A multicENter, randomized, open-label, parallel group, pilot study to evaluate the use of sacubitril/valsartan in HeartMate 3 LVAD recipients

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The primary objective of this study is to assess the safety and tolerability of sacubitril/valsartan compared with standard of care used for treating BP in patients that have been implanted with the HM3 LVAD.

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

Summary

ID

NL-OMON52124

Source
ToetsingOnline

Brief title
ENVAD-HF

Condition

- Heart failures

Synonym
heart failure; heart failure with reduced ejection fraction

Research involving
Human

Sponsors and support

Primary sponsor: University of Zagreb School of Medicine

Source(s) of monetary or material Support: Ministerie van OC&W,Abbott,Novartis

Intervention

Keyword: heart failure, left ventricular assist devices, outcomes, sacubitril/valsartan

Outcome measures

Primary outcome

The primary safety variable is time to first occurrence of all-cause death, or deterioration in renal function (defined as reaching end-stage renal disease, renal death or 50% sustained decline in eGFR), hyperkalemia or symptomatic hypotension leading to drug withdrawal during the active treatment period, based on the following:

• End-stage renal disease defined as one of the following:

a) Initiation of dialysis (e.g., hemodialysis, peritoneal dialysis, or continuous venovenous hemodialysis), continuing for >= 20 days without known recovery of renal function

b) Initiation of dialysis with death before 30 days (excludes dialysis events associated with acute kidney injury with death before 30 days)

c) A drop in eGFR from baseline (randomization, i.e. Visit 101) to a value <15 mL/min/1.73m2 on two consecutive measurements separated by>= 20 days

d) Occurrence of kidney transplantation

• 50% sustained decline in eGFR: 50% decline from baseline (Randomization, Visit 101) as determined by 2 consecutive postbaseline measurements separated by > 20 days.

• Hyperkalemia: serum potassium >=6.0 mmol/L [mEq/L])

• Hypotension: symptomatic reduction in blood pressure requiring withdrawal of study medication or any BP lowering medication

Time-to-event is computed as the number of days from randomization to the start date of the primary endpoint event (first occurrence of any of the above-mentioned outcomes). A patient without an event will be censored at the last date the endpoint status was completely known (this date could include the date of withdrawal of informed consent, date of the patient*s 3-month visit (whichever occurred first)), or at the date of heart transplant, should it occur. Kaplan-Meier and Cox regression analyses will be used for the assessment of the primary outcome, and based on the Safety population.

Secondary outcome

The secondary efficacy variables, assessed from enrolment to 3 months and from enrolment to 12 months, unless stated differently are:

• Change in NT-proBNP from enrolment to 8 weeks

• Change in Burden of hemocompatibility (hemocompatibility score)

• Number of RV failure events (as defined in section 2.2.)

• Time to first unplanned hospitalisation

• Number of unplanned hospitalizations

• Change in blood-pressure lowering medications

• Change in eGFR values

The exploratory variables, assessed from enrolment to 3 months and from enrolment to 12 months, are:

• Change in 6MWT

• Change in Quality of Life related Symptoms assessed by KCCQ and EQ-5D

• Non-surgical bleeding events: an episode of suspected internal or external bleeding that results in one or more of the following:

a. Death,

b. Reoperation,

c. Hospitalization,

d. Any transfusion of packed red blood cells (PRBC) (any transfusion of >= 2U PRBC will be considered a serious bleed)

• Number of haemorrhagic stroke events

• Number of de-novo AI occurrence

• Change in markers of inflammation (change in high-sensitivity CRP)

• Change in left ventricular size

• Change in left ventricular volumes and ejection fraction

• Change in left atrial volumes

• Change in right ventricular size and function

• Change in LVAD low-flow alarms

• Change in PVC and atrial high rate burden in pacing device carriers

In general, secondary and exploratory efficacy variables will be analyzed based on the randomised population. All statistical tests will be performed at the two-sided significance level of 0.05. To better satisfy the normality assumption, the log-transformation is performed on each biomarker for analysis. All continuous outcomes will be analysed using linear regression models

adjusted for the corresponding baseline value, enrolment strata, and treatment assignment. Non-normally distributed biomarkers will be log-transformed prior to analysis and estimated treatment effects will be presented as relative (i.e. proportional) changes. As a sensitivity analysis, the LOCF technique will be used to impute missing data if the last observation is assessed at post-randomization.

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Study description

Background summary

The overwhelming efficacy and safety of sacubitril/valsartan has been demonstrated in patients with chronic, but also acute decompensated heart failure. Its efficacious antihypertensive effects are also well documented. The HeartMate 3 (HM3) LVAD has reduced the incidence of pump thrombosis and strokes, however, other hemocompatibility-related events such as non-surgical bleeding events, LVAD-related issues such as de-novo aortic insufficiency (AI) and right ventricular (RV) failure remain points of concern and areas for improvement. Recently, a large outcomes analysis of the INTERMACS cohort pointed out that blood pressure (BP) extremes during LVAD support increase the risk for adverse events, targeting a mean arterial pressure (MAP) goal >75 mmHg and <90 mmHg or a Doppler opening pressure <105 mmHg in patients with pulsatility. The purpose of this study is to evaluate the safety and tolerability of sacubitril/valsartan in HeartMate 3 LVAD recipients compared to standard of care used for treating blood pressure in this population. Furthermore, we postulate that sacubitril/valsartan would provide further afterload reduction in patients with the HM3 LVAD thus improving the unloading of the LV. In addition to improved BP control, this may be reflected by a decrease in NT-proBNP and improved exercise capacity, with possible additional beneficial effects on RV function and reduction in de-novo AI, as well as improvement of renal function. Finally, the earlier described effect of angiotensin II antagonism should reduce the risk of gastrointestinal bleeding,

thus reducing hemocompatibility-related events.

Study objective

The primary objective of this study is to assess the safety and tolerability of sacubitril/valsartan compared with standard of care used for treating BP in patients that have been implanted with the HM3 LVAD.

Study design

This study is a multicenter, randomized, open-label, parallel group trial designed to evaluate the safety and tolerability of sacubitril/valsartan compared to standard medical therapy in left ventricular assist device (LVAD) recipients.

Intervention

The patients will be assigned to one of the following two treatment arms at Visit 101.
• sacubitril/valsartan at dose levels 1 or 2 (24/26 mg or 49/51 mg twice daily, first dose around 08:00 hours in the morning and second dose around 20:00 hours in the evening)
• standard of care used for treating BP per investigator centre best practice.

Study medication will be titrated to achieve MAP goal >75 mmHg and <90 mmHg (or DOBP/SBP <105 mmHg if Doppler ultrasound method used due to unattainable measurement by automated cuff and palpable pulse present).

Dose levels of sacubitril/valsartan: 24/26 mg (dose level 1), 49/51 mg (dose level 2), 97/103 mg (dose level 3)

Study burden and risks

The overwhelming efficacy and safety of sacubitril/valsartan has been demonstrated in patients with chronic, but also acute decompensated heart failure. Its efficacious antihypertensive effects are also well documented. The HeartMate 3 (HM3) left ventricular assist device (LVAD) has reduced the incidence of pump thrombosis and strokes, however, other hemocompatibility-related events such as non-surgical bleeding events, LVAD-related issues such as de-novo aortic insufficiency (AI) and right ventricular (RV) failure remain points of concern and areas for improvement. Recently, a large outcomes analysis of the INTERMACS cohort pointed out that blood pressure (BP) extremes during LVAD support increase the risk for adverse events, targeting a mean arterial pressure (MAP) goal >75 mmHg and <90 mmHg or a Doppler opening pressure <105 mmHg in patients with pulsatility. The purpose of this study is to evaluate the safety and tolerability of

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Possible risks of participation in the study represent possible adverse reactions to the used medications or diagnostic procedures performed within the scope of the study.
In previous studies with sacubitril/valsartan, some adverse reactions were found to occur commonly in subjects (1:10):
- hyperkalemia (increased potassium levels)
- hypotension (low blood pressure)
- renal impairment
Relatively common side effects are listed (1:100-1:10):
- asthenia (feeling physically weak), fatigue, cough, dizziness, diarrhea, hypokalemia (low potassium levels), headache, hypersensitivity reactions, nausea, orthostatic hypotension (low blood pressure on standing up), renal failure, syncope.
The less common side effects are (1:1000-1:100):
- postural dizziness (dizziness which occurs when standing up) and angioedema (localised swelling of the head, neck, throat, tongue, genitals and/or intestine).
In animal studies (monkeys), increased accumulation of amyloid beta protein, associated with Alzheimer's disease, has been reported. No increase in the incidence of Alzheimer's disease has been observed in a large number of patients in previous clinical studies with this medication.
The adverse reactions that accompany the use of some of the more frequently prescribed antihypertensive medications, which have been investigated in various clinical trials, are well known. The groups of medications that will most likely be used and their known adverse reactions are listed here:
1. Angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB):
- worsening renal function, hypotension, orthostatic hypotension, syncope, dizziness, headache, fatigue, skin rash, abdominal pain, constipation, diarrhea, nausea, vomiting, bronchitis, cough, dyspnea.
- Among the much less frequent side effects (< 1%), angioedema is also included.
2. Beta blockers (common and very common):
- anaemia, heart failure, bradycardia, hypervolemia, hyperhydration, visual disturbances, dry eye, eye irritation, nausea, diarrhea, vomiting, dyspepsia, abdominal pain, asthenia (fatigue), pneumonia and bronchitis, weight gain and abnormal glycemic control, hypercholesterolemia, muscle pain, dizziness,

headaches, depression, pulmonary edema, asthma in predisposed patients, orthostatic hypotension, peripheral disturbances.
3. Nitrates (common and very common):
- headache (*nitrate headache*) especially at the beginning of treatment, usually resolving after several days of continued intake, drowsiness, light dizziness, feeling weak, dizziness when sitting or standing up caused by a fall in blood pressure (orthostatic hypotension), fast heart rhythm (tachycardia), flushing.
Diagnostic procedures conducted during the clinical trial, which may result in a certain degree of discomfort, include blood draws for laboratory tests, most commonly performed via the cubital vein. It can cause pain at the puncture site, sometimes a minor hemorrhage. If you develop a puncture site infection you may be treated using antibiotics according to the antibiogram of the puncture site swab.

Study patients will need to visit the study centre at the following time points (which are equal to standard ambulatory follow-up time points of patients with heart failure and a left ventricular assist device):
Enrolment visit (V101)
Follow-up visit 1 at 2 weeks (V102)
Follow-up visit 2 at 5 weeks (V103)
Follow-up visit 3 at 8 weeks (V104)
Follow-up visit 4 at 3 months (V105)
Follow-up visit 5 at 6 months (V106)
Follow-up visit 6 at 9 months (V107)
Follow-up visit 7 at 12 months (V108).

At every visit, blood will be drawn (total of 28.5 mL), which represents potential discomfort for the study patient in the duration of approximately 5 seconds per visit (a total of 40 seconds per patient for the entire duration of the study). All other study procedures are not expected to cause discomfort to the patient and represent standard ambulatory follow-up procedures for patients with heart failure and a left ventricular assist device, except for quality of life questionnaires. Study patients will be asked to fill out two kinds of quality of life questionnaires (Kansas City Cardiomiopathy Questionnaire and EQ-5D-3L questionnaire) at study visits V101, V105, V106 and V108. We expect it will take approximately 5 minutes for the study patient to fill out both questionnaires per visit.

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. Written informed consent must be obtained before any assessment is performed.
2. >=18 years of age, male or female
3. Recently implanted HeartMate 3 LVAD recipients, in stable condition and deemed ready for discharge or chronic, stable, ambulatory HeartMate 3 LVAD carriers implanted within 1 year prior to enrolment

Exclusion criteria

1. Current acute decompensated HF (including right ventricular failure) requiring therapy with intravenous diuretics or vasodilators and/or inotropic drugs within the past 48 hours
2. History of hypersensitivity to sacubitril/valsartan or to drugs of similar chemical classes, patients with a known history of angioedema
3. Patients with mean blood pressure <=75 mmHg (systolic blood pressure i.e. Doppler opening blood pressure <=90 mmHg in those pulsatile and measured by Doppler method) or symptomatic hypotension
4. eGFR < 30 mL/min/1.73m2 as calculated by the Modification in Diet in

Renal Disease (MDRD) formula at Visit 1
5. Patients with serum potassium >5.4 mmol/L (mEq/L) at Visit 1
6. Hemodynamically unstable patients or those with ongoing MCS other than LVAD or those with planned biventricular support
7. Hemodynamically significant aortic insufficiency in the opinion of the investigator
8. Irreversible end-organ dysfunction
9. Previous sacubitril/valsartan use while on LVAD support
10. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within 30 days prior to enrolment
11. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 bpm at enrolment
12. Any surgical or medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study
13. Active infection with hemodynamic compromise
14. Hemoglobin (Hgb) <8 g/dl
15. Body mass index (BMI) > 45 kg/m2
16. Congenital heart disease
17. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention within the 6 months after enrolment
18. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x ULN, bilirubin >1.5 mg/dl at Visit 1
19. Pregnant or nursing (lactating) women and women of child-bearing potential unless they are using highly effective methods of contraception

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	07-06-2021
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Entresto
Generic name:	sacubitril/valsartan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-04-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2019-003888-22-NL
ClinicalTrials.gov	NCT04103554
CCMO	NL76552.078.21