ANGIOTENSIN–NEPRILYSIN INHIBITION IN DIASTOLIC DYSFUNCTION AFTER AMI

the ARNiAMI study

Product: LCZ696 (Entresto)

Indication:
Acute myocardial infarction with preserved ejection fraction and diastolic dysfunction

Country: Denmark

Sponsor and principal investigator

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1 List of abbreviations

AE	Adverse event
AMI	Acute myocardial infarction
ARNi	Angiotensin receptor – neprilysin inhibition
CI	Cardiac index
EF	Ejection fraction
LV	Left ventricular
PCWP	Pulmonary capillary wedge pressure
SAE	Serious adverse event
SUSAR	Suspected unexpected servere adverse reaction

2 Synopsis

<table>
<tr><td>Drug Name</td><td>LCZ696, Valsartan/sacubitril (Entresto)</td></tr>
<tr><td>Study Design</td><td>A Prospective, multicenter, randomized (1:1) double blind controlled trial of the LCZ696versus placebo.</td></tr>
<tr><td>Objective</td><td>The main objective of this study is to assess the effect of angiotensin–neprilysin inhibition on central hemodynamics, myocardial structure and myocardial function in patients with a recent AMI and Doppler echocardiographic signs of diastolic dysfunction and preserved systolic function.</td></tr>
<tr><td>Study Hypothesis</td><td>LCZ696will compared with placebo improve central hemodynamics, reduce pulmonary capillary wedge pressure (PCWP), and increase cardiac index (CI) during exercise in patients with diastolic dysfunction after AMI. A beneficial effect that is attributed to improved cardiac remodeling (attenuation of cardiac fibrosis).</td></tr>
<tr><td>Number of Subjects</td><td>100 total subjects.</td></tr>
<tr><td>Primary Endpoint and Measurement</td><td>The primary endpoint will be the ratio of mean PCWP at peak exercise divided by cardiac index at peak exercise.</td></tr>
<tr><td>Secondary Endpoints</td><td>Amount of hyperenhancement on cardiac MRI; ST2 concentration at rest; Left atrial volume by echocardiography and left atrial emptying fraction by echocardiography at rest; MR-proANP and NT-proBNP concentration.</td></tr>
<tr><td>Study Population</td><td>A total of 100 male or nonpregnant females aged ≥50 years with a recent documented AMI, diastolic dysfunction, and LVEF ≥45% on echocardiography performed within 72 hours of the AMI will be enrolled at selected invasive centers in Denmark.</td></tr>
<tr><td>Sample Size Considerations</td><td>Based on previous data it is expected that PCWP will increase to 32±8 mmHg and cardiac index to 7.4 ±1.4 l/min/m2, with a PCWP/CI ratio of 4.49±1.4.
To detect a decrease of 20% in primary endpoint with alpha of 0.05 and beta 0.8, a total of 90 patients are required, to allow 10% dropout rate 100 patients are expected to be enrolled.

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<tr><th>Difference in PCWP/CI ratio</th><th>Standardized difference</th><th>N (Total) α=0.05/β= 0.8</th><th>N (Total) α=0.05/β=0.9</th></tr>
<tr><td>10% (0.449)</td><td>0.299</td><td>320</td><td>450</td></tr>
<tr><td>15% (0.674)</td><td>0.449</td><td>150</td><td>200</td></tr>
<tr><td>20% (0.898)</td><td>0.598</td><td>90</td><td>110</td></tr>
<tr><td>25% (1.12)</td><td>0.748</td><td>70</td><td>100</td></tr>
</table>
</td></tr>
<tr><td>Inclusion Criteria</td><td>1. Documented ST segment elevation or non ST- myocardial infarction according to current guidelines
2. Complete revascularization
3. Age ≥50 years
4. LVEF ≥45% on echocardiography performed within 72 hours of the MI.
5. Diastolic dysfunction defined as: Ratio of early diastolic peak mitral inflow velocity (E) to early mitral annulus diastolic velocity (e') ratio > 8 and at least moderate LA dilatation (LA volume index>34 mL/m2).
6. Signed informed consent</td></tr>
<tr><td>Exclusion Criteria</td><td>1. I Intolerance towards study medication
2. Permanent atrial fibrillation,
3. Known history of cardiomyopathy,
4. More than mild valvular heart disease,
5. Severe obstructive or restrictive pulmonary disease,
6. Inability to perform exercise testing,
7. Inadequate acoustic windows on echocardiography,</td></tr>
</table>

	8. Ongoing treatment with an angiotensin converting enzyme inhibitor at randomization. 9. Class I indication for an angiotensin converting enzyme inhibitor 10. Symptomatic hypotension, a systolic blood pressure of less than 100 mm Hg at screening 11. An estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area at any time, 12. A serum potassium level of more than 5.2 mmol per liter at screening, 13. A history of hereditary or idiopathic angioedema or unacceptable side effects during receipt of angiotensin converting enzyme inhibitor or angiotensin receptor blocker 14. Inability to provide informed consent 15. Concomitant use of drugs containing aliskiren in patients with diabetes mellitus. 16. Severe reduced liver function, biliary cirrhosis or cholestasis (Child-Pugh class C) 17. Pregnant or nursing(lactacing) women(see section 8.2.1 for details) 18. Fertile women unless they are using a highly effective method of contraception(see section 8.2.2 for details)
Estimated Start Date, Enrollment Phase and tracking plan	Study start is expected to be June 2018, with an estimated enrollment phase of 2 years. Patients will be enrolled during hospitalization for AMI. Before randomization, spirometry, blood testing, comprehensive resting Doppler echocardiography, resting right heart catheterization, 6-minute walk test, and symptom-limited supine cycle exercise test with simultaneous echocardiography and right heart catheterization will be performed 1-3 weeks after AMI. Subsequently patients will be randomized on the day of exercise test to receive LCZ696 100 mg twice daily or, which will be increased to 200 mg twice daily after 2 weeks if tolerated or matching placebo. After 6 months treatment invasive hemodynamic stress test with simultaneous echocardiography will be repeated. The study will be considered complete with regard to the primary study endpoints after all subjects enrolled have completed their 6 month follow-up.
Informed consent	The study will be conducted according to national and international legislation. Patients will be enrolled after obtaining written informed consent.

3 Study Rationale:

3.1 Diastolic dysfunction after AMI:

Left ventricular (LV) systolic or diastolic dysfunction following acute myocardial infarction (AMI) is common with only 25-33% of the patients having an entirely normal LV function. Based on echocardiographic examinations an estimated 25% of all patients will present with apparently normal systolic function based on LV ejection fraction but diastolic dysfunction based on Doppler echocardiographic criteria (1).

Direct or indirect measurements of increased LV filling pressure is well-established independent risk factor for mortality and morbidity after AMI. Several recent studies have demonstrated that Doppler echocardiographic indices suggestive of increased LV filling pressure and increased pulmonary arterial pressure are associated with excess mortality and morbidity after AMI (2-4). The causal mechanism behind the increased mortality and morbidity due to diastolic dysfunction in patients with preserved systolic function is however poorly understood. Recent data from our group have demonstrated that the underlying pathophysiological response to physical stress in these patients is characterized by a disproportionate increase in LV filling pressure to maintain adequate perfusion (cardiac output) thus suggestive of an upward shift of the pressure volume relationship with increased LV chamber stiffness possibly due to increased myocardial fibrosis (5). Furthermore, this condition is also characterized by an impaired natriuretic and renal endocrine response to acute volume expansion. Thus the pathophysiological characteristics of this condition closely resamples that of heart failure with preserved ejection fraction (6-7).

The optimal management of this group of post-AMI patients is however incompletely understood.

3.2 LCZ696

LCZ696 is a combination drug consisting of two antihypertensives, valsartan and sacubitril. Valsartan acts by blocking the angiotensin II receptor type 1 and thereby causes vasodilation and increases excretion of sodium and water via the kidneys by attenuating aldosterone production. Sacubitril is a prodrug that is activated to an active metabolite (LBQ657) that acts by inhibiting the enzyme neprilysin (8). Neprilysin is responsible for the degradation of natriuretic peptides released from the LV and left atrium in response to increased wall stress and myocyte stretch and act by attenuating the deleterious effects of volume and pressure overload on the heart, a protective mechanism that have been suggested to be deficient in early stage of heart failure with preserved LVEF (9). Augmentation of these mechanisms likely at least partly explain the beneficial effect on outcome of ARNi in heart failure with reduced LVEF that recently was found in the PARADIGM-HF trial, where angiotensin receptor – neprilysin inhibition (ARNi) compared with enalapril treatment was associated with a risk reduction of 20% of composite primary endpoint death and hospitalization for heart failure (10). In patients with heart failure and preserved ejection fraction ARNi has been demonstrated to have a beneficial effects on natriuretic peptides and left atrial remodeling in a clinical Phase II trial (11). Furthermore, recent experimental data also suggest ARNi attenuated cardiac remodeling and dysfunction after experimental AMI in rodents and importantly inhibit cardiac fibrosis in experimental AMI, as well as in vitro beyond that achieved by stand-alone angiotensin receptor blockade (12).

Thus in theory LCZ696 may possess several beneficial properties that may improve hemodynamics and cardiac remodeling in patients with diastolic dysfunction after AMI.

4 Hypothesis:

LCZ696 compared with placebo will improve central hemodynamics (reduce pulmonary capillary wedge pressure (PCWP)), and increase cardiac index (CI) during exercise in patients with diastolic dysfunction after AMI. A beneficial effect that is attributed to improved cardiac remodeling (attenuation of cardiac fibrosis).

5 Objectives:

The main objective of this study is to assess the effect of angiotensin–neprilysin inhibition on central hemodynamics, myocardial structure and myocardial function in patients with a recent AMI and Doppler echocardiographic signs of diastolic dysfunction and preserved systolic function.

5.1 Primary objective:

To assess the effect of 6 months treatment with LCZ696 compared with placebo on ratio of PCWP/CI during exercise in patients with a recent AMI and Doppler echocardiographic signs of diastolic dysfunction and preserved systolic function.

5.2 Secondary objectives:

To assess the effect of 6 months treatment with LCZ696 compared with placebo in patients with a recent AMI and Doppler echocardiographic signs of diastolic dysfunction and preserved systolic function on:

1. Cardiac fibrosis assessed on cardiac magnetic resonance imaging,
2. The ST2 cardiac biomarker
3. Left atrial size and function
4. MR-proANP and NT-proBNP
5. Diastolic dysfunction assessed by Doppler echocardiography

5.3 Primary endpoint:

Ratio of pulmonary capillary wedge pressure to cardiac index at peak exercise after 26 weeks treatment with LCZ696 or placebo.

5.4 Secondary endpoints:

1. Amount of hyperenhancement on cardiac MRI using a semiquantitative assessment of late gadolinium hyperenhacement in a 17 segment model of the LV.
2. ST2 concentration at rest.
3. Left atrial volume by echocardiography and left atrial emptying fraction by echocardiography at rest.
4. MR-proANP and NT-proBNP concentration at rest.
5. Proportion of patients with moderate or severe diastolic dysfunction at rest.

6 Methodology:

The ARNiAMI study is a prospective, multicenter, randomized, double blind clinical trial to evaluate the efficacy, of LCZ696 97/103 mg BID versus matching placebo in subjects aged 50 years or older with a recent documented AMI, diastolic dysfunction and LVEF ≥45% on cardiac physiology and myocardial fibrosis. Patients who meet the study inclusions and none of the exclusion criteria will after signing an Ethics Committee approved Informed Consent Form, be asked to undergo baseline procedures for the study.

Patients will be randomized in a 1:1 double-blind trial to receive LCZ696 or matching placebo using a computer-generated randomization schedule. Randomization will be stratified by PWCP at rest. Production of study medication, matching placebo, packing and handling of study medication will be performed by Sygehusapotek Fyn. Study medication will be delivered to the participating centers in blinded containers. Containers will be labeled with a unique identification number. Randomization will be performed by the investigator and a randomization number is assign to the patient. When dispensing study medication container ID's is requested from Sygehusapotek Fyn via E-mail.
The randomization codes will be kept in sealed envelopes with the Trial Master file and will not be opened before the study has ended. The randomization schedule will also be available through a password protected online form. In case of emergent need for unblinding the coordinating investigator will be contacted pr. telephone and treatment allocation is unblinded either through the online form (with a dedicated user for this purpose with strict logging) or sealed envelopes.
Compliance will be assessed using pill count.

The study will be performed according to ICH-GCP. The ethics Committee for the Region of Southern Denmark will be applied for ethical approval and the study will be registered at ClinicalTrials.gov. All patients will provide written informed consent.

6.1 Justification of key elements of study design:

6.1.1 Selection of endpoints

A key pathophysiological element of diastolic dysfunction and heart failure with preserved ejection fraction is the inability to increase cardiac output without concomitant excessive increase in LV filling pressure during physical strain. Thus the ratio between LV filling pressure to cardiac output will be abnormally increased during exercise. In many patients filling pressure will be normal or mildly elevated at rest where cardiac output will be normal. Thus resting assessment will often be misleadingly normal in these patients where as evaluation during exercise will uncover the pathophysiology (5,6). By combining filling pressure and cardiac output it will be possible indirectly to assess changes in the pressure volume relationship of the LV which not would be the case if either PCWP or cardiac index alone were chosen.

Cardiac MRI with late gadolinium enhancement is a useful tool for detection of myocardial fibrosis, based on differences in the volume of distribution of gadolinium (13). Although the method is especially well suited to detect the presence of fibrosis in the myocardium in ischemic cardiomyopathy, it may also detect myocardial fibrosis in a wide variety of non-ischemic cardiomyopathies. Modification of myocardial fibrosis will provide an important pathophysiological link between assessment of central hemodynamics during exercise and effects of ARNi. In addition cMRI provides detailed information on cardiac structure thus it will provide very precise data on LV remodeling (LV volumes and LV mass) and LA remodeling. Thus provide important explanatory data.

ST2 is a member of the interleukin 1 receptor family. The ST2 gene is highly expressed by cardiomyocytes and fibroblasts when strained in this setting ST2L becomes receptive for interleukin-33 which has antihypertrophic and antifibrotic effects (14). Thus ST2 concentration reflects cardiac

remodeling and myocardial fibrosis. After AMI ST2 has been demonstrated to predict prognosis (15) and be associated with presence of heart failure. Differences in ST2 concentrations between groups will provide insights into the mechanisms of the potential effect of ARNi.

6.1.2 Selection of comparator

Current guidelines recommend treatment with an angiotensin II receptor blocker or an angiotensin comverting enzyme inhibitor in all patients with signs or symptoms of heart failure and/or evidence of LV dysfunction in the absence of hypotension, hypovolaemia, or renal failure with a class I indication (17,18). Thus the patiens selected in the present study do noth have a class I indication for blocade of the renin angiotensin system. Thus the comparator will be placebo which also will provide the strongest insight into the effect of ARNi on myocardial structure and function.

6.1.3 Sample size

Based on previous data it is expected that PCWP will increase to 32±8 mmHg and cardiac index to 7.4 ±1.4 l/min/m2, with a PCWP/CI ratio of 4.49±1.4 (19).

To detect a decrease of 20% in primary endpoint with alpha of 0.05 and beta 0.8, a total of 90 patients are required, to allow 10% dropout rate 100 patients are expected to be enrolled.

Difference in PCWP/CI ratio	Standardized difference	N (Total) α=0.05/β= 0.8	N (Total) α=0.05/β=0.9
10% (0.449)	0.299	320	450
15% (0.674)	0.449	150	200
20% (0.898)	0.598	**90**	110
25% (1.12)	0.748	70	100

7 Timelines and Study duration:

Start date: June 2018

Approval from relevant authorities: Medio august 2018

Inclusion start: 1/9 2018

Last patient last visit: July 2020

End date: July 2020

Clinical study report date: August 2020

Publication date: September 2020 – May 2021

8 Population:

8.1 Key inclusion criteria

1. Documented ST segment elevation or non ST- myocardial infarction according to current guidelines (20).
2. Complete revascularization.
3. Age ≥50 years
4. LVEF ≥45% on echocardiography performed within 72 hours of the MI.
5. Diastolic dysfunction defined as: Ratio of early diastolic peak mitral inflow velocity (E) to early mitral annulus diastolic velocity (e') ratio > 8 and LA dilatation (LA volume index>34 mL/m2).
6. Signed informed consent

8.2 Key exclusion criteria

1. Intolerance towards study medication
2. Permanent atrial fibrillation,
3. Known history of cardiomyopathy,
4. More than mild valvular heart disease,
5. Severe obstructive or restrictive pulmonary disease,
6. Inability to perform exercise testing,
7. Inadequate acoustic windows on echocardiography,
8. Ongoing treatment with an angiotensin converting enzyme inhibitor at randomization.
9. Class I indication for an angiotensin converting enzyme inhibitor
10. Symptomatic hypotension, a systolic blood pressure of less than 100 mm Hg at screening
11. An estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area at any time,
12. A serum potassium level of more than 5.2 mmol per liter at screening,
13. A history of hereditary or idiopathic angioedema or unacceptable side effects during receipt of angiotensin converting enzyme inhibitor or angiotensin receptor blocker
14. Inability to provide informed consent
15. Concomitant use of drugs containing aliskiren in patients with diabetes mellitus.
16. Severe reduced liver function, biliary cirrhosis or cholestasis (Child-Pugh class C)
17. Pregnant or nursing(lactacing) women(see section 8.2.1 for details)
18. Fertile women unless they are using a highly effective method of contraception(see section 8.2.2 for details)

8.2.1 Fertile women

In fertile women measurement of human chorionic gonadotropin must negative prior to randomization. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

8.2.2 Contraception

Highly effective contraception (failure rate < 1% pr. year) is defined as one of the following;

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral

    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

Contraception must continued until 3 days after the last visit.

9 Number of centers & patients:

9.1 Planned number of centers:

The following tertiary centers will participate:
Site A
Department of Cardiology,
Odense University Hospital
Sønder Boulevard 29
DK 5000 Odense C

Site B
Department of Cardiology
Rigshospitalet
Blegdamsvej 9
DK 2100 Copenhagen Ø

Sponsor and principal investigator at site A

Professor Jacob Eifer Møller, MD PhD DmSc
Phone
E-mail

Principal investigator at site B
Finn Gustafsson, MD, PhD, DmSc
Phone:
E-mail:

9.2 Total number of patients:

In total one hundred patients are planned to be randomized according to sample size estimation, 50 patients in each arm.

10 Collaborators

Production of study medication, matching placebo, packing and handling of study medication:

Sygehusapotek Fyn, hovedapotek
Indgang 208, Solfaldsvej 38,

5000 Odense C
Denmark

GCP-monitoring:

GCP-enheden
Odense Universitetshospital
J. B. Winsløws Vej 19, 2.sal
5000 Odense C
Denmark

Data management and randomization:

Odense Patient data Explorative Network (OPEN)
J.B. Winsløws Vej 9 a, 3. etage
5000 Odense C
Denmark

Storage and analysis of blood samples

Department of Clinical Biochemistry and Pharmacology
Kløvervænget 40, indgang 40
5000 Odense C
Denmark

11 Evaluation schedule:

Visit number **Time of Visit**	**0** **day 1**	**1** **week 2-4**	**2** **Week 4-6**	**3** **month 6**
Inclusion/Exclusion criteria	x			
Information & Informed consent	x			
Physical examination	x	x	x	x
Vital signs (pulse and blood pressure)	x	x	x	x
Spirometry	x			
Echocardiography	x			x
Right heart catheterization	x			x
Cardiac MRI	x			x
Dispense study medication	x	x	x	x
Laboratory test[a]	x	x	x	x
Concomitant medication	x	x	x	x
Adverse events		x	x	x

[a] Unblinded measurements: Hemoglobin, platelet count, white blood cell count(WBC), WBC differential, alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, blood urea nitrogen, calcium, creatinine, potassium, sodium, glucose, lipid profile(total cholesterol, LDL, HDL and triglycerides). Additional blood samples are drawn and stored for later analysis of NT-proBNP, MR-pro-ANP, ST2 and possible future biomarkers.

Patients who meet the study inclusions and none of the exclusion criteria will after signing an Ethics Committee approved Informed Consent Form, will undergo conventional spirometry, blood testing, comprehensive resting Doppler echocardiography, cardiac MRI with late enhancement imaging, resting right heart catheterization, and symptom-limited supine cycle exercise test with simultaneous echocardiography and right heart catheterization will be performed before randomization.

After randomization patients will be started on LCZ696 49/51 mg twice daily or matching placebo twice daily titrated to their final doses of LCZ696 97/103 mg twice daily or matching placebo twice daily over a period of 2–4 weeks. Succeeding up titration to final dose a visit is planed after two weeks (visit 2) to assess tolerability. In case of clinical concern regarding tolerability additional follow up is left at discretion of the investigator.

Background therapy will be decided at the discretion of treating physicians. The double-blind design will continued for 26 weeks. After 26 weeks treatment cardiac MRI, echocardiography, right heart catheterization and exercise test will be repeated.

Patients will in addition to the above mentioned be followed in the "Prevention and aftercare out-patient clinic" as per standard care following AMI.

11.1 Discontinuation of study treatment

Patients can voluntarily and for any reason discontinue study treatment and withdraw consent to participate at any time. If one of the following circumstances emerges study treatment will be discontinued

- Withdrawal of informed consent
- The investigator believes the study treatment has an overall negative influence on the patient's wellbeing.
- Clinical suspicion of significant angioedema.
- Decline in kidney function assed by an estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area.
- Symptomatic hypotension that is not overcome by appropriate actions as described in section 11.1.1

11.1.1 Hypotension

If symptomatic hypotension occurs treatable causes must be corrected, i.e. hypovolemia. Hypotension in euvolemic patients require through evaluation of concomitant medication. If possible concomitant medication may be reduced in dose or discontinued. If hypotension persists in patients receiving 97/103 mg or matching placebo treatment dose can be reduced to 49/51 mg or matching placebo.

11.2 Hemodynamic stress echocardiography:

Transthoracic echocardiography, including additional images for regional tissue Doppler and 2D speckle tracking analysis and 3D analysis, will be performed at rest. All of these images will be recorded by an experienced echocardiographer on GE Vivid 9 ultrasound machine and stored digitally. Guided by ultrasound a 7Fr-Swan-Ganz catheter is placed via the right internal jugular vein. The catheter is advanced into wedge position. Simultaneous with echocardiography resting pulmonary arterial pressure, mean right atrial pressure, cardiac output and wedge pressure is measured. Cardiac output is estimated by thermodilution as a mean of 3 measurements with less than 10% variation. At each exercise level a central venous blood sample will be taken for measurement of central venous oxygen saturation, pH and lactate. Arterial blood pressure is measured noninvasively and is repeated every third minute during the stress test. ECG and arterial saturation is measured continuously. The resistance is increased with 25W every third minute until exhausting.

The following echocardigraphic images will be saved at each exercise level and after 5 minutes of rest: Apical 2, 4 chamber images with zoom on the LV cavity zoom of RV cavity; PW Doppler mitral inflow; PW Doppler LVOT flow.

At every exercise level the following parameters are measured: Pulmonary arterial systolic, diastolic and mean blood pressure; Central venous pressure; Arterial saturation; Heart rate; Cardiac output and PCWP.

11.3 Blood samples

Before invasive stress test and at every visit venous blood samples will be taken and stored as frozen plasma for analyzes of plasma ST2 using an enzyme-linked immunosorbent assay NT-proBNP, plasma MR-pro-ANP, and possible other further analyses. In addition eGFR will be assessed at each visit.

11.4 Cardiac magnetic resonance imaging

Patients will be screened for contraindications for MRI, and if none exist MRI-scan will be performed before randomization and repeated after 26 weeks using a 1.5T scanner (Siemens Healthcare Solultions, Forcheim, Germany) with a 32-channel cardiovascular array coil (InVivo, Orlando, Florida, USA). Images will be obtained 10 minutes after intravenous injection of 0.1-mmol/kg body weight gadolinium-diethylenetriamine pentaacetic acid (Gadovist, Bayer Schering, Berlin, Germany). An 11-heart-beat modified Look Locker sequence with inversion recovery will be used for T1 mapping. Slice thickness 8 mm, slice gap 0 mm, echo time 1.4 ms, resolution matrix 192 x 192, field of view 300–360 mm. In a single slice the inversion time was adjusted to null the signal from the normal myocardium, after which time multiple slices in the short-axis image plan will be acquired covering the entire LV. The endocardial and epicardial borders will be manually traced in all short axis images and the LV mass was calculated. Papillary muscles will be considered as part of the LV cavity.

Late gadolinium enhancement will be assessed semiquantitatively, using the American Heart Association 17 segment model and giving each segment a score from 0 to 4 depending on the extent of scar (0: no scar, 4: 100% scar). A final score is given by the summation of all segments' scores and division of the result by number og segments. In addition diffuse fibrosis will be assessed using T2 weigthed images.

11.5 Investigational & Reference Therapy:

Treatment Arm	# of Patients Entered Treatment	Type of Study Drug	Compound	Min Dose	Max Dose	Frequency	Admin. Route	Generic Acceptable? (applies only for comparator)
	100	Investigational	LCZ696		400	Daily	Oral	No
		Comparator	Placebo				Oral	

12 Ethical considerations:

The study will not be initiated before relevant authorities including The regional committee of science ethics for the Region of Southern Denmark have approved the study. Informed consent will be obtained according to national and international legislation. Below is a detailed description of risks with the planned procedures and medication. As described earlier diastolic dysfunction following AMI is associated with increased mortality and morbidity. The optimal treatment for this large group of patients is incompletely understood. In this light, neither the individual procedures or the study as whole is indefensible.

12.1 Risk of procedures

Placement of the Swan-Ganz catheter is associated with a low risk of complications. A hematoma can develop around the location of the placement sheat, which usually doesn't require treatment. Rarely perforation of the right atrium or ventricle (less than 1:1000) has been reported. This is usually treated by extraction guided by ultrasound (pericardiocentesis), but operation can be required. Arrhythmias that require treatment (cardioversion) may rarely be seen. All participating sites have extensive experience in performing invasive exercise testing. At the participating centres more than 250 patients have been evaluated with the technique with no serious adverse events.

The most common side effects of MRI contrast agent (Gadoterinsyre (Dotarem®)) are brief transient headache, nausea and dizziness following the injection. This occurs in 1% to 5% of contrast injections. Allergic reactions to gadolinium contrast medium have occurred but are extremely rare (less than 1 in 10,000). As gadolinium contrast medium in patients with kidney failure (either chronic or acute) has been associated with nephrogenic systemic fibrosis, Gadoterinsyre despite being classified as a low-risk agent by EMA will not be used in patients with eGFR < 30 ml/min/1,73 m2.

12.2 Risk of LCZ696

In previous clinical trials LCZ696 has been well tolerated (10,11). Because of its vasodilator effects, treatment with LCZ696 may be associated with symptomatic hypotension. In previous studies this has not been associated with increased risk of renal failure and has not been associated with increased discontinuation rate (10,11). Previous studies have not indicated increased risk of hyperkalemia or angioedema with LCZ696 (10,11).

13 Pharmacovigilance requirements:

Any SUSAR will immediately be reported to Danish Medcines Agency and the Regional Ethics Committee of Southern Denmark. Fatal SUSAR's or life threatening reactions will be reported within 7 days after sponsor has knowledge of the event. Sponsor will provide detailed follow-up information regarding the event within 8 days. Other SUSAR's will be reported within 15 days of knowledge. The product resume for LCZ696 is reference document when assessing adverse events.

13.1 Adverse events (AE)

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on an Adverse Event Case Report Form and will be followed up as appropriate.

An AE is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Study treatment includes the study medication under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

Medical conditions/diseases present before starting study treatment will only be considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form will be recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce

clinical signs or symptoms, are considered clinically significant or require therapy, and are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

13.2 Serious Adverse Events (SAEs)

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form.

An SAE is defined as an event which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Transmission of infectious agent via medicinal product

Any SAEs exempt from this reporting process must be clearly identified in the study protocol with a scientific/medical justification e.g. SAEs due to disease progression, SAEs due to a planned surgical procedure, etc.

Any SAE occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation will be reported.

As far as possible, each SAE will also be described by (but not limited to):

- Its duration (onset date = date of 1st signs or symptoms, and end dates)
- The seriousness criteria and severity if applicable (mild, moderate, severe)
- Its relationship to current investigational drug (suspected / not suspected as judged by the investigator),

- The action(s) taken and investigation results if applicable
- Concomitant medication details
- Outcome

13.3 SUSAR

Any SUSAR will immediately be reported to Danish Medcines Agency and the Regional Ethics Committee of Southern Denmark. Fatal SUSAR's or life threatening reactions will be reported within 7 days after sponsor has knowledge of the event. Sponsor will provide detailed follow-up information regarding the event within 8 days. Other SUSAR's will be reported within 15 days of knowledge.

14 Data collection

Data is collected from hospital records and results from echocardiography, exercise testing and cardiac MRI. Data from the exercise testing is written directly in the electronis case repport form, all other data are copied from other sources. Information that is needed for the study before the patient have given consent is disclosed to the investigators.

14.1.1 Access to data

In the written information to patients, it is specified that when given consent to participate in the study patients also allow that investigators, the GCP-unit and control authority (Danish Medical Agency) have access to all data collected in the study and hospital records (including electronic records). Access are allowed in order to conduct mandatory monitoring and control.

15 Data analysis

Data required by the protocol will be entered into an internet based Electronic Case Report Form using fully validated RedCap software. Data storage will be managed by Odense Patient data Explorative Network (OPEN). The full analysis set will consist of all randomized patients. Following the intent to treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization, and efficacy variables will be analyzed based on the full analysis set.

15.1 Baseline characteristics

Summary statistics will be provided by treatment group for demographics and baseline characteristics. Continuous variables will be summarized using n, mean, standard deviation, median, 25'th and 75' percentile. Categorical variables will be summarized using frequency and percentage. The difference between treatment groups will be compared using the Chi-square test for categorical variables or using t-test for continuous variables. A p value <0.05 will be considered statistically significant.

15.2 Analysis of primary endpoint

Primary endpoint, PCWP/CI ratio, will be analyzed using ANCOVA with treatment as fixed effect factor. Additionally, the baseline value of the corresponding variable may be included as a covariate if appropriate. The estimated treatment effect and the corresponding two-sided 95% confidence interval will be provided.

15.3 Analysis of secondary endpoints

The secondary hypotheses will be tested and statistical inferences will be made only if the primary hypothesis is rejected. The five secondary efficacy variables will be tested for superiority of LCZ696 to placebo for all randomized patients following the intent-totreat principle.

16 Funding

The study is conducted independently of the manufacture and is thus supported by Hjerteforeningen, OUH-RH puljen and OUH's frie forskningsmidler. None of the investigators has financial attachment to the manufacture.

17 Presentation of data and timeframe

All results from the study will be published in international peer reviewed scientific journals irrespective of a positive, negative or neutral result. It is anticipated that the main hypothesis will generate a publication in a top ranking cardiologic journal. The study is expected to start June 2018 and be finalized May 2021 with presentation of main results November 2021 at the American Heart Association Scientific Sessions.

18 Key-references

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