

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

<b>Submission date</b> 02/03/2025	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 03/03/2025	<b>Overall study status</b> Completed	<input checked="" type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 22/07/2025	<b>Condition category</b> Circulatory System	<input type="checkbox"/> 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  $\geq$  400 pg/mL, eGFR  $>$  25 mL/min/1.73 m<sup>2</sup>, 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)

Who is the main contact?

dlungeanu@umft.ro

lala.radu@uvvg.ro

pop-moldovan.adina@uvvg.ro

hoza-mocan.daniela@student.uvvg.ro

## Contact information

### Type(s)

Principal investigator

### Contact name

Dr Radu Lala

### ORCID ID

<https://orcid.org/0000-0003-0063-8410>

**Contact details**

Faculty of Medicine, "Vasile Goldis" Western University  
Liviu Rebreanu 86  
Arad  
Romania  
310025  
+40 740147286  
lala.radu@uvvg.ro

**Type(s)**

Scientific

**Contact name**

Dr Diana Lungeanu

**ORCID ID**

<https://orcid.org/0000-0002-0274-1377>

**Contact details**

"Victor Babes" University of Medicine and Pharmacy  
Piata E. Murgu 2  
Timisoara  
Romania  
300041  
+40 722488775  
dlungeanu@umft.ro

**Type(s)**

Public

**Contact name**

Dr Adina Pop-Moldovan

**ORCID ID**

<https://orcid.org/0000-0002-6971-2669>

**Contact details**

Arad County Clinical Emergency Hospital  
Andrényi Károly 24  
Arad  
Romania  
310037  
+40 257220000  
pop-moldovan.adina@uvvg.ro

**Type(s)**

Public

**Contact name**

Dr Daniela Mocan

**ORCID ID**

<https://orcid.org/0009-0002-4849-8963>

**Contact details**

Arad County Clinical Emergency Hospital, Andrényi Károly 2 4

Arad

Romania

310037

+40 257220000

hoza-mocan.daniela@student.uvvg.ro

**Additional identifiers****Clinical Trials Information System (CTIS)**

Nil known

**ClinicalTrials.gov (NCT)**

Nil known

**Protocol serial number**

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

## Study type(s)

Treatment

## 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-naïve 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

**Phase**

Phase II/III

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

Dapagliflozin

**Primary outcome(s)**

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).

**Key secondary outcome(s)**

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).

**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  $\geq 400$  pg/mL
3. eGFR  $> 25$  mL/min/1.73 m<sup>2</sup>
4. Clinical and paraclinical signs of congestion

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**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

Andrényi Károly 24

Arad

Romania

310037

## Sponsor information

**Organisation**

Vasile Goldis Western University of Arad

**ROR**

<https://ror.org/01e0stw12>

## Funder(s)

## Funder type

University/education

## Funder Name

"Vasile Goldis" Western University

# Results and Publications

## 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)  
dlungeanu@umft.ro

## IPD sharing plan summary

Available on request

## Study outputs

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