

## **Supplementary Online Content 1**

**Effect of a Strategy of Comprehensive Vasodilation vs Usual Care on Mortality or Heart Failure Rehospitalization among Patients with Acute Heart Failure: The GALACTIC Randomized Clinical Trial**

# Study Protocol

## Goal-directed Afterload Reduction in Acute Congestive Cardiac Decompensation

(GALACTIC Study)



## Summary

**Background:** In contrast to treatment for chronic heart failure, which is based on several large prospective randomized controlled trials, treatment for acute heart failure is largely based on uncontrolled studies, clinical experience and expert opinion. Perhaps at least in part related to the uncertainties in the treatment of acute heart failure, outcome of patients with acute heart failure is extremely poor. Mortality is 50% at three years. More than 85% of patients with acute heart failure are treated in the non-ICU / CCU setting - the Emergency Department and the regular medical ward. Unfortunately, appropriate treatment is particularly ill-defined in this setting.

**Aim:** to test the hypothesis that a comprehensive approach using an early goal-directed decrement of preload and afterload with a target systolic blood pressure of 90 to 110 mm Hg by aggressive vasodilatation in patients with acute heart failure in the non-ICU setting is safe, and leads to a better clinical and economical outcome.

**Methodology:** This is a prospective, randomized, controlled multicenter study designed to enroll 770 patients presenting with acute heart failure at the emergency departments at the participating study sites. Patients will be randomly assigned 1:1 after stratification for site and B-type natriuretic peptide (BNP, NT-proBNP) levels to an early goal-directed therapy or standard care according to current guidelines. Early goal-directed therapy applies aggressive vasodilatation using sublingual and transdermal nitrates, hydralazine to avoid tolerance to nitrates, and rapid up-titration of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with a target systolic blood pressure of 90mm Hg to 110 mm Hg. Timing and dosing of diuretics and all other treatments are left to the discretion of the treating physician in both groups. The primary endpoint is death or heart failure readmission within 180 days. Secondary endpoints include the quantitative assessment of dyspnea, need for admission to the intensive care unit, surrogate markers like BNP or NT-proBNP, the digitally recorded third heart sound, renal function, time to discharge, functional status and quality of life, falls, total treatment cost, and cost-effectiveness. Patients will receive extensive clinical and economic follow-up of at least 360 days. Endpoints will be adjudicated by a clinical endpoint committee blinded to group assignment.

**Potential significance:** It is our hypothesis, that a comprehensive approach using an early goal-directed therapy has the potential to more rapidly improve dyspnea, to more rapidly and more extensively reduce heart failure disease severity as quantified by B-type natriuretic peptide levels and most importantly to reduce the occurrence of death and heart failure readmission. Due to the high cost associated with hospitalizations for heart failure, our study has the potential to define a novel treatment strategy that might also significantly reduce the treatment cost associated with acute heart failure.

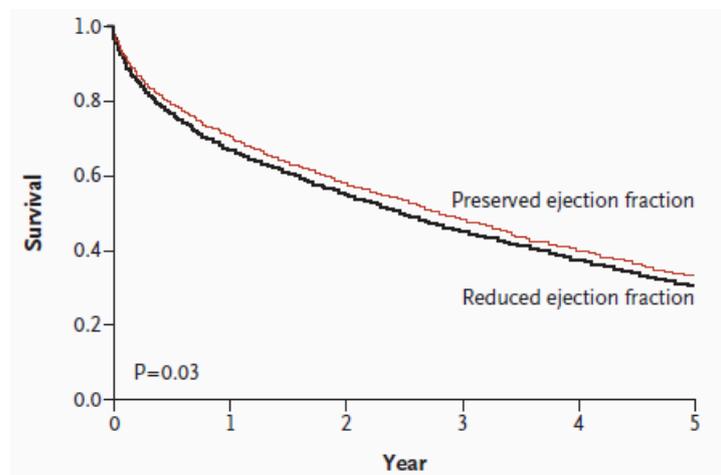
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## 1. Introduction

**Heart failure (HF)** is a major public health problem especially in industrialized nations. Approximately 15 million Europeans and North Americans have HF and over 1.5 million new cases of HF are diagnosed each year (1,2). Despite advances in diagnosis and treatment, the number of HF admissions has increased steadily, in part due to improved survival rates of patients with acute myocardial infarctions. During the past years, remarkable improvements in outcome of **chronic HF** could be achieved by introducing angiotensin converting enzyme inhibitors (ACE-inhibitors)(3), angiotensin II receptor blockers (ARB) (4,5), beta-blockers (6,7) and spironolactone (8) into the therapeutic strategy, making these agents standard of care and indispensable part of the medication regimen (1).

In contrast to medical therapy for chronic HF, which is scientifically based on several large prospective randomized controlled trials, therapy for **acute HF** is largely based on uncontrolled studies, clinical experience and expert opinion (2). The treatment guidelines of the European Society for Cardiology (ESC) for acute HF recommend the use of supplemental oxygen, morphine, vasodilators, diuretics and mechanical ventilatory support if necessary (2). Perhaps at least in part related to the uncertainties in the treatment of acute HF, outcome of patients with acute HF is extremely poor. Mortality is 50% at three years (9,10) even for patients treated in centers of excellence.



**Figure 1:** After hospitalization for acute HF, patients experience high mortality (9).

Although less than 15% of patients with acute HF are treated in the ICU / CCU setting, recent industry-initiated studies have enrolled predominately ICU / CCU patients and investigated single agents for their ability to impact on clinical outcome (11–15). None of these was able to show clinical benefit to the patient until now.

For multiple reasons including need for restrictive use of the limited number of ICU hospital beds available, the vast majority (more than 85%) of in general elderly patients with acute HF are treated in a **non-ICU setting**. Unfortunately, the optimal treatment of acute HF in the non-ICU setting is particularly ill defined. Uncertainties include the questions which drug to use, when to initiate them, which doses to use, and what pathophysiologic aims to pursue. Pathophysiological considerations and

preliminary data from the ICU setting suggest that aggressive venous and arterial vasodilatation may improve short and long-term outcome. Despite the presence of multiple undisputed differences between the ICU and non-ICU setting, the results of recent ICU studies can be seen as hypothesis generating regarding the optimal treatment in the non-ICU setting.

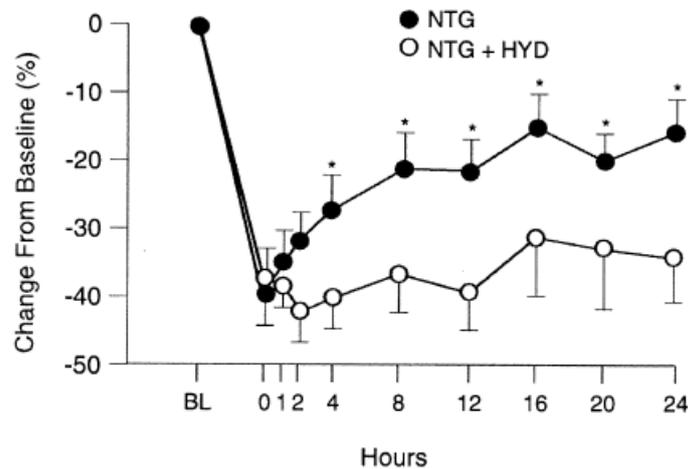
First, there is evidence from a recent ICU study using ultrafiltration for removal of excess fluid in selected patients unresponsive to standard doses of diuretics that improvements in initial in-hospital therapy have the potential to reduce re-hospitalizations and days in hospital during long-term (16). Second, aggressive decrement of preload and afterload in the ICU by intravenous nitrates seems to improve initial outcome (17–19). Cotter et al. compared low vs. high doses of intravenous nitrates in combination with diuretics in acute HF with pulmonary edema. Aggressive vasodilatation was associated with a reduced number of myocardial infarctions, higher oxygen saturation and reduced endotracheal intubations rates (17). Comparable results supporting aggressive vasodilatation in acute HF were achieved by Sharon et al. who compared high-dose intravenous nitrates versus BiPAP (non-invasive) ventilation combined with standard treatment in patients with pulmonary edema due to acute HF. Patients treated by aggressive vasodilatation had lower mortality rates, lower incidence of myocardial infarction and lower requirement for intubation as compared to the patients in the BiPAP group (18).

The transfer of an aggressive treatment strategy from the ICU to the non-ICU setting will require multiple adjustments (20), particularly considering limited patient monitoring, as well as the higher age and increased comorbidity in the non-ICU patients.

**Nitrates** have been used in the treatment of acute HF for several decades. Nitrates are converted to nitric oxide thereby stimulating the production of cyclic guanosine-monophosphate in smooth muscle cells thus promoting relaxation. In the last years, various preparations of organic nitrates have been extensively evaluated for their hemodynamic effect in patients with HF. All available formulations including oral (21), intravenous (19), and transdermal (22) share a similar hemodynamic effect and cause a substantial reduction in right and left ventricular filling pressure, systemic vascular resistance, systemic blood pressure, an increase in cardiac output and little or no change in heart rate (21). Increase in cardiac output is mostly related to the reduction in left ventricular afterload, but also influenced by a decrease in pulmonary vascular resistance (11), improvement in myocardial ischemia and reduction in the degree of mitral regurgitation (21). These acute hemodynamic effects make organic nitrates suitable for the treatment of acute HF in the setting of acute myocardial infarction or worsening of chronic HF(21).

Already in 1985, the dose requirements of transdermal nitroglycerin to achieve a significant and consistent drop in left ventricular filling pressure has been defined (23). According to these invasive hemodynamic studies, 60 mg / 24h of Nitroderm TTS are necessary to obtain a drop of 30% in left ventricular filling pressure in the majority of patients with HF. For unknown reasons, clinical practice has ignored this finding and used doses of 5 mg to 10 mg / 24 h Nitroderm TTS in the setting of acute HF.

Continuous administration or frequent dosing of nitrates may lead to early development of nitrate tolerance, associated with significant attenuation of nitrate-mediated hemodynamic effects (21,22). Hemodynamic and clinical studies have suggested that nitrate tolerance can be avoided and both, hemodynamic and clinical response improved if nitrates are used in combination with hydralazine.



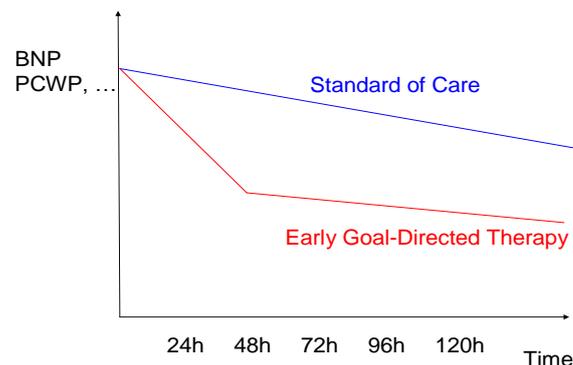
**Figure 2:** Effects of 24 h of nitroglycerin infusion alone (NTG) or in combination with hydralazine (NTG + HYD) on mean pulmonary capillary wedge pressure (21).

**Hydralazine** is a peroral applicable vasodilator with direct relaxant effect on arteriolar smooth muscle, which also has anti-oxidative effects. Several studies could show that the concomitant use of nitrates and hydralazine in patients with HF prevents development of nitrate tolerance and results in a persistent nitrate-mediated hemodynamic effect (21–24). The initial rationale for use of organic nitrates in combination with hydralazine was their complementary “nitroprusside-like” hemodynamic effect caused by the predominant venodilatory action of organic nitrates and the arterial-dilatory effect of hydralazine. This combination leads to a significant improvement in cardiac function, with a concomitant reduction in right and left ventricular filling pressures and augmentation of cardiac output (21). Based on this hemodynamic profile, the Vasodilator Heart Failure Trial (V-HeFT) compared the effect of nitrates in combination with hydralazine vs. placebo on outcome of patients with chronic HF and demonstrates improvements in left ventricular ejection fraction (LVEF), exercise tolerance, and survival in patients treated with isosorbide dinitrate (ISDN) and hydralazine (25). The V-HeFT II study compared the effects of ISDN and hydralazine versus the ACE-inhibitor enalapril and could demonstrate a significant improvement in LVEF during treatment with ISDN and hydralazine (26). A retrospective analysis of V-HeFT I and V-HeFT II showed that the benefit of ISDN and hydralazine was seen predominately in African Americans. This observation led to the design of the African American Heart Failure Trial (A-HeFT), which confirmed the survival benefit of these drugs in combination vs. placebo in African American patients with chronic HF(27).

It is currently unknown whether a strategy of cautiously unloading the heart and slowly increasing the dose of disease modifying therapy with ACE-inhibitors - the standard of care in the non ICU setting - is superior, equal, or inferior to an early goal directed therapy that targets a rapid and maximal reduction in the severity of HF (as

theoretically quantifiable by B-type natriuretic peptide or pulmonary capillary wedge pressure values; Figure 3) using aggressive vasodilatation.

Recent evidence from pilot studies for a long-term benefit of early aggressive therapeutic intervention in acute HF and the promising results obtained by vasodilatation with nitrates and hydralazine in chronic HF provide the rationale for our hypothesis that an early goal-directed decrement of preload and afterload with a target systolic blood pressure of 90 mm Hg to 110 mm Hg by aggressive vasodilatation in patients with acute HF in the non-ICU setting is safe, and leads to a better clinical and economical outcome. The early goal directed therapy as implemented by our protocol is expected to result in a more rapid resolution of symptoms, reduced time to discharge and reduced disease severity at the time of discharge. In addition, patients in the intervention group will receive a significantly higher dose of disease-modifying drugs like ACE-inhibitors and ARBs at the time of discharge. The difference in the dose of ACE-inhibitors and ARBs between both groups is expected to prevail within the first months of follow-up. The combination of both, improved disease state at discharge and higher doses of disease-modifying drugs during most of the study period is expected to result in a significant improvement in patient morbidity and mortality (11,28). This project is well in line with our previous research in this setting (10,29–31).



**Figure 3:** Theoretical model of expected effects of two different treatment strategies on quantitative markers of HF (B-type natriuretic peptide (BNP) or pulmonary capillary wedge pressure (PCWP)). Due to the aggressive preload and afterload decrement especially during the first 48 h of early goal directed treatment therapy, B-type natriuretic peptide and pulmonary capillary wedge pressure are expected to decrease faster and more pronounced than in the standard of care group.

## 2. Study Objectives

The aim of our study is to determine the safety and efficacy of an early goal-directed preload and afterload decrement with a target systolic blood pressure of 90 mm Hg to 110 mm Hg by aggressive vasodilatation versus standard medical care in a non-ICU setting in patients with acute HF.

### 2.1 Primary Endpoints

- Death or HF re-hospitalization at 180 days.

### 2.2 Secondary Endpoints

- All-cause mortality at 180 days.
- HF re-hospitalization at 180 days.
- Death or re-hospitalization from all causes at 180 days.
- Need for ICU admission during initial hospitalization.
- Acute coronary syndrome during initial hospitalization.
- Symptomatic hypotension during initial hospitalization.
- B-type natriuretic peptide (BNP) and creatinine level at 48 h and at discharge.
- Changes in circumferences of both legs and central venous pressure during hospitalization.
- Change in patient-assessed dyspnea at 48 h and prior to discharge.
- Blood pressure course over the first 6 days.
- Time to disappearance of a third heart sound (if present initially).
- Time to discharge.
- In-hospital days for HF at 180 days and 360 days.
- Total treatment cost at 180 days and 360 days.
- Functional status at 180 days and 360 days.
- Quality of life at 180 days and 360 days.
- Fractures due to falls within 180 days and 360 days.
- Death or HF re-hospitalization at 360 days.

Predefined subgroup analyses will be performed in patients younger or older than 75 years of age, men and women, systolic (LVEF < 45%) HF and HF with preserved LVEF, systolic blood pressure at presentation lower or higher than 140 mm Hg, coronary artery disease present or not, BNP levels lower or higher than 1000 pg/ml and isolated or concurrent right HF.

### 3. Study Design

This trial is designed as a prospective, randomized, controlled multicenter study coordinated by the University Hospital Basel. Patients will be enrolled in the emergency departments of participating sites:

- University Hospital Basel, Switzerland  
(Christian Mueller, MD, FESC, Professor of Medicine)
- Lucerne Cantonal Hospital, Switzerland  
(Paul Erne, MD, FESC, Professor of Medicine)
- Cantonal Hospital Aarau, Switzerland  
(Beat Mueller, MD, Professor of Medicine)
- Cantonal Hospital St. Gallen, Switzerland  
(Hans Rickli, MD, Professor of Medicine; Micha Maeder, MD)
- Hospital Clinic of the Faculty of Medicine University of São Paulo, Brazil  
(Múcio Tavares de Oliveira Jr., MD)
- University Medicine Mainz, Federal Republic of Germany  
(Thomas Muenzel, MD, Professor of Medicine)
- Faculty of Medicine University of Latvia, Riga, Latvia  
(Andrejs Ērglis, MD, Professor of Medicine)
- Hull and East Yorkshire Hospitals, United Kingdom  
(John Cleland, MD, Professor of Medicine)
- University Medicine Nürnberg, Federal Republic of Germany  
(Michael Christ, MD, Professor of Medicine)
- Mafraq Hospital Abu Dhabi, United Arab Emirates  
(Alexander Nicholas Jacobsen, MD)
- Hospital Universitari Germans Trias i Pujol Barcelona, Spain  
(Antoni Bayés-Genís, MD, Professor of Medicine)
- Hospital de la Santa Creu i Sant Pau Barcelona, Spain  
(Alessandro Sionis, MD, Professor of Medicine)
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(Petar Seferovic, MD, Professor of Medicine)
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(Assen R. Goudev, MD PhD, Professor and Chief of Cardiology)
- National Transport Hospital “Tsar Boris III” Sofia, Bulgaria  
(Valentina Mincheva, MD PhD, Professor of Medicine)
- 5-th Multifunctional Hospital for Active Treatment Sofia, Bulgaria  
(Bojidar Dimov, MD)
- University Hospital “Alexandrovska” Sofia, Bulgaria  
(Nikolay Runev, MD PhD, Professor of Medicine)

If necessary, further study sites can be enrolled.

Consulting experts (in alphabetical order):

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- Alexandre Mebazaa (MD, Professor of Anesthesiology and Critical Care  
Medicine), Paris, France
- Matthias Pfisterer (MD, FESC, FACC, FAHA, Professor of Cardiology),  
Basel, Switzerland
- Jürg Schifferli (MD, PhD, Professor of Medicine),  
Basel, Switzerland
- Christian Schindler (PhD in Mathematics),  
Basel, Switzerland

## 4. Study Subjects

To be enrolled in the study, each patient must meet all of the following inclusion criteria and none of the following exclusion criteria.

### 4.1 Patients Selection and Inclusion Criteria

Acute HF expressed by acute Dyspnea New York Heart Association (NYHA) class III or IV and a BNP level  $\geq 500$  ng/l (or NTpro-BNP level  $\geq 2000$  ng/l). Due to inverse association of BNP levels and BMI, for Patients presenting with BMI of  $\geq 35$  kg/m<sup>2</sup>, the BNP cut point is  $\geq 350$  ng/l (or NTpro-BNP level  $\geq 1400$  ng/l) (32–34). Only NTpro-BNP, but not BNP, can be used for the inclusion of patients treated with LCZ696 (“Entresto”) (35,36). The diagnosis of acute HF is additionally based on typical symptoms and clinical findings, supported by appropriate investigations such as ECG, chest X-ray, and Doppler-echocardiography as recommended by current ESC guidelines on the diagnosis and treatment of acute HF(1,2). For inclusion in this study, all of the following criteria must apply:

- Acute HF.
- Age at least 18 years.
- Informed consent.
- Negative pregnancy test (only in female patients younger than 60 years).

### 4.2 Exclusion Criteria

- Cardiopulmonary resuscitation less than 7 days ago.
- Cardiogenic shock, ST-elevation myocardial infarction, or other clinical conditions that require immediate ICU admission or urgent PTCA.
- Systolic blood pressure lower than 100 mm Hg at presentation.
- Primary rhythmogenic cause of acute decompensation (ventricular tachycardia, reentry tachycardia, atrial fibrillation or atrial flutter with a ventricular rate exceeding 140 beats per minute).
- Non-ST-elevation myocardial infarction as primary diagnosis.
- Severe aortic or mitral stenosis.
- Adult congenital heart disease as primary cause of acute HF.
- Hypertrophic obstructive cardiomyopathy.
- Isolated right ventricular failure due to pulmonary hypertension.
- Chronic kidney disease with creatinine levels  $> 250$   $\mu$ mol/l.
- Bilateral renal artery stenosis.
- Severe sepsis or other causes of high output failure.
- Liver Cirrhosis Child-Pugh class C.
- Systemic Lupus erythematosus and related diseases.
- Acute aortic dissection.

- Porphyria.
- Previous adverse reactions to nitrates.
- Known hypersensitivity to hydralazine or dihydralazine.
- Patient in an emergency situation resulting in an inability to give informed consent.

## 5. Procedures

Figure 4: Study procedures.



## Diagnosis

To ensure maximal diagnostic accuracy at the time of inclusion in this study, the diagnosis of acute HF will be established as recommended by the current guidelines of the European Society of Cardiology for acute HF(1,2,37). The diagnosis of HF is based on patient history, physical examination, chest X-ray, ECG and BNP testing. Some patients will also have echocardiography performed in the acute setting. The diagnosis of HF results from a careful integration of the results of all of these investigations (Figure 4). The following findings suggest the presence of HF: history of HF, orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, distended neck veins, pulmonary rales, edema, laterally displaced and increased apical impulse, third heart sound, pathological ECG, radiologic signs of congestion or cardiomegaly in chest X-ray, BNP levels above 500 ng/l (respectively NT-proBNP levels above 2000 ng/l) and 350 ng/l if BMI  $\geq$  35 kg/m<sup>2</sup> (respectively NT-proBNP levels above 1400 ng/l), as well as severely impaired systolic or diastolic left ventricular function. If there are no clear clinical signs or symptoms (e. g. rales) or radiological findings (e. g. signs of congestion or cardiomegaly) ruling out an isolated right heart failure, echocardiography should be performed to confirm that there is no isolated right heart failure due to pulmonary hypertension.

When after integration of these findings the ED physicians quantifies the likelihood for the presence of HF using a visual analogue scale (38,39) as 80% or higher, a senior ED physician or a board certified cardiologist will examine the patient. When this one agrees with the proposed diagnosis and also judges the diagnosis of acute HF to be 80% or higher, the patient will be considered for inclusion in the study.

## Study inclusion and Randomization

Patients who fulfil all of the inclusion criteria and none of exclusion criteria will thoroughly be informed about study protocol and informed consent will be obtained.

Group assignment will be accomplished with the use of a computer-generated randomization scheme in a 1:1 ratio. Randomization will be stratified for enrolling site and the severity of HF as quantified by the BNP level (below or above 1000 ng/l/1000 ng/l) or NTpro-BNP level (below or above 4000 ng/l). Patients will be randomized to either the early goal directed group or the control group. The initial therapeutic goal is identical in both groups: the rapid resolution of dyspnea at rest.

## Study Therapy Early Goal-Directed Group

Early goal-directed preload and afterload decrement with a target systolic blood pressure of 90 mm Hg to 110 mm Hg for the entire hospitalization. This blood pressure target is considered to represent the maximal feasible afterload decrement without impairment of critical organ perfusion (40). This pathophysiologic goal is pursued by predominately applying nitrates, ACE-inhibitors and ARBs at maximal tolerable (avoiding arterial hypovolemia and inadequate arterial perfusion pressure) doses.

The treatment schedule is displayed in Figure 5a. Accordingly, on day 1 (0 h till 24 h) treatment will be started with one capsule of sublingual nitrates (containing usually 0.8 mg glyceryl trinitrate) or two applications of nitrospray (containing usually 0.4 mg

glyceryl trinitrate per application) in combination with transdermal nitrates (for example Nitroderm TTS<sup>®</sup> 10 mg / 24h) in a dosage between 40 to 80 mg / 24 h depending on admission systolic blood pressure. 10 and 20 minutes after the initial sublingual nitrates capsule or nitrospray application, one additional capsule of sublingual nitrates (containing usually 0.8 mg glyceryl trinitrate) or two applications of nitrospray (containing usually 0.4 mg glyceryl trinitrate per application) will be administered (in total three capsules sublingual nitrates or six applications of nitrospray). After 6 hours a dose adjustment of the transdermal nitrates dependent on systolic blood pressure will be performed (Figure 5a). On day 1 and 2, transdermal nitrates will be applied as continuous therapy for 24 hours each patch. In patients without severe renal dysfunction (defined as calculated glomerular filtration rate below 30 ml/min) and without evidence of an acute coronary syndrome (accompanying chest pain, new ECG changes, elevated cardiac Troponin T), hydralazine will be added orally to achieve an early maximal vasodilative effect and to avoid tolerance to nitrates. Hydralazine will be administered in a fix dosage of 25 mg every 6 hours (1 - 1 - 1 - 1) for the first 48 hours after study inclusion. Patients with evidence for an acute coronary syndrome (Cave: “coronary steal”) or with severe renal dysfunction (Cave: accumulation) will not receive hydralazine, but nitrates only.

On day 2 (24 h till 48h) the dosage of transdermal nitrates will be adjusted according to systolic blood pressure. In addition, at 24 hours after study inclusion, therapy with a peroral ACE-inhibitor or in case of ACE-inhibitor intolerance an ARB will be initiated. Should the patient be already on an ACE-inhibitor, the dosage remains unchanged for the first 24 hours. On day 2 (after 24 hours) the ACE-inhibitor will be up-titrated according to therapy schedule (Figure 5a) starting from day 2. Thereby, the up-titration will be performed on the top of the precedent ACE-inhibitor / ARB dosage. Should the patient be already on a maximal dosage of an ACE-inhibitor, an ARB will be added at low dose once daily and up-titrated according to the therapy schedule. In patients with chronic HF and a LVEF below 35%, the treating physician may at any time (both in-hospital and after hospitalization) consider to replace a preexisting therapy with an ACE-inhibitor or ARB with LCZ696 as recommended in the 2016 ESC guidelines (37). Should the patient already be on LCZ696 (“Entresto”), the dosage remains unchanged for the first 24 hours. On day 2 (after 24 h) the dose of LCZ696 will be up-titrated by 25% if not already on target dose (200 mg b.i.d.). Again, the dose should be increased by 25% at the end of hospitalization (if not already at 200 mg b.i.d.).

Intervention group	day 1 at hospital admission		day 1 6 h after admission		
	< 130 <sup>1)</sup>	> 130 <sup>1)</sup>	90 - 110	111 - 130	> 130
systolic blood pressure [mm Hg]	< 130 <sup>1)</sup>	> 130 <sup>1)</sup>	90 - 110	111 - 130	> 130
per oral Glyceryl trinitrate capsule (i.e. Nitroglycerin Streuli <sup>®</sup> ) 0.8 mg <sup>2)</sup> or Spray (i.e. Corangin Nitrospray <sup>®</sup> ) 0.4mg	3 or 6 applic.	3 or 6 applic.			
transdermal Glyceryl trinitrate (i.e. Nitroderm <sup>®</sup> TTS) [mg / 24 h]	40 - 60	60 - 80	+ 0	+ 20 - 40	+ 20 - 60
Hydralazine (i. e. Hydrapres <sup>®</sup> ) 25 mg	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1
Ramipril (i. e. Triatec <sup>®</sup> ) [mg/d] <sup>3)</sup>					
Lisinopril (i. e. Zestril <sup>®</sup> ) [mg/d] <sup>3)</sup>					
Enalapril (i. e. Reniten <sup>®</sup> ) [mg/d] <sup>3)</sup>					

- <sup>1)</sup> The lowest blood pressure value measured at the emergency department before study inclusion will be considered.
- <sup>2)</sup> The first capsule should be administered at study inclusion, 10 and 20 minutes after the first capsule one more capsule should be administered (total three capsules).
- <sup>3)</sup> Only one ACE-inhibitor should be started.
- <sup>4)</sup> ARB will only be administered initially if patients already receive the maximal dosage of an ACE-inhibitor or if ACE-inhibitor intolerance is known.
- <sup>5)</sup> An additional treatment with ARB should be considered (according to the ARB up-titration days 2 to 7).

Captopril (i. e. Capoten®) [mg/d] <sup>3)</sup>					
Candesartan (i. e. Atacand®) [mg/d] <sup>4)</sup>					
Losartan (i. e. Cozaar®) [mg/d] <sup>4)</sup>					

**Figure 5a:** Treatment algorithm for the early goal-directed therapy group.

Intervention group continuation	day 2 24 h till 48 h after admission				day 3 48 h till 72 h after admission			
	90 - 110	111 - 130	131 - 150	> 150	90 - 110	111 - 130	131 - 150	> 150
systolic blood pressure [mm Hg]	90 - 110	111 - 130	131 - 150	> 150	90 - 110	111 - 130	131 - 150	> 150
transdermal Glyceryl trinitrate (i.e. Nitroderm® TTS) [mg / 12 h]	+ 20 - 40	+ 20 - 60	+ 40 - 80	+ 40 - 80	50% of day 2	50% of day 2	75% of day 2	100% of day 2
Hydralazine (i. e. Hydrapres®) 25 mg	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1	1 - 1 - 1 - 1				
Ramipril (i. e. Triatec®) [mg/d] <sup>3)</sup>	1.25	1.25	2.5	2.5	2.5 - 3.75	2.5 - 3.75	2.5 - 5	2.5 - 5
Lisinopril (i. e. Zestril®) [mg/d] <sup>3)</sup>	2.5	2.5	5	5	2.5 - 5	5 - 7.5	10 - 15	10 - 20
Enalapril (i. e. Reniten®) [mg/d] <sup>3)</sup>	5	5	10	10	5 - 10	5 - 10	10 - 15	10 - 20
Captopril (i. e. Capoten®) [mg/d] <sup>3)</sup>	37.5	37.5	50	50	37.5 - 50	37.5 - 50	50 - 75	50 - 75
Candesartan (i. e. Atacand®) [mg/d] <sup>4)</sup>	4	4	8	8	8 - 16	8 - 16	16 - 24	16 - 24
Losartan (i. e. Cozaar®) [mg/d] <sup>4)</sup>	25	25	50	50	25 - 50	25 - 50	50 - 75	50 - 75

Intervention group continuation	day 4 72 h till 96 h after admission				day 5 96 h till 120 h after admission			
	90 - 110	111 - 130	131 - 150	> 150	90 - 110	111 - 130	131 - 150	> 150
systolic blood pressure [mm Hg]	90 - 110	111 - 130	131 - 150	> 150	90 - 110	111 - 130	131 - 150	> 150
transdermal Glyceryl trinitrate (i.e. Nitroderm® TTS) [mg / 12 h]	25% of day 2	25% of day 2	50% of day 2	75% of day 2			25% of day 2	50% of day 2
Ramipril (i. e. Triatec®) [mg/d] <sup>3)</sup>	3.75 - 5	3.75 - 5	5 - 7.5	5 - 7.5	5 - 7.5	5 - 7.5	7.5 - 10	7.5 - 10
Lisinopril (i. e. Zestril®) [mg/d] <sup>3)</sup>	5 - 10	10 - 15	15 - 20	15 - 25	10 - 15	15 - 20	20 - 30	20 - 30
Enalapril (i. e. Reniten®) [mg/d] <sup>3)</sup>	10 - 15	10 - 15	15 - 20	20 - 30	15 - 20	15 - 20	20 - 30	30 - 40
Captopril (i. e. Capoten®) [mg/d] <sup>3)</sup>	50 - 75	50 - 75	75 - 100	75 - 100	75 - 100	75 - 100	100 - 150	100 - 150
Candesartan (i. e. Atacand®) [mg/d] <sup>4)</sup>	12 - 24	12 - 24	16 - 24	16 - 24	16 - 24	24 - 32	24 - 32	24 - 32
Losartan (i. e. Cozaar®) [mg/d] <sup>4)</sup>	50 - 75	50 - 75	75 - 100	75 - 100	75 - 100	75 - 100	75 - 100	75 - 100

Intervention group continuation	day 6 120 h till 144 h after admission				day 7 144 h till 168 h after admission			
	90 - 110	111 - 130	131 - 150	> 150	90 - 110	111 - 130	131 - 150	> 150
systolic blood pressure [mm Hg]	90 - 110	111 - 130	131 - 150	> 150	90 - 110	111 - 130	131 - 150	> 150
transdermal Glyceryl trinitrate (i.e. Nitroderm® TTS) [mg / 12 h]								
Ramipril (i. e. Triatec®) [mg/d] <sup>3)</sup>	7.5 - 10	7.5 - 10	10	10 <sup>5)</sup>	10	10	10 <sup>5)</sup>	10 <sup>5)</sup>
Lisinopril (i. e. Zestril®) [mg/d] <sup>3)</sup>	15 - 20	20 - 30	20 - 30	30 <sup>5)</sup>	20 - 30	20 - 30	30 <sup>5)</sup>	30 <sup>5)</sup>
Enalapril (i. e. Reniten®) [mg/d] <sup>3)</sup>	20 - 30	20 - 30	30 - 40	40 <sup>5)</sup>	30 - 40	30 - 40	40 <sup>5)</sup>	40 <sup>5)</sup>
Captopril (i. e. Capoten®) [mg/d] <sup>3)</sup>	100 - 150	100 - 150	150	150 <sup>5)</sup>	150	150	150 <sup>5)</sup>	150 <sup>5)</sup>
Candesartan (i. e. Atacand®) [mg/d] <sup>4)</sup>	24 - 32	24 - 32	32	32	24 - 32	24 - 32	32	32
Losartan (i. e. Cozaar®) [mg/d] <sup>4)</sup>	75 - 100	75 - 100	100	100	75 - 100	100	100	100

### Important Treatment Rules

- ACE-inhibitor can be administered once or twice per day. ARB should be administered only once a day.
- If Patient is already on ACE-inhibitor or ARB continue dosage unchanged during day 1 and perform up-titration following day 2 till 7 schedule.
- If the patient is already treated with another ACE-inhibitor / ARB than listed in the schedule, previously prescribed ACE-inhibitor / ARB should be continued unchanged during day 1. A daily up-titration of approximate 50% (25% to 75% depending on blood pressure response) starting from day 2 is recommended. The maximal dosage should be achieved at day 5 to 7 of treatment if well tolerated.
- If creatinine levels rise more than 50% from baseline continue ACE-inhibitor / ARB in unchanged dosage to creatinine levels begin to decline. Then continue up-titration according to the treatment schedule.
- If creatinine levels rise more than 100% from baseline reduce ACE-inhibitor / ARB treatment by 50% and continue therapy with unchanged dosage until creatinine levels decline more than 30%.
- Treatment with any diuretics or aldosterone-antagonists at any time is at discretion of treating physician and not determined by the study protocol.

**Figure 5a:** Treatment algorithm for the early goal-directed therapy group (continuation).

On day 3 a further up-titration of the ACE-inhibitor / ARB depends on systolic blood pressure according to Figure 5a will be performed. In patients on LCZ696, the dose of LCZ696 remains unchanged. The dosage of transdermal nitrates will be gradually decreased from day 3 till hospital discharge (Figure 5a). Also, intermittent dosing (12 hours nitrates, 12 hours nitrate-free period) will be used from day 3 on. Typically, we would use in half the dose applied at day 2 and apply the patches from 8:00 h am till 8:00 h pm.

On day 4 till day 7 a further up-titration of the ACE-inhibitor / ARB dependent on systolic blood pressure according to Figure 5a will be performed. In patients on LCZ696 the dose of LCZ696 will be up-titrated by again 25% if not already on target dose (200 mg twice daily).

If patients are pre-treated with either ACE-inhibitor or ARB, therapy with these agents will be continued during the first 24 hours at the pre-existing dosage and afterwards up-titrated following the therapy schedule starting with day 2. Should the patient be already treated with another ACE-inhibitor / ARB than listed in the therapy schedule (Figure 4), the previously prescribed ACE-inhibitor / ARB will be continued in an unchanged dosage. The up-titration will then be performed in a comparable way like demonstrate in the schedule (Figure 5a). A daily up-titration of approximate 50% (25% to 75% depending on blood pressure response) starting from day 2 is recommended. The maximal dosage should be achieved after 5 to 7 days of treatment if well tolerated.

Hydralazine Hydrochlorid:

Until December 2012 Hydralazine Hydrochlorid was administered using Apresoline® 25mg (Hydralazine Hydrochlorid). From January 2013 Hydralazine Hydrochlorid will be administered using Hydrapres® 25mg (Hydralazine Hydrochlorid) as the former no longer was commercially available.

### **Study Therapy Control Group**

The current guidelines of the European Society of Cardiology do not recommend the use of ACE-inhibitors or ARB in the early stabilization of patients with acute HF (41). (37). The administration of previously prescribed ACE-inhibitors or ARB should be continued on admission with AHF, except in the presence of hemodynamic instability, hyperkalemia or severely impaired renal function. In these cases, the daily dosage of oral therapy may be reduced or stopped temporarily until the patient is stabilized. In the absence of a prescription, an initiation of the medication before discharge from hospital and up-titration every two to four weeks is recommended (37). Accordingly, patients in the control group will receive (1,2) oxygen application, treatment with diuretics based on extent of fluid overload and recent weight gain. The dosage thereby will be adjusted to renal function. Further on, after 24 to 48 hours, treatment with an ACE-inhibitor (or ARB) will be started in low dosages displayed in Figure 5b. After six to eight days of treatment, dosage of the ACE-inhibitor / ARB will be up-

titrated following the schedule displayed in Figure 5b dependent on hemodynamic and renal tolerance. As in the Intervention group, in patients with chronic HF and a LVEF below 35%, the treating physician may at any time (both in-hospital and after hospitalization) consider to replace a preexisting therapy with an ACE-inhibitor or ARB with LCZ696 as recommended in the 2016 ESC guidelines (36). Should the patient already be on LCZ696 (“Entresto”), the dosage will remain unchanged for the first 4 to 5 days with the option of increasing the dose by 25% at the end of hospitalization (if not already at 200 mg b.i.d).

Transdermal nitrates can be used, but only in the doses currently approved in Switzerland (e. g. Nitroderm TTS 5 mg / 12 h or 10 mg / 12h). The use of nitrates or hydralazine in higher doses is strongly discouraged. The use of a specific blood pressure target is up to the discretion of the treating physician.

Should the patient be already treated with another ACE-inhibitor / ARB not listed in the therapy schedule (Figure 5b), again the previously prescribed ACE-inhibitor / ARB will be continued in an unchanged dosage if tolerated for the first two to three days after which up-titration will then be performed in a comparable way like demonstrate for the ACE-inhibitors / ARBs listed in Figure 5b. Accordingly up-titration of 50% will be performed every seven to 21 days to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (37).

Control group	Starting dose (mg)	Target dose (mg) <i>* if patient is still hospitalised</i>
transdermal Glyceryl trinitrate (i.e. Nitroderm® TTS) [mg / 12 h]	0 - 10	0 - 10
Ramipril (i. e. Triatec®) [mg/d] <sup>3)</sup>	2.5 o.d.	10 o.d.
Lisinopril (i. e. Zestril®) [mg/d] <sup>3)</sup>	2.5–5.0 o.d	20–35 o.d.
Enalapril (i. e. Reniten®) [mg/d] <sup>3)</sup>	2.5 b.i.d.	20 b.i.d.
Captopril (i. e. Capoten®) [mg/d] <sup>3)</sup>	6.25 t.i.d.	50 t.i.d.
Candesartan (i. e. Atacand®) [mg/d] <sup>4)</sup>	4–8 o.d	32 o.d
Losartan (i. e. Cozaar®) [mg/d] <sup>4)</sup>	50 o.d.	150 o.d.

<sup>3)</sup> Only one ACE-inhibitor should be started.  
<sup>4)</sup> ARB will only be initiated if ACE-inhibitor intolerance is known.

**Figure 5b:** Treatment algorithm for the control group as recommended by the current ESC guidelines.

### Duration of Treatment with Study-Specific Medication

The study-specific medication with hydralazine in the goal-directed therapy group ends after 48 h after enrolment in the study. The dosage of glycerol trinitrate and up-titration with ACE-Inhibitors and / or ARBs in both groups will be performed according to the treatment algorithms in Figures 5a and 5b during the hospital stay until discharge. Information about discharge medication will be given for both groups; if necessary the discharge summary will provide instructions for maintenance dosage or further up-titration of ACE-inhibitors and / or ARBs to the treating physician in ambulant setting.

### Patient Safety: Symptomatic Arterial Hypotension

If systolic blood pressure should fall below the target of 90 mm Hg to 110 mm Hg and signs or symptoms of arterial hypotension occur, an adjustment of medical therapy following a predefined schedule will be performed:

- **Day 1 and 2 (0 h till 48 h):** Reduction of 50% of the transdermal applied nitrates by immediate removal of the patches and temporary withdrawal of hydralazine. Additionally blood pressure monitoring will be performed every 30 minutes to 60 minutes until hemodynamic stability has been reestablished.
- **Day 3 till discharge:** Reduction of 50% of the transdermal applied nitrates by immediate removal of the patches and temporary dosage reduction of the ACE-inhibitor or ARB to the dosage of the last day when the patient was asymptomatic. Additionally blood pressure monitoring may be performed if deemed necessary.
- **At any time during the study:** If these measures do not help to increase systolic arterial blood pressure, physical measures like the elevation of the patient's legs and as an ultima ratio intravenous administration of crystalloid fluid can remove symptoms and hemodynamic impairment. After termination of the symptomatic hypotensive episode, a stepwise augmentation of transdermal nitrates, hydralazine or ACE-inhibitor / ARB will be reinitiated.

Importantly, asymptomatic hypotension without evidence for critical organ dysfunction will not lead to any change in medical therapy, as maximal afterload reduction is an integral part of the intervention.

### **Patient Safety: Worsening Renal Function**

Some rise in creatinine and blood urea nitrogen levels is commonly seen in patients with acute HF. Often it is not possible to identify a single cause, but hypovolemia induced by diuretic treatment, low output as part of acute HF, renal venous congestion or initiation of ACE-inhibitors / ARB may play a role. Regarding the up-titration of ACE-inhibitors / ARB current guidelines suggest that changes in creatinine or blood urea nitrogen levels should not be considered clinically important unless they are rapid and substantial (41). Accordingly, a creatinine rise less than 50% from baseline values will be carefully monitored without adjustment of treatment schedule. In case of a rise of more than 50% of the baseline value, the treatment with ACE-inhibitors / ARB will be continued without augmentation and creatinine levels will be monitored every 24 hours to 48 hours. As soon as creatinine levels begin to decline, dosage of ACE-inhibitor / ARB will be up-titrated according to the treatment schedule (Figures 4a / 4b). In case of acute renal injury, defined as a doubling in serum creatinine levels compared to baseline levels (42), the following procedural schedule will be applied: A 50% reduction of the last ACE-inhibitor / ARB dosage will be performed and creatinine levels will be measured 24 hours to 48 hours later. When creatinine levels continue to rise despite this measure, a further stepwise decrease of 50% of the ACE-inhibitor / ARB is scheduled and will be repeated every 48 hours until creatinine levels begin to decline. When creatinine levels remain unchanged or decrease less than 30% of peak level, the current dosage of ACE-inhibitor / ARB will remain unchanged. As soon as creatinine levels decrease at least 30% to peak value, the initial study therapy schedule will be continued (Figures 4a / 4b). As the

dose of diuretics is an important contributor to renal injury, diuretic dose will also be reduced by at least 50% in patients with renal injury.

If systolic blood pressure still persists over 140 mm Hg despite the treatment schedule described above during day 3 to 6, higher doses of ACE-inhibitors or ARBs are recommended. The addition of a calcium-channel blocker (preferably amlodipine, Norvasc®(43) can be considered alternatively. The use of beta-blockers and spironolactone will be identical to that described in the control group.

### **General Procedure for Both Groups**

At any time in the study the use of further treatment including loop diuretics, aldosterone antagonists, morphine or other drugs or non-pharmacological therapies (including non-invasive ventilation) will always be dependent on the clinical conditions and will be at the discretion of the treating physician.

Non-invasive hemodynamic monitoring will be performed every 10 to 30 minutes during the first hour, every 30 to 90 minutes in the second to the fourth hour, and every 6 to 8 hours for the rest of the hospitalization as currently in practice at the enrolling institutions. Continuous recording of a three-channel ECG and transdermal oxygen saturation provided by automated monitoring systems will be applied as clinically indicated.

At the time of initial presentation and before discharge the patient leg circumference will be measured at three distinct points on either side: 10 cm distal from the caput fibulae, 5 cm above the ankles and at the middle of the metatarsi. The points of measurement will be marked. A special tape measure incorporating a spring exercising constant tension will be used ensuring a measurement independent of the strain applied by the investigator. Simultaneously and when possible, the central venous pressure will be obtained with a high resolution ultrasound imaging device combined with a translucent pressure manometer.

In addition, 15 ml of serum, EDTA plasma and urine will be collected at five time points (at baseline, at day 1, day 2, day 6 and discharge) for the measurement of biomarkers such as BNP, NT-proBNP, mid-regional pro-atrial natriuretic peptide, pro-adrenomedullin, copeptin, N-GAL, Cystatin C, Troponin T, and pro-endothelin that also reflect the response to treatment. The determination of NT-proBNP, mid-regional pro-atrial natriuretic peptide, pro-adrenomedullin, copeptin, N-GAL, Cystatin C, Troponin T, and pro-endothelin and pro-endothelin will be performed collectively after hospital discharge of patients and has no effect on patient treatment.

Transthoracic echocardiography (TTE) for the detailed assessment of systolic, diastolic, and valvular function will be performed as clinically indicated in the majority of patients. Response to therapy will be documented by daily clinical patient assessment using a predefined questionnaire as well as a visual analogue scale to record subjective course of dyspnea. Periodical measurements of electrolytes (sodium, potassium) and creatinine at study inclusion, every 24 to 72 hours during the first week and at discharge will be accomplished.

In the further course of treatment (usually one or two days before discharge), a beta-blocker will be added to this therapy at very low dose. Augmentation of the beta-blocker dosage will only be performed after discharge during the outpatient phase. Spironolactone (an aldosteron-receptor-antagonist) may be added in patients who remain in NYHA classes III and IV and in patients with low potassium concentration at presentation, as long as they have a serum creatinine below 150 µmol/l.

Despite early blood pressure intervention in the study group, special attention will be given to the final drug-treatment in both study groups. As ACE-inhibitors / ARB and beta-blockers provide the best documented survival benefit in patients with HF (3,7), initiation of a beta-blocker before hospital discharge will be strongly endorsed, and treatment of an equal percentage of patients in both arms with these two agents remains crucial.

### **Patient-assessed Dyspnea**

In order to assess the subjective sensation of dyspnea in the different treatment arms, patients will undergo a specific dyspnea test using a questionnaire and a visual analogue scale (VAS) according to the newest expert recommendations (41). This test will be performed at randomization, after 24 hours of treatment and prior to discharge. First, in sitting position (60°), patients will be asked how short of breath (SOB) they feel. There will be five different possible categories, reaching from “I am not SOB” to “I am severely SOB”. Afterwards, patients will be asked to draw a line on a VAS reaching from “I am not breathless at all” to “I am the most breathless I have ever been” indicating their subjective dyspnea. Afterwards, patients will be placed in laying position (20°) for three minutes and again subjective sensation of dyspnea using the above mentioned questionnaire as well as the VAS will be assessed. The difference in the VAS values between sitting (60°) and laying (20°) position will be documented. Furthermore, patients have to classify the difference in SOB lying down compared to sitting up using four categories reaching from “no difference” to “markedly worse”.

### **Questionnaire**

In order to estimate the possible effects of this open labelled study on patients' subjective outcome, a questionnaire is carried out at day 6 and discharge, respectively. It aims to assess to what extent the patient recalls in which study group he/she was enrolled in.

### **Discharge**

To minimize the effects of conditions unrelated to the acute HF episode on the length of hospital stay, a dedicated discharge protocol has been implemented in the months preceding this study. This interdisciplinary protocol was designed to optimize the transition from hospital to outpatient care. In addition, the protocol will help reduce the effects of treatment of co-morbidities and social issues related to placement of patients after discharge on the non-medical on the duration of hospitalization. To provide an objective measurement of physical performance permitting discharge, we will assess the ability of the patient to cover a simple standardized walking distance

on the ward without being limited by dyspnea. This walking test will in general be performed at day six after study inclusion.

Identical detailed discharge instructions (instructions and written instructions and / or educational material) including information about levels of activity, diet, discharge medication, follow-up appointment, weight monitoring, and what to do if symptoms worsen will be given in both groups.

### **Follow up**

90 days, 180 days and 360 days after hospital discharge, patients would be contacted by telephone and re-hospitalization, current medication, NYHA-classification as well as mortality if occurred would be documented. Further quality of life will be questioned using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EQ-5D index (EuroQol group) during initial hospitalization and after 180 days. The KCCQ is a disease specific questionnaire designed to measure the effects of HF and treatments for HF on an individual's quality of life. The EQ-5D is a generic questionnaire, applicable to a wide range of health conditions and treatment, providing a simple descriptive profile and an index value for health status.

### **Biobank**

Blood and urine samples are cryogenic stored (biobank) for up to ten years at a specific location at the University Hospital of Basel to analysis of emergent biomarkers associated with decompensated heart failure. All information are stored in order to protect from unauthorized access, loss, destruction and transformation. All samples are stored in a reversible anonym way. The biobank follows the OECD guidelines in order to guarantee protection in the process of sample submission and sample storage. Access to the samples is strictly restricted to the members of the research group. There are special regulations concerning the extraction, storage and use of human biological material (biobank reglament).

The samples are shipped in dry ice by specialized shipment company. Sample and data are anonymized before the shipment. Patients are informed about the existence and location of the biobank, the reasons of the storage and for how long the sample will be stored. Patients are informed about their right to request the destruction of the stored sample without giving any reason.

Every transfer has to be regulated by a Material Transfer Agreement and documented.

## **6. Risks and Benefits**

Early goal-directed preload and afterload decrement by aggressive vasodilatation with a target systolic blood pressure of 90 mm Hg to 110 mm Hg by using a fix therapy schedule has the potential to achieve faster cardiac re-compensation without jeopardizing major organ blood supply. Therapy with nitrates in dosages known to decrease preload and afterload in acute HF has been tested in two clinical trials and found to be superior to low dose nitrates in patients treated in mobile ICU. However,

the main potential adverse event induced by aggressive vasodilatation is arterial hypotension and consecutive decrement in renal and other major organ blood flow. Data from the A-HeFT study assure that the risk for an aggravation of a preexisting arterial hypotension (systolic blood pressure below 110 mm Hg) in therapy with nitrates and hydralazine is low, and that also patients with preexisting arterial hypotension will benefit from this therapy option (44). It is the concept of this study that the clinical hemodynamic monitoring available in the emergency department (first 24 hours) and general medical ward (second 24 hours and remaining hospitalization) allows the judicious use of this fix therapy schedule to achieve requested vasodilatation and the target blood pressure. It is important to note that in case of symptomatic arterial hypotension easy applicable measures to increase blood pressure are available. A major advantage of the transdermal application form of nitrates during the initial part of the study is the option to stop drug resorption by removing the patch.

During the first 48 hours patients would be encouraged to perform gymnastics of their calves before standing up and leave their beds only in company of the responsible nurse, in order to avoid symptoms of orthostatic hypotension. In case of headache, which is a common side effect in nitrate therapy, treatment would be effectuated with paracetamol (e. g. Perfalgan<sup>®</sup>) 1 g intravenous.

In order to avoid a possible “steal phenomenon” of hydralazine, patients with evidence for an acute coronary syndrome will be treated only with nitrates and will not receive hydralazine.

For routine clinical monitoring withdrawal of blood specimen will be necessary. This is associated with a minimal residual risks associated with peripheral venipuncture including hematoma, bruising, and skin infection that is unrelated to this study as it is clinically indicated. All patients can expect to receive superior patient care as compared with patients not entered in this trial. In addition, on the long-term, patients themselves may benefit from improvement in treatment options documented in this study. HF is characterized by recurrent decompensations. Therefore, chances are high, that the insight gained by this study will be available for the clinical care of the majority of patients during their next episode of decompensation.

## **7. Study Withdrawal**

A) Discontinuation of participation of the patient due to withdrawal of consent

B) Discontinuation of participation due to:

- a) disclosure of exclusion criteria after enrolment;
- b) occurrence during participation in study of a serious new clinical event which contraindicates vasodilatation, e.g. acute stroke, acute traumatic brain injury with cerebral edema;
- c) decision of the treating medical team to switch towards palliative care

If there are findings that indicate that a further participation in the study would lead to a disproportionate risk for the patient’s health or life, the patient may be excluded from the study.

In case of an adverse event or a serious adverse event (e. g. symptomatic hypotension, acute coronary syndrome, acute kidney injury etc.) or known or unexpected side effects related to the study medication the treatment with the concerning medication will be adjusted or suspended. All other procedures remain unaffected and the patient will not be excluded from the study.

## **8. Data Management and Statistics**

### **8.1 Data Management and Monitoring**

To appropriately describe the patient population, a dedicated case report form (CRF) including detailed patient history, physical examination, vital parameters during hospitalization and adverse events will be completed. Cost data will be converted in US dollar using the exchange rate of February 1<sup>st</sup>, 2009. All relevant data will be entered into SecuTrial® (interActive Systems GmbH, Berlin Germany) and Microsoft® Access® 2010 (Version 14.0.7162.5001, Microsoft®, USA). The use of these data is restricted to scientific purposes. Data management and monitoring support will be provided by the Clinical Trial Unit of the University Hospital Basel.

### **8.2 Statistical Analysis**

The statistical analyses will be performed using the SPSS / PC (version 14.0, SPSS Inc., USA) software package. A statistical significance level (p-value) of 0.05 will be used. All data will be analyzed on an intention-to-treat basis. Comparisons will be made using the t-test, Mann Whitney U-test, Fisher's exact test, survival analysis (Kaplan Meier method), Cox regression analysis and chi-square test as appropriate. All hypothesis testing will be two-tailed. Statistical support will be performed by Dr. Christian Schindler from the Institute of Social and Preventive Medicine of the University of Basel.

### **8.3 Power and Sample Size of the Trial**

Based on the data from the BASEL study (31), a hypothesized 20%-decrease of the composite endpoint death or HF re-hospitalization at 180 days, will require 385 patients per treatment arm to obtain, with a probability of 80, a log rank test result that is statistically significant at the 5%-level.

## **9. Study Schedule**

- Recruitment of first patient: November 10<sup>th</sup>, 2007
- Recruitment of last patient: if n = 770
- 180 day follow up complete: n = 770 + 180 days
- 360 day follow up complete: n = 770 + 360 days (last visit last subject)
- Main manuscript submission: n = 770 + 540 days

## **10. Regulatory Considerations, Ethical Review, Confidentiality Informed Consent and Liability**

### **10.1 Regulatory Considerations**

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable International Conference on Harmonization (ICH) guidelines on good clinical practice, whichever represents the greater protection of the individual.

### **10.2 Ethical Review**

This protocol will be submitted for approval by the conjoined local ethic committee of the Northwestern and Central part of Switzerland, respectively the competent local ethic committees or IRBs for all other participating sites.

### **10.3 Confidentiality**

All medical records and data are bound to professional discretion and will be kept in confidence. Data will be organized, managed, and stored in a password protected software database and only study team members and the ethical committee will be able to access them. No data will be sent over the internet unless it is de-identified.

### **10.4 Informed Consent**

Patients will be asked to give written informed consent before study entry. They will agree on the use of their data for scientific purposes. The informed consent document will be used to explain in simple terms the aim of the study, and required procedures. The informed consent document contains a statement that the consent is freely given, and that the patient is free to withdraw from the study at any time.

### **10.5 Liability**

Diagnostic and therapeutic procedures in this clinical trial are covered by liability insurances. Study subjects at centers in Switzerland are insured by the University Hospital Basel with Zurich Versicherungen AG. For centers outside Switzerland, the coverage will be organized by the sponsor when possible. Alternatively, the participating center will seek and -previously approved by the sponsor - hire an insurance policy whose cost will be reimbursed by the sponsor.

### **10.6 Definition and Reporting of Adverse Events**

According to the Federal Law on Medicinal Products and Medical Devices (Law on Therapeutic Products - LTP) and the Federal Law on Clinical Trials with Medicinal Products (VKlin) the following predefined events that occur during trial period must be recorded and reported to the authorities:

- Adverse Events (AE)
- Serious Adverse Events (SAE)

- Suspected Unexpected Serious Adverse Reaction (SUSAR)

### **10.6.1 Definition of Adverse Events according to the International Conference of Harmonization (ICH)**

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject, who has been administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medical (investigational) product.

A **Serious Adverse Event (SAE)** means an adverse event that requires either in-patient hospitalization, prolongation of existing hospitalization, is a congenital anomaly / birth defect, results in persistent or significant disability or incapacity, is life threatening, or results in death.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is defined as a serious adverse event / drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigators Brochure for an unapproved investigational medicinal product).

### **10.6.2 Reporting of Adverse Events**

AEs must be recorded by clinical investigator using the predefined section of the case report form. Annually, the sponsor reports every adverse event to Swissmedic (Swiss Agency for Therapeutic Products).

In case of SAE, the clinical investigator must inform the sponsor within 24 hours by fax or telephone using a predefined SAE reporting formulary. Furthermore the clinical investigator must report life-threatening SAE to the responsible institutional review board (IRB) or institutional ethical committee (IEC) in written form within 7 days. All other serious adverse events must be reported by the clinical investigator to the IRB / IEC within 15 days.

Life-threatening serious adverse events that fulfil the definition of a SUSAR must further be reported by the sponsor to Swissmedic using the Council for International Organization of Medical Sciences (CIOMS) formulary within seven days. The reporting deadline for all other SUSARS to Swissmedic is 15 days. Furthermore, all participating institutes have to be informed immediately by the sponsor about SUSARs. As deaths or HF rehospitalizations are part of the primary endpoint, these events will only be reported to Swissmedic in the annual AE report.

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# Statistical Analysis Plan

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Study: Goal-directed Afterload Reduction in Acute Congestive Cardiac Decompensation (GALACTIC Study)

EudraCT Number: 2011-004977-10

**Protocol:** Version 8.6 / 04.07.2016

Authored by: Dayana Flores

Date: 25.JUN.2019

Version: 2.0

## Approved by:

Prof. Christian Müller      USB

Change history:

Version	Date	Major changes
2	25.June.2019	Section 6.6.2. Adjustments for covariates.

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## 1. Study synopsis

In contrast to treatment for chronic heart failure (HF), which is based on several large prospective randomized controlled trials, treatment for acute heart failure is largely based on uncontrolled studies, clinical experience and expert opinion. Perhaps at least in part related to the uncertainties in the treatment of acute heart failure, outcome of patients with acute heart failure is extremely poor with mortality arising to 50% at three years. As more than 85% of patients with acute heart failure are treated in the non-ICU / CCU setting - the Emergency Department and the regular medical ward-, it is still notable that appropriate treatment is particularly ill-defined in this setting.

Based on the aforementioned premise, our aim is to test the hypothesis that a comprehensive approach using an early goal-directed therapy with a target systolic blood pressure of 90 to 110 mmHg by aggressive vasodilatation in patients with acute heart failure in the non-ICU setting, is safe and has the potential to more rapidly improve dyspnea, to more rapidly and more extensively reduce heart failure disease severity as quantified by B-type natriuretic peptide levels and most importantly to reduce the occurrence of death and heart failure readmission. Due to the high cost associated with hospitalizations for heart failure, our study has the potential to define a novel treatment strategy that might also significantly reduce the treatment cost associated with acute heart failure.

This trial was designed as a prospective, randomized, controlled multicenter study aimed to enroll 770 patients presenting with acute heart failure at the emergency departments at the participating study sites. Patients will be randomly assigned 1:1 after stratification for site and B-type natriuretic peptide (BNP, NT-proBNP) levels to an early goal-directed therapy or standard care according to current guidelines. Early goal-directed therapy aims to aggressive vasodilatation by using sublingual and transdermal nitrates, hydralazine (to avoid tolerance to nitrates) and rapid up-titration of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with a target systolic blood pressure of 90 mmHg to 110 mmHg. Timing and dosing of diuretics and all other treatments are left to the discretion of the treating physician in both groups. The primary endpoint is death or heart failure readmission within 180 days. Secondary endpoints include the quantitative assessment of dyspnea, need for admission to the intensive care unit, surrogate markers like BNP or NT-proBNP, the digitally recorded third heart sound, renal function, time to discharge, functional status and quality of life, falls, total treatment cost, and cost-effectiveness. Patients will receive extensive clinical and economic follow-up of at least 360 days. A clinical endpoint committee blinded to group assignment will adjudicate endpoints.

## 2. Study objectives

### a. Primary objective

The aim of our study is to determine the safety and efficacy of an early goal-directed preload and afterload decrement with a target systolic blood pressure of 90 mmHg to 110 mmHg by aggressive vasodilatation versus standard medical care in a non-ICU setting in patients with acute HF. The primary endpoint is **death or heart failure re-hospitalization** up-to 180 days of follow-up.

### b. Secondary objectives

Secondary endpoints are:

- All-cause mortality at 180 days.
- HF re-hospitalization at 180 days.
- Death or re-hospitalization from all causes at 180 days.
- Need for ICU admission during initial hospitalization.
- Acute coronary syndrome during initial hospitalization.
- Symptomatic hypotension during initial hospitalization.
- B-type natriuretic peptide (BNP) and creatinine level at 48 h and at discharge.
- Changes in circumferences of both legs and central venous pressure during hospitalization.
- Change in patient-assessed dyspnea at 48 h and prior to discharge.
- Blood pressure course over the first 6 days.
- Time to disappearance of a third heart sound (if present initially).
- Time to discharge.
- In-hospital days for HF at 180 days and 360 days.
- Total treatment cost at 180 days and 360 days.
- Functional status at 180 days and 360 days.
- Quality of life (EQ-5D-3L) at 180 days and 360 days.
- Fractures due to falls within 180 days and 360 days.
- Death or HF re-hospitalization at 360 days.

### **c. Assessment of objectives**

Overall, the endpoints are assessed during the initial hospitalization and the follow up period. The patients are contacted after 90, 180 and 360 days by telephone calls or in written form. The family physicians are called if these individuals could not be contacted. Information is furthermore obtained by institutional chart review and the national registry on mortality.

The primary endpoints will be adjudicated by a clinical endpoint committee blinded to group assignment and using all the information available corresponding to the event.

Additional, for the assessment of the secondary endpoints, all the events occurring during the initial hospitalization, leg edema and vital signs measurements are collected.

### **d. Changes of the primary objective during the conduct of the study**

No changes in the primary objective occurred during the conduct of the study.

## **3. Study design**

### **e. General design and plan**

This trial is designed as an open label, prospective, randomized, controlled multicenter study.

### **f. Sample size**

Sample size calculation is based on the on the data from the BASEL V study<sup>1</sup>. A hypothesized 20%-decrease of the composite endpoint death or HF re-hospitalization at 180 days, will require 385 patients per treatment arm to obtain, with a probability of 80%, a log rank test result that is statistically significant at the 5%-level. In order to compensate for an expected 1-2% of patients in whom the primary endpoint could not be assessed at 180 days due to loss to follow-up or complete withdrawal of ICF, it was planned to enroll approximately 780 patients.

#### **3.1. Randomization**

Group assignment was accomplished with the use of a computer-generated randomization scheme in a 1:1 ratio. Randomization will be stratified for enrolling site and the severity of HF as quantified by the BNP level (below or above 1000 ng/l) or NTpro-BNP level (below or above 4000 ng/l). Patients will be randomized to either the early goal directed group or the control group.

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<sup>1</sup> Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, et al. Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea. N Engl J Med. 2004;350(7):647–54.

**g. Blinding**

Blinding of physicians and patients during hospitalization is not possible/feasible with this specific intervention. However, physicians responsible for the long-term care of patients after the index hospitalization will remain blinded to the group assignment. Also, endpoints will be adjudicated by experts blinded to group assignment.

## h. Study assessments

The following study assessments are planned:

Study assessment schedule	Screening	D1	D2	D3	D4	D5	D6	Discharge	FU	D90	D180	D360
Screening of Patient in Emergency Department	S/I											
Check Inclusion/ Exclusion Criteria	S/I											
Inclusion: Patient signed the Informed Consent	S/I											
Inclusion: Randomize Patient in Secu Trial	S/I											
No inclusion: Enter Patient in " Screening Enrolment Log"	S/I											
HF assessment	S/I											
Measure vital signs 0h/ 30min/ 1h/2h/3h/4h/6h	S/I											
Give oral Capsule of Nitroglycerine (1)		I										
Apply the nitro patches according to the blood pressure		I										
Increasing nitro patches according to BP, stick for 24hrs (2)			I									
Reduction of nitro patches according to BP (2)			I	I	I	I						
Give one oral Hydralazine Tbl à 25mg every 6hours		I										
Collect Urine and Blood Samples		S/I	S/I	S/I			S/I					
Dyspnea Assessment		S/I	S/I				S/I	S/I				
Edema measurement		S/I					S/I					
Hand out the QOL and KCCQ Questionnaire				S/I						S/I	S/I	S/I
Collected the QOL and KCCQ Questionnaire					S/I					S/I	S/I	S/I
Actively search for AE's/ SAE's			S/I	S/I			S/I			S/I	S/I	S/I
Ask about Patient's Health status										S/I	S/I	S/I
Ask for medication										S/I	S/I	S/I
Ask about Dyspnea										S/I	S/I	S/I
Rehospitalization (3)										S/I	S/I	S/I

S= Standard group/ I= Interventions group

(1) every 10min x 3times

(2) target systolic BP  $\leq$ 110mmHg

(3) SAE, yes/no?

## **4. Data management**

### **i. Data export**

Initially, data from Basel site were captured into an Access (Microsoft, USA) and data from external centers into SINATRAS EDC software (developed by SAKK). As from April 2016, new data for all the centers participating in this trial were captured inside the secuTrial EDC system and former data imported to the same EDC at the Clinical Trial Unit of the University Hospital Basel reassuring that the outcome measures remain independent from the investigators.

SecuTrial EDC system:

<https://secutrial.insel.ch/apps/WebObjects/ST21-productive-DataCapture.woa/wa/>

Data will be exported using the secuTrial data export tool:

<https://secutrial.insel.ch/apps/WebObjects/ST21-productive-ExportSearchTool.woa/wa/>

Data are exported as comma delimited files, and are labelled using the codebook provided by secuTrial in the same export.

### **j. Data validation**

The following data validation checks will be performed:

1. For critical items, univariate, multivariate and cross-module checks will be performed. This will include valid-value (e.g. selections of only “yes” or only “no”), valid-range (e.g. range of vital signs), and missing-value (e.g. age).
2. Occurrence of events or items containing dates, will be checked whether they occurred on/after the date of randomization with the only exception being items from the medical history (e.g. date of previous stroke, previous echocardiogram) which could have occurred before the randomization.

## 5. Study populations

### k. Patient flow

The number of patients randomized will be taken from the randomization eCRF and the following flow chart will be produced:

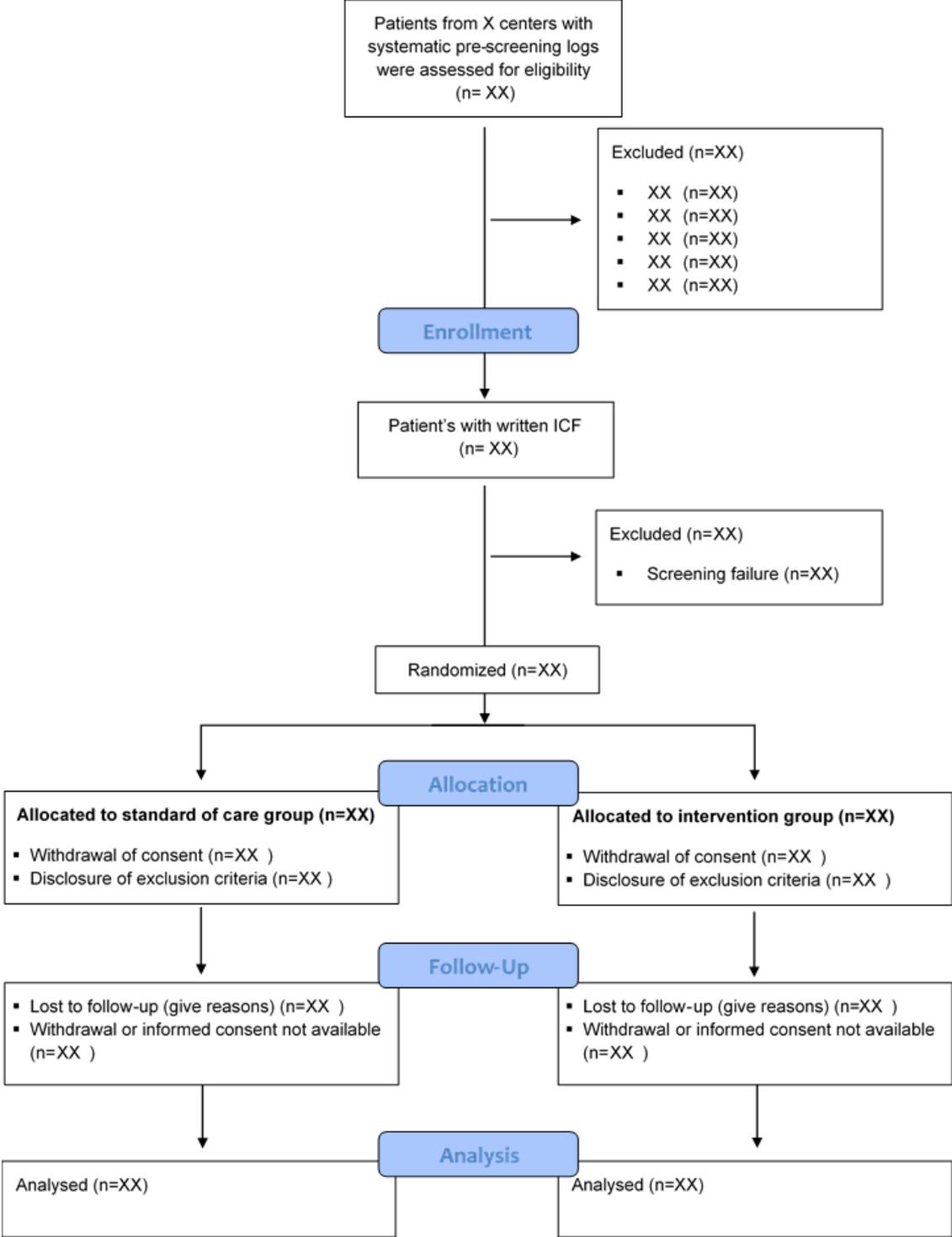


Figure 1 Study Flowchart

## **I. Definition of populations for analysis**

All patients attending to the ED with acute decompensated heart failure will be pre-screened by the local Investigators. Each potential candidate will be individually assessed for inclusion and exclusion criteria. If the candidate qualifies, he or she will be invited to participate in the GALACTIC Trial.

### **m. Intention- To -Treat (ITT)**

The intention to treat population consists of all patients randomized. The primary and secondary endpoints of patients randomized to early goal-directed decrement of preload and afterload (intervention group) will be compared to the patients randomized to standard of care by the intention-to-treat principle.

Patients without a follow-up assessment at 6 months for the primary endpoint will be censored at the time of the last follow-up information available.

### **n. Per-protocol (PP)**

The per-protocol population PP consists of all patients randomized, who received at least one dose of the study drug (Hydralazine and/or nitrates in the form of capsules, spray and/or transdermal application) and had a baseline plus follow-up assessment (180 days) of the primary endpoint completing the study without major protocol deviations<sup>2</sup>. PP analyses are planned as part of sensitivity analyses.

### **o. As Treated (AT)**

The as treated population AT consist of all the patients randomized analyzed not to the allocation group but according to the treatment they actually received. No AT analyses are currently planned.

### **p. Safety population**

For the analysis of safety, including protocol pre-defined adverse events, all randomized patients will be included in the safety population if they received at least one dose of the randomized study drug, and had at least one subsequent safety-related visit.

### **q. Definition of sub-group populations in different analyses**

Predefined subgroups are as follows: patients younger versus older than 75 years of age, men versus women, HF with reduced LVEF (LVEF< 40%) versus HF with mid-range LVEF (LVEF 40-49%) versus HF with preserved LVEF (LVEF≥50%), systolic blood pressure at randomization lower versus ≥120 mmHg, coronary artery disease present or not, BNP

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<sup>2</sup> Major protocol deviations defined as the disclosure of exclusion criteria after enrollment.

concentration at randomization lower or  $\geq 1000$  pg/ml, patients with versus without known chronic heart failure, and estimated glomerular filtration rate  $< 60$  ml/min versus  $\geq 60$  ml/min.

## **6. Statistical analysis**

### **r. General**

The general approach is to quantify the cumulative incidence of the composite primary endpoint using Cox proportional hazards models stratified by study centers and randomization factor as previously described.

Statistical analyses will be performed using SPSS / PC version 22.0 or higher and/or R version 3.4 or higher.

### **s. Pooling of sites**

Any sites with fewer than 10 subjects will be pooled by country/region. If a country/region has fewer than 10 subjects, that country/region will be pooled with its nearest neighboring country/region.

### **t. Interim analyses**

No interim analyses are planned.

### **u. Time-points for analysis**

Time-points for primary and secondary endpoint assessments are the follow-up at 180 and 360 days.

### **v. Methods for handling missing data and sensitivity analyses**

Sensitivity analyses will be conducted in: patients without evidence of systemic, infection/inflammation at presentation (defined as CRP  $< 20$  mg/L), in patients without major protocol deviation and in patients enrolled in outside Europe and Central Europe.

To deal with data with  $> 10\%$  missing values, sensitivity analyses will be conducted using multiple imputations by chained equations methods and 20 data-sets will be created.

### **w. Statistical analytical issues**

#### **i. Assessment of statistical assumptions**

Violation of the proportional hazards assumption in Cox models will be assessed by examining clog-log transformed Kaplan-Meier figures and by examination of Schoenfeld residuals.

**ii. Adjustments for covariates**

The primary analysis will be adjusted for four strong predictors of the composite primary endpoint (death or HF-rehospitalisation within 6 months): age, HF hospitalization in the year before inclusion, systolic blood pressure, and serum creatinine<sup>3</sup>.

**iii. Multicenter studies**

HR by center will be visually plotted to assess how strong the heteroscedasticity is. No adjustment of center effects are reported, except in the Sensitivity analyses

**iv. Multiple comparisons**

All secondary analyses are explorative and therefore no multiple comparisons will be performed. P-values of secondary analyses will be interpreted as a continuous measurement of the level of surprise for seeing the observed result, and not in relation to a threshold of significance.

**v. Use of efficacy subset**

All patients will be analyzed by intention-to-treat and reported according to their randomized arm, irrespective of whether and how much of the study drug they received. Note that the last assessment of the endpoints will be used if otherwise no measurement of the endpoint could be conducted at 180 days, due to withdrawal of consent or due to lost to follow-up incl. failure to collect all the required documents for endpoint adjudication.

**vi. Active-control studies intended to show equivalence**

Not applicable.

**vii. Examination of subgroups**

Time to primary endpoint of intervention arm vs standard of care arm will be explored for all the patients and again for the predefined subgroups plus interaction test HR within groups.

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<sup>3</sup> Voors, AA, Ouwerkerk, *et al.* Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *Eur J Heart Fail* 2017; 19: 627– 634.

## 7. Evaluation of characteristics and medication

### x. Baseline clinical characteristics

P-values, standard errors, and confidence intervals are not shown in baseline tables following the CONSORT Statement.

The following baseline table will be produced:

**Table 1. Baseline Clinical Characteristics and Medical History**

	<b>Total Patients (N=)</b>	<b>Intervention arm (N=)</b>	<b>Standard of care arm (N=)</b>
Age – years ( $\pm$ SD)	XX $\pm$ XX	XX $\pm$ XX	XX $\pm$ XX
Male gender – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
BMI - kg ( $\pm$ SD)	XX $\pm$ XX	XX $\pm$ XX	XX $\pm$ XX
<b>Cardiovascular Risk Factors:</b>			
Diabetes mellitus – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Dyslipidemia – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Ever smoked – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Hypertension – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
<b>Structural heart disease:</b>			
Hypertensive heart disease – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Chronic Heart failure – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
CAD – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
PCI – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Coronary Bypass – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Myocardial infarction – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Valvular replacement – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Atrial Fibrillation – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
ICD/CRT – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
<b>Chronic Comorbidities:</b>			
COPD/ Asthma – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Renal insufficiency – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Peripheral vascular disease – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Stroke – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Pneumonia – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Pulmonary embolism – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Liver disease – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Active malignancy – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
<b>Symptoms at admission or shortly before</b>			
NYHA class – no. (%)			
III	xx (xx%)	xx (xx%)	xx (xx%)
IV	xx (xx%)	xx (xx%)	xx (xx%)
Days with dyspnea – days ( $\pm$ SD)	XX $\pm$ XX	XX $\pm$ XX	XX $\pm$ XX
Chest pain – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Nycturia – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Weight gain – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)

Orthopnea – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Paroxysmal nocturnal dyspnea – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Coughing – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Sputum – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Fever – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Night sweats – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
<b>Clinical examination:</b>			
Heart murmur – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Murmur radiation – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Third heart sound – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Positive HJR – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Jugular ingurgitation – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Edema – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Ascites – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Pulmonary attenuation – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Pulmonary wheezing – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Pulmonary Rales – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
<b>Vital parameters:</b>			
Diastolic blood pressure –mmHg (±SD)	xx±xx	xx±xx	xx±xx
Systolic blood pressure -mmHg (±SD)	xx±xx	xx±xx	xx±xx
Heart frequency – bpm (±SD)	xx±xx	xx±xx	xx±xx
Breathing frequency – rpm (±SD)	xx±xx	xx±xx	xx±xx
Oxygen saturation – % (±SD)	xx±xx	xx±xx	xx±xx
Temperature – °C (±SD)	xx±xx	xx±xx	xx±xx
<b>Trigger of the current AHF episode</b>			
Dietary and medication related causes			
Dietary indiscretion – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Volume overload – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Alcohol – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Non-compliance to medication – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Medication (NSAID, changes of diuretics) – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Cardiac causes			
Myocardial ischemia / necrosis – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Myocarditis – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Uncontrolled hypertension – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Arrhythmia (Afib, VT, bradycardia, AV-Block) – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Progressive valvular disease (MI, AS) – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Non-cardiac causes			
Pulmonary disease (PE, COPD) – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Thyroid disorders – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Physical, emotional, environmental stress – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Infection – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Anemia (<100g/l) – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)
Unknown – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)

Data are presented as absolute number and percentages (%) or means  $\pm$  standard deviations SD or median (25% to 75% interquartile range IQR) or median.

BMI= body mass index, CAD= coronary artery disease, PCI= percutaneous coronary intervention, ICD= implantable cardioverter-defibrillator, CRT= cardiac resynchronization therapy, COPD= chronic obstructive pulmonary disease, HJR= hepatjugular reflux, AHF= acute heart failure, NSAID= Nonsteroidal anti-inflammatory drugs, Afib= atrial fibrillation, VT= ventricular tachycardia, AV Block= atrial ventricular block, MI= mitral insufficiency, AS= aortic stenosis, PE= pulmonary embolism

Table 1 Baseline Clinical Characteristics and Medical History

## **8. Evaluation of treatment compliance and exposure**

### **y. Compliance to study drug and treatment**

The study drugs are administered to the patient during the index hospitalization by either the study physician and/or attending nurses following the study prescription forms. Nitrate capsules will be administered orally 3 times every 10 minutes whereas hydralazine will be given to the patient every 6 hours for 48 hours. Nitroderm patches will be adhered to the patient and the dosage adjusted according to the blood pressure.

#### **i. Compliance to study drug**

The study medication is administered only during the patient's hospitalization by either the study physician and/or attending nurses ensuring the best compliance possible.

**Table 2: Medication at baseline and during follow-up**

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	Medication at baseline		Medication at 180 days FU			Medication at 360 days FU		
	Intervention arm (N=)	Standard of care arm (N=)	Intervention arm (N=)	Standard of care arm (N=)	p-value	Intervention arm (N=)	Standard of care arm (N=)	p-value
Beta blockers – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
ACE inhibitor – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
ARBs – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Calcium antagonist – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Diuretics– no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Aldosterone antagonist – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Statins – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Digoxin – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Nitrates – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Vitamin K antagonists – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
ASA – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx
Clopidogrel – no. (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xx	xx (xx%)	xx (xx%)	x.xx

1

2

3 ACE inhibitor= angiotensin-converting-enzyme inhibitor, ARBs = Angiotensin II receptor blockers, ASA=acetylsalicylic acid.

4

5 Table 2 Medication

6

7 **z. Exposure to study drug**

8 **i. Extent of exposure**

9 Intervention arm: on top of the standard of care therapy, the patients will receive:

- 10 – sublingual nitrates three times every 10 minutes;
- 11 – hydralazine 25 mg p.o. four times a day (QID) for 2 days;
- 12 – nitroglycerin patches in a dosage between 40 to 80 mg in 24 h depending on systolic
- 13 blood pressure following the therapy schedule.
- 14 – If patients are pre-treated with either ACE-inhibitor or ARB, therapy with these agents
- 15 will be continued during the first 24 hours at the pre-existing dosage and afterwards
- 16 up-titrated following the therapy schedule starting with day 2.
- 17 Standard of care arm: patient will receive the standard of care treatment according to local
- 18 and current guidelines.

19 The study medication (hydralazine) will be provided by the pharmacy of the University

20 Hospital Basel.

21 **ii. Duration of exposure**

22 Six days after admission or until discharge from the index hospitalization.

23 **iii. Dose of exposure and concentration**

- 24 – sublingual nitrates: 0.8 mg glyceryl trinitrate, sublingual, 3 times every ten minutes.
- 25 Sublingual nitrates have an approximate onset of action of 1-3 minutes and a half-life
- 26 of 1–4 min.
- 27 – hydralazine 25 mg p.o. four times a day (QID) for 2 days. Half-life, 2–8 hours,
- 28 – nitroglycerin patches in a dosage between 40 to 80 mg in 24 h depending on systolic
- 29 blood pressure and for 5 days. Elimination half-life takes around 10 minutes.
- 30

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33 **9. Evaluation of patients at follow-up**

34 Patient are contacted at 90, 180 and 360 days follow-up (telephone calls, letters). During the  
35 FU patients will be asked about current medication, functional NYHA class and additionally,  
36 to complete Quality of life (EQ-5D-3L) and Kansas City Cardiomyopathy Questionnaire  
37 (KCCQ).

38 **aa. Follow-up at 90 days**

39 The follow-up 90 days months contains a self-reported medicament list update, potential  
40 endpoints assessment, a functional NYHA class assessment and Quality of Life (EQ-5D-3L)  
41 assessment.

42 **bb. Follow-up at 180 days**

43 The follow-up 180 days months contains a self-reported medicament list update, potential  
44 endpoints assessment, a functional NYHA class assessment and Quality of Life (EQ-5D-3L)  
45 and KCCQ assessment.

46 **cc. Follow-up at 360 days**

47 The follow-up 360 days months contains a self-reported medicament list update, a functional  
48 NYHA class assessment and Quality of Life (EQ-5D-3L) and KCCQ assessment.

49 .

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51 **10. Evaluation of efficacy parameters**

52 **dd. Analysis of primary, secondary, and other efficacy endpoints**

53 **i. Analysis of primary endpoint**

54 The primary endpoint will be analyzed using survival analysis for cumulative incidence (e.g.  
55 Cox regression, Kaplan-Meier and Hazard Ratio) and log rank testing for significance at 180  
56 days.

57 **ii. Analysis of secondary endpoints**

58 Secondary endpoints will be analyzed using the same approach as for the Primary endpoints  
59 and interaction test (p-value) will be conducted between the treatment group and the sub-  
60 group variables.

61 **iii. Analysis of other endpoints**

62 All other endpoints, including novel biomarkers or neurohormones not yet specified in the  
63 protocol will be analyzed using the same approach as for the **Secondary endpoints**.

64 **iv. Endpoint tables**

65 The following table will be produced and

66 Table 3 will be provided in the main publication:

67

68 **Table 3: Primary and secondary endpoint events**

<i>Event</i>	<i>Intervention arm (N=)</i>	<i>Standard of care arm (N=)</i>	<i>Hazard Ratio (95%CI)</i>	<i>p-value</i>
Primary composite endpoint – no. (%)†	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
All-cause mortality — no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
Heart failure hospitalization – no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
Secondary endpoints – no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
All-cause mortality at 180 days.— no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
Heart failure hospitalization – no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
Death or re-hospitalization at 180 days. — no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
Need for ICU admission during initial hospitalization — no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
Acute coronary syndrome during initial hospitalization — no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
Symptomatic hypotension during initial hospitalization — no. (%)	xx (xx%)	xx (xx%)	x.xx (x.xx-x.xx)	x.xx
B-type natriuretic peptide (BNP) level – ng/l (±SD)	xx±xx	xx±xx	x.xx (x.xx-x.xx)	x.xx
at 48 hours	xx±xx	xx±xx	x.xx (x.xx-x.xx)	

69

	Intervention arm				Standard of care arm				Intervention vs standard of care	
	Baseline (N=)	Follow-up (N=)	Change FU vs Baseline	p-value	Baseline (N=)	Follow-up (N=)	Change FU vs Baseline	p-value	Mean difference of the change	p-value
at discharge										
Creatinine level – µmol/l (±SD)		XX±XX			XX±XX				x.xx (x.xx-x.xx)	
at 48 hours										
at discharge		XX±XX			XX±XX				x.xx (x.xx-x.xx)	
Changes in circumferences of both legs during initial hospitalization – cm (±SD)		XX±XX			XX±XX				x.xx (x.xx-x.xx)	
Blood pressure course over the first 6 days – mmHg (±SD)		XX±XX			XX±XX				x.xx (x.xx-x.xx)	
Time to disappearance of a third heart sound (if present initially) – days (±SD)		XX±XX			XX±XX				x.xx (x.xx-x.xx)	
Quality of life assessed at 90 days (±SD)	N= xx	N= xx	N= xx	x.xx	N= xx	N= xx	N= xx	x.xx	N= xxx	
Total triAS scale – mean score (±SD)	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	x.xx
Fractures due to fall within 180 days and 360 days – no. (%)		xx (xx%)			xx (xx%)				x.xx (x.xx-x.xx)	
Death or HF re-hospitalization at 360 days – no. (%)		xx (xx%)			xx (xx%)				x.xx (x.xx-x.xx)	

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† The primary composite endpoint was the first occurrence of any component of the composite of death from all-cause mortality or hospitalization for heart failure in the time-to-event analysis. Data for all endpoint events, irrespective of whether the event was the patient's first occurrence of the event, are shown

Table 3 Endpoint assessment

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It is expected that the Quality of Life (EQ-5D-3L) data will be reported in secondary publications:

79

**Table 4 Quality of Life assessments at Baseline and Follow-up**

80

81

Table 4 Quality of Life (EQ-5D-3L) assessments at Baseline and Follow-up

82

Mobility – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Self-care – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Usual activities – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Pain/discomfort – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Anxiety/depression – mean score (±SD)	XX±XX	XX±XX	XX±XX		XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Quality of life assessed at 180 days	N= xx	N= xx	N= xx		N= xx	N= xx	N= xx		N= xx	
VAS scale – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Mobility – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Self-care – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Usual activities – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Pain/discomfort – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Anxiety/depression – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Quality of life assessed at 360 days	N= xx	N= xx	N= xx		N= xx	N= xx	N= xx		N= xx	
VAS scale – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Mobility – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Self-care – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Usual activities – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Pain/discomfort – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX
Anxiety/depression – mean score (±SD)	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	XX±XX	XX±XX	X.XX	XX±XX	X.XX

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84

85 It is expected that the Kansas city  
86 will be reported in secondary

87 **Figure 2 KCCQ summary change**

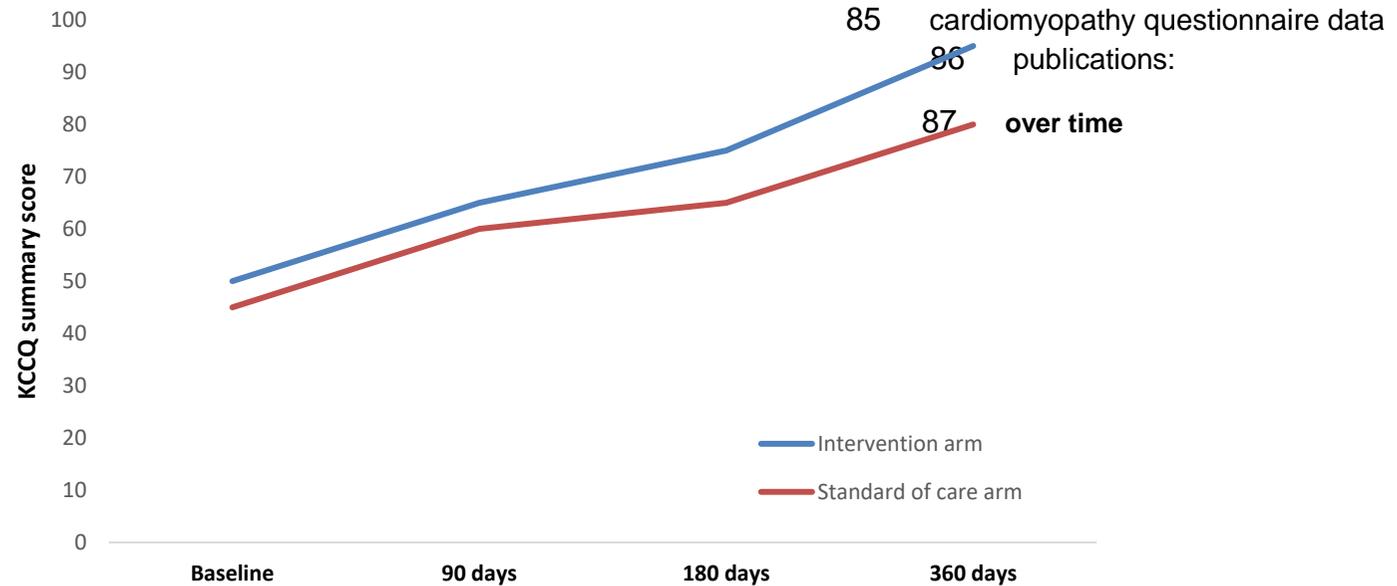
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101 KCCQ summary score ranges from 0 to 100 with higher scores indicating better health status. An increase of 10 points or more from baseline  
102 corresponds to moderate or great clinical improvement.

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104

105

106 It is expected that additional  
107 reported in secondary publications:

**Change from baseline**

Intervention arm	xx±xx	xx±xx	xx±xx
Standard of care arm	xx±xx	xx±xx	xx±xx
95 % CI for difference	(xx.xx – xx.xx)	(xx.xx – xx.xx)	(xx.xx – xx.xx)

biomarkers will be

108

109 **Table 5 Baseline and follow-up biomarkers assessments.**

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112 Table 5 Baseline and follow-up biomarkers assessments.

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	Intervention arm				Standard of care arm				Intervention vs standard of care	
	Baseline (N=)	Follow-up (N=)	Change FU vs Baseline	p-value	Baseline (N=)	Follow-up (N=)	Change FU vs Baseline	p-value	Mean difference of the change	p-value
-xx (±SD)	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	x.xx
-xx (±SD)	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	x.xx
-xx (±SD)	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	x.xx
-xx (±SD)	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	x.xx
-xx (±SD)	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	xx±xx	xx±xx	x.xx	xx±xx	x.xx

116

**v. Sensitivity Analyses of endpoints**

To deal with missing data in the baseline assessment of the endpoint and to deal with missing data of the follow-up assessment of the endpoint, sensitivity analyses will be conducted, where missing follow-up values and baseline values will be multiple imputed using chained equations.

The missing data for the primary and secondary endpoints (as applicable what is actually missing, including baseline and follow-ups) are imputed using chained equations, 20 data-sets will be created. The equations include the baseline clinical characteristics, the non-missing primary from the previous follow-up assessment (baseline if none available). Endpoints are taken from baseline and all the follow-ups, as applicable (typically baseline, 180 days and 360 days).

Afterwards all sensitivity analyses are conducted on the 20 data-sets for the composite endpoint, The sensitivity analyses will be shown in the Supplementary Material following the same structure as the Tables 3 – 5.

**ee. Method for analysis**

**i. Binary data**

Binary data will be compared Intervention arm vs Standard of care using Fisher's exact test for 2 x 2 tables with two-sided p-values.

**ii. Count data**

Count data will be compared Intervention arm vs Standard of care using Pearson's chi-squared test with two-sided p-values.

**iii. Continuous scale data**

Continuous data will be compared Intervention arm vs Standard of care using Mann–Whitney U test with two-sided p-values.

**iv. Time-to-event data**

Median observation time in each group and overall incidence rate up-to 180 days will be reported. Intervention group vs standard of care will be compared using Cox proportional hazards models with time to last assessment as offset (i.e. days between baseline and 1 year follow-up or last contact).

**v. Ordinal scales and non-ordered scales data**

Ordered data will be reported as counts, compared Intervention arm vs Standard of care using chi-square tests for 2 x n tables with two-sided p-values.

## 11. Evaluation of safety parameters

### ff. Adverse events

Specific adverse events (AE) will be documented and investigated only during the course of

	Intervention arm (N=)	Standard of care arm (N=)
--	--------------------------	------------------------------

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the index hospitalization (see “11.1.1.Brief summary of adverse events”). Additionally, during the first 180 days, all serious adverse events (SAEs) as defined by current Good Clinical Practice standards will be collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompasses the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed (last FU at 360 days).

#### i. Brief summary of adverse events

The following AEs will be collected:

- Headaches
- Dizziness
- Fall
- Creatinine increase > 30% of baseline
- Hypokalemia < 3.5 mmol/l
- Hyperkalemia > 5 mmol/l
- Arrhythmia requiring therapy
- Systolic arterial hypotension < 80 mm Hg over 30 minutes
- Acute coronary syndrome
- Transfer to the intensive care unit
- Cardiopulmonary resuscitation

The following SAEs will be collected

- In-patient hospitalization
- Prolongation of existing hospitalization
- Life threatening event
- Death

#### ii. Display of adverse events

A supplementary material table will be produced with all adverse events if applicable and requested:

	Nr of patients with the event	Total nr of events	% of events intervention stopped	Nr of patients with the event	Total nr of events	% of events intervention stopped	p-value
<b>Adverse events</b>							
Headaches	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Dizziness	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Fall	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Creatinine increase > 30% of baseline	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Hypokalemia < 3.5 mmol/l	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Hyperkalemia > 5 mmol/l	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Arrhythmia requiring therapy	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Systolic arterial hypotension*	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Acute coronary syndrome	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Transfer to the intensive care unit	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Cardiopulmonary resuscitation	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
<b>Serious adverse events</b>							
Death	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
In-patient hospitalization	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
Prolongation of existing hospitalization	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx
SAE other than any of the above	xx(%)	xx	xx%	xx(%)	xx	xx%	x.xx

**Supplemental Table 1. Events in all Patients**

Data expressed as nr of patients with event (% of patients) and total nr of event reported.

\*defined as Systolic arterial pressure < 80 mmHg over 30 minutes

Supplemental Table 1. Events in all Patients

### **iii. Analysis of adverse events**

Intention- To -Treat (ITT): adverse events will be reported as rates: total nr of events per patient and compared intervention arm vs standard of care arm using Chi square test with two-sided p-values.

Safety population are the patients who received at least once the study drugs (hydralazine and/or nitrates in the form of capsules, spray and/or transdermal application), and events are reported up to last confirmed intake of the study drug.

### **iv. Listing of adverse events by patient**

Listing of adverse events per patient are provided on request.

### **gg. Concomitant medications**

Concomitant medications are reported inside the medication tables. No important interactions are to be noted.

### **hh. Vital signs and physical examination**

#### **i. Findings in vital signs and physical examinations**

Clinical examinations are conducted at baseline and again at 30min, 1, 2, 4, 6, 12, 18 hours, as well as at 2-6 days one time measurement during the index hospitalization. Assessment will include heart rate, oxygen saturation, blood pressures, breathing rates and weight. Dyspnea assessment are planned at baseline and at 24 hours and/or day six or discharge (whichever comes first). Edema assessment are planned at baseline and/or day six or discharge.

#### **ii. Other safety evaluations**

##### **11.1.1. Other observations related to safety**

No other safety observations, assessments or analyses are currently defined and planned for this statistical analysis plan.