretics within 24 hours of hospital presentation in AHF patients would lead to improved congestion relief, with no safety concerns in regard to changes in renal function and serum electrolyte abnormalities (such as hypo /hyperkalemia or hyponatremia).

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 21/08/2021, Ethics Commission for Clinical Trials, Arad County Clinical Emergency Hospital (Andrényi Károly 24, Arad, 310037, Romania; +40 257 220 000; secretariat@scjarad.ro), ref: 41/21.08.2021

Study design
Prospective interventional single-center open-label randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital, University/medical school/dental school

Study type(s)
Treatment

Participant information sheet
See outputs table

Health condition(s) or problem(s) studied
Treatment in hospitalized patients with acute heart failure.

Interventions
Patients were randomly assigned to two groups: (A) to receive dapagliflozin 10 mg once daily in addition to a structured intravenous furosemide therapy within 24 hours from admission; (B) to receive structured intravenous furosemide therapy alone.
At baseline, each patient was assessed for the following parameters: natriuretic peptide and CD146 serum concentration, standing weight, EVEREST congestion score, lung ultrasound measurement of B-lines, and inferior vena cava diameter. The EVEREST composite congestion score (with a range from 0 to 18) is based on the assessment of simple clinical parameters including dyspnoea, orthopnoea, jugular vein distention, rales, edema, and fatigue; it was introduced by the investigators in the EVEREST trial.
Lung ultrasound was performed on a Siemens Acuson SC2000 ultrasound machine using a phased array transducer and an eight-zone protocol (four zones on each hemidiaphragm) to assess lung congestion (the sum of B-lines across all zones) at admission and discharge. For the inferior vena cava, the maximum diameter was measured.
Trans-thoracic echocardiography was conducted for each patient upon admission and at a one-month follow-up. Three patients died before the one-month planned echocardiography. Structural and functional parameters assessed included: left ventricular end-diastolic volume (EDV), systolic pulmonary artery pressure (SPAP), global longitudinal strain (GLS), right ventricular strain, and ejection fraction (by 3D echocardiography). Two independent investigators analyzed the echocardiographic data.
Serum cluster of differentiation 146 (CD146) was determined for each patient at admission, discharge, and one month post-discharge. For CD146 analysis, blood samples were collected into serum-separating tubes, centrifuged, and stored at -80 °C for subsequent analysis. Serum CD146 levels were measured using an optimized enzyme-linked immunosorbent assay kit (Human MCAM/CD146 ELISA kit PicoKine - Boster Biological Technology, Pleasanton CA, USA #EK1675) and analyzed on a Secan Sunrise microplate reader (Texan Austria GmbH, Untersbergstr. 1A, A-5082 Grodig, Austria). Calibration and standardization of the assay were conducted following the manufacturer's protocol.
Structured intravenous furosemide therapy was utilized in both study arms. For loop diuretic-naive patients, dosages of 20-40 mg furosemide intravenously were administered upon admission, with a similar dose given at 12 hours, targeting a 24-hour urine output of 3-4 L (and doubling the loop diuretic dose if congestion persisted). For patients already on oral diuretic

therapy, the initial dose doubled their home 24-hour oral dose, and was subsequently administered every 12 hours (with dose doubling until the maximum loop diuretic dose was reached if congestion persisted and urine output remained < 3-4 L after 24 hours). A 24-hour urine collection was performed 24 hours post-admission to measure natriuresis and urine output induced by intravenous furosemide alone or in combination with SGLT2i.
At discharge, patients underwent evaluations for natriuretic peptide and CD146 serum concentrations, weight change, congestion EVEREST score, and ultrasound assessments of lung B-lines and inferior vena cava diameter. One month post-discharge, patients were re-evaluated for any adverse events and underwent echocardiography to measure changes in ejection fraction, EDV, and SPAP. Additionally, a blood sample was taken to measure plasma CD146 levels at one month.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Dapagliflozin

Primary outcome measure
1. Congestion relief: changes in congestion markers from baseline (at hospital admission) to discharge: weight change, EVEREST score, lung ultrasound B-lines, inferior vena cava echo measurement, NT-proBNP, and cluster of differentiation 146 (CD146).
2. Safety: changes in renal function (such as worsening renal function, and serum electrolyte abnormalities, including hypo/hyperkalemia or hyponatremia), and any adverse events documented daily from admission until discharge. Worsening renal function is defined as any increase in creatinine level > 0.3 mg/dL from baseline, hypokalemia (< 3.5 mmol/L), hyperkalemia (> 5.5 mmol/L), or hyponatremia (< 130 mmol/L).

Secondary outcome measures
1. Diuresis and natriuresis (mean diuresis over three days, 24-hour urinary sodium output, and total furosemide dose per hospitalization);
2. Hospitalization duration, 30-day heart failure readmissions, and mortality measured using patient records;
3. One-month echocardiographic changes in heart failure function (ejection fraction, left-ventricular end-diastolic volume, systolic pulmonary artery pressure; global longitudinal strain and right ventricle strain).

Overall study start date
01/05/2021

Completion date
30/09/2024

Eligibility

Key inclusion criteria
1. Adults (male or female) aged over 18 years
2. Admitted for an episode of acute heart failure, regardless of ejection fraction or diabetes status. NT-proBNP ≥ 400 pg/mL
3. eGFR > 25 mL/min/1.73 m²
4. Clinical and paraclinical signs of congestion

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
100

Total final enrolment
100

Key exclusion criteria
1. Infections
2. Active cancer
3. Severe aortic stenosis
4. Exacerbated COPD
5. Pulmonary embolism
6. Acute coronary syndrome

Date of first enrolment
01/10/2021

Date of final enrolment
14/06/2024

Locations

Countries of recruitment
Romania

Study participating centre
Arad County Clinical Emergency Hospital
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Funder(s)

Funder type
University/education

Funder Name
"Vasile Goldis" Western University

Results and Publications

Publication and dissemination plan
Results article in a peer-reviewed medical journal.
PhD thesis

Intention to publish date

31/12/2025

Individual participant data (IPD) sharing plan

Available on request – upon reasonable motivation and institutional contact information, such as individual patient data meta-analysis (IPD meta-analysis)
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IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	English	30/09/2021	03/03/2025	No	Yes
Participant information sheet	Romanian	30/09/2021	03/03/2025	No	Yes
Statistical Analysis Plan			03/03/2025	No	No
Results article		26/06/2025	22/07/2025	Yes	No