Clinical Study Protocol

Angiotensin receptor-neprilysin inhibitor (Sacubitril/Valsartan) versus Enalapril in patients with acute anterior wall ST-elevation myocardial infarction after emergency PCI: a prospective randomized trial

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Table of contents

List of tables

List of figures

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List of abbreviations

PCI	Percutaneous Coronary Intervention
AMI	Acute Myocardial Infarction
HF	Heart Failure
STEMI	ST-Segment Elevation Myocardial Infarction
RAAS	Renin-Angiotensin-Aldosterone System
CABG	Coronary Artery Bypass Graft
ACEI	Angiotensin-Converting Enzyme Inhibitors
ARB	Angiotensin Receptor Blocker
SBP	Systolic Blood Pressure
AUC	Area Under Curve
ANP	Atrial Natriuretic Peptide
BNP	Brain Natriuretic Peptid
cGMP	Cyclic Guanosine Monophosphate
HTN	Hypertension
eGFR	Estimated Glomerular Filtration Rate
MDRD	Modification of Diet in Renal Disease
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ULN	Upper Limit of Normal
hCG	Human Chorionic Gonadotropin
FSH	Follicle-Stimulating Hormone
Bid	Bis In Die
ARNI	Angiotensin Receptor Neprilysin Inhibitor
CCB	Calcium Channel Blockers
AM	Ante Meridiem
PM	Post Meridiem
MRA	Mineralocorticoid Receptor Antagonist
CV	Cardiovascular
AEs	Adverse Event(s)
SAEs	Serious Adverse Event(s)
LVEDV	Left Ventricular End-Diastolic Volumes
LVESV	Left Ventricular End-Systolic Volumes
LVEF	Left Ventricular Ejection Fraction
BUN	Blood Urea Nitrogen
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein
Hs-cTnI	High Sensitivity Cardiac Troponin I
ECG	Electrocardiogram
NEP	Neutral Endopeptidase

DMC	Data Monitoring Committee
eCRFs	Electronic Case Report Form(s)
BMI	Body Mass Index
FAS	Full Analysis Set
REB	Research Ethics Board

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol synopsis

Protocol title: Angiotensin receptor-neprilysin inhibitor (ARNI, Sacubitril/Valsartan) versus Enalapril in patients with acute anterior wall ST-elevation myocardial infarction after emergency PCI: a prospective randomized trial

Rationale & background information: Ventricular remodeling after acute myocardial infarction (AMI) is closely related to the occurrence of heart failure (HF)[1]. Despite opening the infarct-related artery as early as possible and using the best medical treatment, about 41.5% of STEMI patients still have ventricular remodeling at 6 months[2]. LV remodeling is a complex pathophysiological process that develops gradually over time[3]. Neuroendocrine hormones, persistently activated, play an important role in this process, except for the extent of initial myocardial injury, and are closely associated with the progression of heart failure (HF)[4].
In recent years, the application of Sacubitril/Valsartan (Sac/Val) has brought bright sight to patients with heart failure. Sac/Val can inhibit the activation of endorphinase and renin-angiotensin-aldosterone system (RAAS) at the same time. According to PARADIGM-HF study and other researches, Sac/Val could reduce cardiovascular mortality and re-admission rate of heart failure patients who had a reduced heart ejection fraction[5,6]. Whether the initiation of Sac/Val immediately is effective and safe among patients with acute anterior STEMI (a high-risk factor for HF) is unknown. Therefore, the purpose of this study is to evaluate the safety and effectiveness of immediate initiation of Sac/Val in patients with acute anterior STEMI after PCI.

Objectives:

Primary objective:
The primary objective of this study is to test if Sac/Val is superior to enalapril in reducing the concentration of NT-proBNP and improving the main cardiac ultrasound parameters in patients with acute anterior STEMI after PCI.
Secondary objective:
The Secondary objective of this study is to test if Sac/Val is superior to enalapril in reducing the incidence of cardiovascular events (a composite of death, reinfarction, outpatient HF or HF hospitalization, arrhythmia, and stroke).

Population
Inclusion criteria
Patients eligible for inclusion in this study have to fulfill all of the following criteria:
1. Patients must give written informed consent before any assessment is performed
2. Outpatients ≥ 18 years of age, male or female
3. Had typical pain and Diagnosed as acute anterior STEMI according to electrocardiogram, high-sensitivity troponin, and coronary angiography

4. Systolic blood pressure ≥ 100mmHg without symptoms of dizziness during the last 12 hours prior to randomization

Exclusion criteria

1. Previous history of myocardial infarction or chronic heart failure
2. Previous PCI, coronary artery bypass graft (CABG), implantation of other heart assist devices or heart transplantation
3. Known history of angioedema
4. Previous history of intolerance to recommended target doses of ACEIs or ARBs.
5. Previous use of sacubitril/valsartan
6. History of hypersensitivity or contraindications to the study drugs including ACEI, ARB, sacubitril/valsartan
7. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening), Visit 2 (randomization), Visit 3 (outpatient dose titration) or Visit 4 (follow-up)
8. Estimated GFR < 30 mL/min/1.73m^{2}as measured by the simplified MDRD formula at Visit 1 (screening), Visit 2 (randomization), Visit 3 (outpatient dose titration) or Visit 4 (follow-up) or > 25% decline in eGFR between Visit 1 and Visit 2 or between Visit 2 and Visit 3 or between Visit 3 and Visit 4
10. Serum potassium > 5.2 mmol/L at Visit 1 (screening), Visit 2 (randomization), Visit 3 (outpatient dose titration) or Visit 4 (follow-up)
11.History of severe pulmonary disease
12.Diagnosis of peripartum or chemotherapy induced cardiomyopathy prior to Visit 1
13.Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1
14.Symptomatic bradycardia or second or third degree heart block without a pacemaker
15. Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation
16. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis
17. Life expectancy is less than 1 year
18. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following
- History of active inflammatory bowel disease during the 12 months before Visit 1.
- Current duodenal or gastric ulcers during the 3 months prior to Visit 1
- Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 2 x ULN at Visit 1, history of hepatic encephalopathy, history of esophageal varices, or history of portacaval shunt
- Active treatment with cholestyramine or colestipol resins

19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been

sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method
•Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progesterone agent.
•Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.
• Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Investigational drugs

after PCI
The following study drugs will be provided:
• Enalapril 2.5 mg tablets
• Enalapril 5 mg tablets
• Enalapril 10 mg tablets

Randomization, Outpatient dose titration and follow-up
All eligible patients will be randomized to receive either Sac/Val or enalapril in addition to optimal AMI therapy, as considered appropriate by the investigator and in accordance with standard therapy guidelines, but with the exception of an ACEI or ARB as this will be replaced by study drug. The use of an ACEI or an ARB in addition to study drug after randomization is strictly prohibited.

The following study drugs will be provided:
• Enalapril 2.5 mg tablets (enalapril dose level 1)
• Sacubitril/Valsartan 50 mg tablets (Sacubitril/Valsartan dose level 1, Sacubitril/Valsartan to match enalapril 2.5 mg film-coated tablets)
• Enalapril 5 mg tablets (enalapril dose level 2)
• Sacubitril/Valsartan 100 mg tablets (Sacubitril/Valsartan dose level 2, Sacubitril/Valsartan to match enalapril 5 mg film-coated tablets)
• Enalapril 10 mg tablets (enalapril dose level 3)
• Sacubitril/Valsartan 200 mg tablets (Sacubitril/Valsartan dose level 3, Sacubitril/Valsartan to match enalapril 10 mg film-coated tablets)
Target doses: Sacubitril/Valsartan 200 mg bid and enalapril 10 mg bid.

Study design

This study is a single-center, prospective, double-blind, randomized, parallel-group, two-arm, short-term trial to compare Sacubitril/Valsartan 200 mg bid to enalapril 10 mg bid in concentration of NT-proBNP reduction and main cardiac ultrasound parameters improvement in patients with acute anterior STEMI after PCI.

Duration of the study

As planned, it is expected to be up to 18 months: a recruitment period of approximately 12 months and a minimal follow-up of 6 months.

Study visits

Screening

Visit 1 (Screening Visit)

All patients must provide informed consent before any study-specific procedure is performed. At Visit 1, patients' eligibility for entering the randomization period, including whether the patient's vital signs are stable after PCI, will be assessed by the investigator. Whether enalapril is included in the medicine used immediately after the operation. Screening potassium levels and eGFR will be assessed by sending blood samples to the central laboratory and only patients with the required values per the entry criteria will be eligible for entering the randomization period, which will begin at Visit 2.

Randomization

Visit 2 (Randomization Visit)

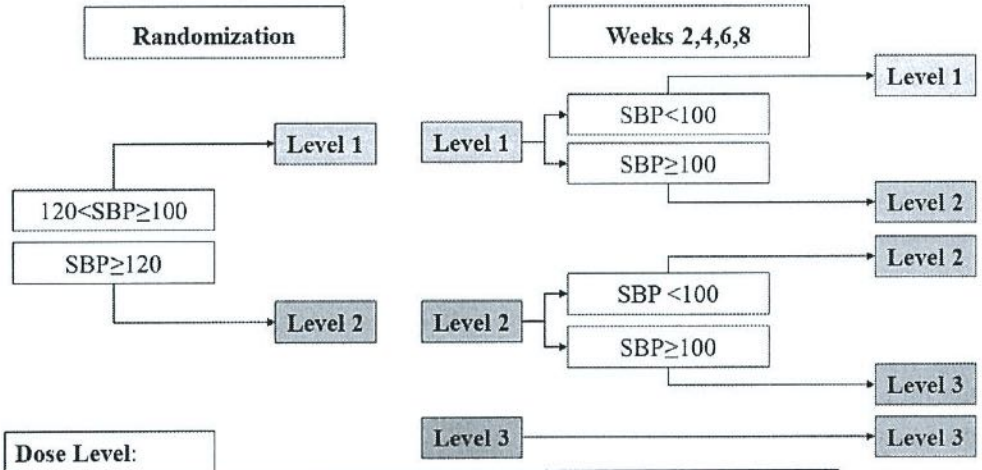
Patients who have met all the inclusion criteria and none of the exclusion criteria at the end of the screening period will be randomized to either enalapril or Sacubitril/Valsartan in a 1:1 ratio. Patients randomized to enalapril continue to receive enalapril, while patients randomized to sacubitril/valsartan discontinue enalapril to ensure a minimum 36-hour washout period prior to initiation of ARNi therapy. The first dose of sacubitril/valsartan is followed by 6 hours of monitoring for hypotension. After the condition is stable, patients can be discharged from the hospital at any point in time at the discretion of the clinician-investigator. The starting dose during the in-hospital initiation phase is selected using a dose titration algorithm based on systolic blood pressure (SBP) (**Figure 1**).

Outpatient dose titration period

Visit 3 (Outpatient dose titration period Visit)

During the outpatient dose titration phase, patients continue to receive sacubitril/valsartan or enalapril. There are 3 available doses of study drug administered twice daily. All subsequent dose changes during the medication titration period is selected using a dose titration algorithm based on systolic blood pressure (SBP) (**Figure 1**). Clinician-investigators are encouraged to up titrate sacubitril/valsartan to target dose (i.e., dose level 3) as tolerated during the medication titration phase. every attempt should be made to complete the dose titration period within 8 weeks regardless of any down-titration that may occur.

Figure 1 dose titration algorithm



Dose Level:	
1	Sacubitril/Valsartan 50mg twice daily or Enalapril 2.5mg twice daily
2	Sacubitril/Valsartan 100mg twice daily or Enalapril 5mg twice daily
3	Sacubitril/Valsartan 200mg twice daily or Enalapril 10mg twice daily

Follow-up period

Visit 4 (Follow-up Visit)

Follow-up visits are scheduled for Weeks 4, 12 and 24. Blood and urine samples are sent to a central laboratory for hematology, chemistry, and serum biomarkers. Professionals use Philips IE33 ultrasound system (Philips Medical System, Bothell, Washington, USA) for echocardiographic measurements. In addition to the protocol-required visits, patients may be seen at any time throughout the study at the discretion of the investigator to investigate or follow any new lab abnormalities or adverse events. Monitoring of safety and tolerability will include: (1) hyperkalemia; (2) symptomatic hypotension; (3) increase in serum creatinine; (d) angioedema; and (e) adverse events and serious adverse events. If, in the opinion of the investigator, the patient cannot tolerate the target dose of study drug, the investigator should consider whether non-life saving medication (e.g., CCBs, nitrates, α- blockers) can be reduced to rectify the situation before considering reducing the dose of the study drug to the lower dose level. The dose of background disease modifying drugs, such as β-blockers and mineralocorticoid receptor antagonists, should not be reduced to facilitate maintenance of study drug. If the situation is not rectified despite adjusting/discontinuing nonlife-saving medications or if adjusting non-life-saving concomitant medications is not possible, patients who no longer tolerate the target dose at any time during the course of the trial can be down-titrated to the lower dose level at the investigator's discretion (please refer to Figure 1 for dose levels available for titration). However, every attempt should be made to re-challenge the patients so that they are kept on the maximal tolerated dose of study drug for as long a duration as possible throughout the outpatient dose titration and follow-up period of the trial. Please refer to Section 6.4.3 for a guidance on study drug dose adjustment.

Primary assessment:

- NT-proBNP
- LVEF
- LVEDV
- LVESV

Secondary assessments:

- Death
- Reinfarction
- hospitalization for heart failure or outpatient heart failure
- arrhythmia
- stroke

Safety assessments:

- AEs and SAEs
- hypotension
- Angioedema
- Laboratory values
- Hyperkalemia

Data analysis: Analyses of the change from baseline in NT-proBNP and echocardiographic parameter was performed using an analysis-of-covariance model adjusted for baseline values. Logarithmic transformation is used for NT-proBNP, due to its skewed distribution.

The secondary efficacy variables will be analyzed using Kaplan-Meier estimates and Cox proportional hazards models. The hazard ratios, 95% confidence intervals, and two-sided P values are calculated using the model to adjust the following baseline prognostic factors: Age, gender, body mass index, total cholesterol, triglycerides, history of hypertension, diabetes and Previous smoking.

We will use Fisher's exact test to compare rates of Safety outcomes.

The targeted sample size mainly is driven by the LVEF of the primary composite endpoint. Assuming that the increase in LVEF is 3%±6%, the patients are included in the ratio 1:1 when α=0.05 and the test power is 80%, and the sample size for each group is predicted to be 64 cases.

1 Background

Angiotensin receptor-neprilysin inhibitor (ARNI, Sacubitril/Valsartan) is superior to angiotensin-converting enzyme inhibitors (ACEI) on cardiac remodeling in patients with heart failure (HF). However, there is little data describing the effects of sacubitril/valsartan in patients with acute anterior ST-segment elevation myocardial infarction (STEMI). The objective is to assess the safety and efficacy of sacubitril/valsartan compared with Enalapril in patients with acute anterior STEMI after PCI.

This study is a single center, prospective, randomized, double-blind trial, planning to recruit patients with acute anterior STEMI at the Second Affiliated Hospital of Nanchang University. Patients are randomly assigned 1:1 to in-hospital initiation of sacubitril/valsartan and enalapril. The starting dose during the in-hospital initiation phase and all subsequent dose changes during the titration period is selected using a dose titration algorithm (Figure 1). Patients are followed up at 4, 12, and 24 weeks after discharge from the hospital, blood test and echocardiograph are performed. The primary efficacy outcomes are the changes in NT-proBNP concentrations and in echocardiographic parameters (LVEF, LVEDV, LVESV) from baseline through weeks 4, 12 and 24. Secondary outcomes include the incidence of a composite of death, reinfarction, hospitalization for heart failure or outpatient heart failure, arrhythmia, stroke. Safety endpoints are the incidence of angioedema, hypotension, renal insufficiency, and hyperkalemia.

2 Purpose and rationale

The purpose of this study is to evaluate the effect of sacubitril/valsartan compared to enalapril in reducing the concentration of NT-proBNP and improving the main cardiac ultrasound parameters in patients with acute anterior STEMI after PCI.

3 Study goals and objectives

3.1 Primary objective:

The primary objective of this study is to test if sacubitril/valsartan is superior to enalapril in reducing the concentration of NT-proBNP and improving the main cardiac ultrasound parameters in patients with acute anterior STEMI after PCI.

3.2 Secondary objective:

The Secondary objective of this study is to test if sacubitril/valsartan is superior to enalapril in reducing the incidence of cardiovascular events (a composite of death, reinfarction, outpatient HF or HF hospitalization, arrhythmia, and stroke).

4 Study design

This study is a single-center, prospective, randomized, double-blind, parallel-group, two-arm, short-term trial to compare sacubitril/valsartan 200 mg bid to enalapril 10 mg bid in concentration of NT-proBNP reduction and main cardiac ultrasound parameters improvement in patients with acute anterior STEMI after PCI.

4.1 Justification of key elements of the study design

4.1.1 Selection of the primary endpoint

We chose NT-proBNP as the primary endpoint in this study because natriuretic peptide concentrations are associated with adverse outcomes in patients with AMI[7-9]. Although both ANP and BNP undergo degradation by neprilysin, the biologically inert NTproBNP, cleaved from proBNP along with BNP, is not a substrate for neprilysin degradation, and changes in this marker still reflect reduction in left ventricular wall stress even in the setting of neprilysin inhibition[10].

4.1.2 Choice of enalapril as the comparator

Major clinical trials have established ACEI treatment as the standard of care for RAAS blockade and are recommended by treatment guidelines as the treatment of choice for all patients with AMI, unless ACEI-intolerant. Since the ultimate goal of the sacubitril/valsartan development program is to replace ACEIs as the guideline-recommended RAAS based agent in HF, an ACEI has been selected as the control in this study. As a well-studied ACEI in HF, enalapril is used as the comparator in this study. Enalapril was studied in a number of previous large, outcome-driven studies, such as OVERTURE[11], CONSENSUS[12], SOLVD-Treatment [13], and SOLVD-Prevention [14].
Enalapril dose of 10 mg bid has been selected as the comparator target dose for this study based on its ability to reduce the risk of death or hospitalization as demonstrated in the SOLVD-Treatment study [13].

4.1.3 sacubitril/valsartan dose and dosing regimen

A strong rationale exists for the selection of sacubitril/valsartan 200 mg bid as the target dose.

Importantly, a dose of sacubitril/valsartan 200 mg bid delivers similar exposures of valsartan (assessed by AUC) as Diovan® 160 mg bid, the maximal approved Diovan® dose for HF after AMI and the dose recommended in international guidelines for the treatment of HF after AMI. In addition, biomarker analysis (increase in ANP and cGMP) indicates that this dose delivers approximately 90% of its maximal NEP inhibition. The biomarker data are also consistent with results obtained in a dose ranging study in HTN, which demonstrated additive effects of the ARB moiety and the NEPi moiety with sacubitril/valsartan 400 mg and 200 mg once daily, with a minimal incremental BP reduction from sacubitril/valsartan 200 mg/d to sacubitril/valsartan 400 mg/d. sacubitril/valsartan 400 mg/d and 200 mg/d were well tolerated in this study.

Rather than 400 mg once daily dosing of sacubitril/valsartan that was used in the HTN study, this dose will be split and sacubitril/valsartan will be dosed at 200 mg twice daily in the current study. This will ensure sustained NEP inhibition over 24 hours, which is thought to be critical for patients with HF after AMI. Furthermore, twice daily dosing will also mitigate the likelihood of hypotension, particularly in those with more severe HF impairment (NYHA III-IV).

4.1.4 Duration of the study

As planned, it is expected to be up to 18 months: a recruitment period of approximately 12 months and a minimal follow-up of 6 months.

4.2 Study visits

4.2.1 Screening

Visit 1 (Screening Visit)

All patients must provide informed consent before any study-specific procedure is performed. At Visit 1, patients' eligibility for entering the randomization period, including whether the patient's vital signs are stable after PCI, will be assessed by the investigator. Whether enalapril is included in the medicine used immediately after the operation. Screening potassium levels and eGFR will be assessed by sending blood samples to the central laboratory and only patients with the required values per the entry criteria will be eligible for entering the randomization period, which will begin at Visit 2.

4.2.2 Randomization

Visit 2 (Randomization Visit)

Patients who have met all the inclusion criteria and none of the exclusion criteria at the end of the screening period will be randomized to either enalapril or sacubitril/valsartan in a 1:1 ratio. Patients randomized to enalapril continue to receive enalapril, while

patients randomized to sacubitril/valsartan discontinue enalapril to ensure a minimum 36-hour washout period prior to initiation of ARNi therapy. The first dose of sacubitril/valsartan is followed by 6 hours of monitoring for hypotension. After the condition is stable, patients can be discharged from the hospital at any point in time at the discretion of the clinician-investigator. The starting dose during the in-hospital initiation phase is selected using a dose titration algorithm based on systolic blood pressure (SBP) (**Figure 1**).

4.2.3 Outpatient dose titration period

Visit 3 (Outpatient dose titration period Visit)

During the outpatient dose titration phase, patients continue to receive sacubitril/valsartan or enalapril. There are 3 available doses of study drug administered twice daily. All subsequent dose changes during the medication titration period is selected using a dose titration algorithm based on systolic blood pressure (SBP) (**Figure 1**). Clinician-investigators are encouraged to up titrate sacubitril/valsartan to target dose (i.e., dose level 3) as tolerated during the medication titration phase. every attempt should be made to complete the dose titration period within 8 weeks regardless of any down-titration that may occur.

4.2.4 Follow-up period

Visit 4 (Follow-up Visit)

Follow-up visits are scheduled for Weeks 4, 12 and 24. Blood and urine samples are sent to a central laboratory for hematology, chemistry, and serum and urinary biomarkers. Professionals use Philips IE33 ultrasound system (Philips Medical System, Bothell, Washington, USA) for echocardiographic measurements. In addition to the protocol-required visits, patients may be seen at any time throughout the study at the discretion of the investigator to investigate or follow any new lab abnormalities or adverse events.

Monitoring of safety and tolerability will include: (1) hyperkalemia; (2) symptomatic hypotension; (3) increase in serum creatinine; (d) angioedema; and (e) adverse events and serious adverse events. If, in the opinion of the investigator, the patient cannot tolerate the target dose of study drug, the investigator should consider whether non-life saving medication (e.g., CCBs, nitrates, α- blockers) can be reduced to rectify the situation before considering reducing the dose of the study drug to the lower dose level. The dose of background disease modifying drugs, such as β-blockers and mineralocorticoid receptor antagonists, should not be reduced to facilitate maintenance of study drug. If the situation is not rectified despite adjusting/discontinuing nonlife-saving medications or if adjusting non-life-saving concomitant medications is not possible, patients who no longer tolerate the target dose at any time during the course of the trial can be down-titrated to the lower dose level at the investigator's discretion (please refer to Figure 1 for dose levels available for titration). However, every attempt should be made to re-challenge the patients so that they are kept on the maximal tolerated dose of study drug for as long a duration as possible throughout the outpatient

dose titration and follow-up period of the trial. Please refer to Section 6.4.3 for a guidance on study drug dose adjustment.

5 Population

5.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:
1. Patients must give written informed consent before any assessment is performed
2. Outpatients ≥ 18 years of age, male or female
3. Had typical pain and Diagnosed as acute anterior STEMI according to electrocardiogram, high-sensitivity troponin, and coronary angiography
4. Systolic blood pressure ≥ 100mmHg without symptoms of dizziness during the last 12 hours prior to randomization

5.2 Exclusion criteria

1. Previous history of myocardial infarction or chronic heart failure
2. Previous PCI, coronary artery bypass graft (CABG), implantation of other heart assist devices or heart transplantation
3. Known history of angioedema
4. Previous history of intolerance to recommended target doses of ACEIs or ARBs.
5. Previous use of sacubitril/valsartan
6. History of hypersensitivity or contraindications to the study drugs including ACEI, ARB, sacubitril/valsartan
7. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening), Visit 2 (randomization), Visit 3 (outpatient dose titration) or Visit 4 (follow-up)
8. Estimated GFR < 30 mL/min/1.73m^{2}as measured by the simplified MDRD formula at Visit 1 (screening), Visit 2 (randomization), Visit 3 (outpatient dose titration) or Visit 4 (follow-up) or > 25% decline in eGFR between Visit 1 and Visit 2 or between Visit 2 and Visit 3 or between Visit 3 and Visit 4
10. Serum potassium > 5.2 mmol/L at Visit 1 (screening), Visit 2 (randomization), Visit 3 (outpatient dose titration) or Visit 4 (follow-up)
11.History of severe pulmonary disease
12.Diagnosis of peripartum or chemotherapy induced cardiomyopathy prior to Visit 1
13.Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1
14.Symptomatic bradycardia or second or third degree heart block without a pacemaker
15. Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation

16. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis
17. Life expectancy is less than 1 year
18. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following
- History of active inflammatory bowel disease during the 12 months before Visit 1.
- Current duodenal or gastric ulcers during the 3 months prior to Visit 1
- Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 2 x ULN at Visit 1, history of hepatic encephalopathy, history of esophageal varices, or history of portacaval shunt
- Active treatment with cholestyramine or colestipol resins

19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method
- Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progesterone agent.
- Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Investigational drugs

after PCI

The following study drugs will be provided:
• Enalapril 2.5 mg tablets
• Enalapril 5 mg tablets
• Enalapril 10 mg tablets

Randomization, Outpatient dose titration and follow-up
All eligible patients will be randomized to receive either sacubitril/valsartan or enalapril in addition to optimal AMI therapy, as considered appropriate by the investigator and in accordance with standard therapy guidelines, but with the exception of an ACEI or ARB as this will be replaced by study drug. The use of an ACEI or an ARB in addition to study drug after randomization is strictly prohibited.

The following study drugs will be provided:
• Enalapril 2.5 mg tablets (enalapril dose level 1)
• Sacubitril/Valsartan 50 mg tablets (Sacubitril/Valsartan dose level 1, Sacubitril/Valsartan to match enalapril 2.5 mg film-coated tablets)
• Enalapril 5 mg tablets (enalapril dose level 2)
• Sacubitril/Valsartan 100 mg tablets (Sacubitril/Valsartan dose level 2, Sacubitril/Valsartan to match enalapril 5 mg film-coated tablets)
• Enalapril 10 mg tablets (enalapril dose level 3)
• Sacubitril/Valsartan 200 mg tablets (Sacubitril/Valsartan dose level 3, Sacubitril/Valsartan to match enalapril 10 mg film-coated tablets)
Target doses: Sacubitril/Valsartan 200 mg bid and enalapril 10 mg bid.

6.2 Treatment arms

Patients who are eligible for randomization at Visit 2 will be assigned to one of the following two treatment arms in a 1:1 ratio:
• Sacubitril/Valsartan dose level 1 or 2
• Enalapril dose level 1 or 2

6.3 Treatment assignment

At Visit 2, the researcher or his representative will call the researcher in charge of randomization, enter the patient's patient number, and confirm that the patient is eligible for randomization. The researcher in charge of randomization will assign a random number to the patient, which will be used to connect the patient to the treatment arm.
During the titration of the drug, the researcher will decide whether to increase or decrease the dose of the drug based on the patient's blood test and physical examination.
Randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the researcher provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked

to the different treatment arms, which in turn will be linked to medication. The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

6.4 Treating the patient

6.4.1 Patient numbering

Each patient is uniquely identified in the study by a patient number. After the patient has signed the informed consent form, the researcher will telephone the researcher responsible for randomization and provide the requested identifying information for the patient. Then, the researcher responsible for randomization will assign the patient number, which is a 3-digit number (for example, 001, 002, 003, etc.) once assigned to a patient, the patient number will not be reused.

6.4.2 Instructions for prescribing and taking the study drug

The Second Affiliated Hospital of Nanchang University will supply the investigators with all medications sufficient for the course of the study. Patients will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit.

Patients will be instructed to take their morning study drug doses at approximately 08:00 (8 AM) and their evening study drug doses at approximately 19:00 (7 PM). The study medications should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless if it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record electronic case report form.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable to take the study drug as prescribed for any reason.

6.4.3 Permitted study drug dose adjustments and interruptions

Every attempt should be made to maintain patients on the target study drug dose level for as long a duration as possible throughout the trial. If, however, in the opinion of the investigator, the patient does not tolerate the target dose of study drug (dose level 3), the investigator should consider whether non-life saving medication (e.g., CCBs, nitrates, α-blockers) can be reduced to rectify the situation, before considering to reduce the dose of the study drug to the next lower dose level. If adjustment/elimination of

other non-life-saving HF medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the study drug to the next lower level up to complete withdrawal of the study drug. The patient should be re-challenged with the higher dose when the investigator feels it is appropriate to do so per the directions provided below in this section. If needed, the study drug may be stopped completely, but the patient should continue to attend the study visits and be followed until the completion of the study. Ultimately the goal is to keep the patient on the highest study drug dose possible for as long as possible and to follow the patient in the study as long as possible.

Study drug dose level adjustments should mainly be based on overall safety and tolerability with special focus on a) hyperkalemia; b) symptomatic hypotension; and c) clinically significant decrease in eGFR/increase in serum creatinine (see Appendices 2, 3 and 4 for treatment guidelines for hyperkalemia, management of BP, and renal dysfunction, respectively).

Adjustment of study drug dose level

Study drug dose adjustments during the dose titration period

Once the condition is stable, the patient should increase the titration to the next higher dose level every 2 weeks in an attempt to gradually titrate the patient to the target study drug dose level (dose level 3).

At the investigator's discretion, sacubitril/valsartan 200 mg bid can be down-titrated to sacubitril/valsartan 100 mg bid until such time that investigator believes the patient may be able to tolerate titration back up to sacubitril/valsartan 200 mg bid. If the investigator does not feel that the patient will ultimately be able to tolerate this dose, he/she may withdraw the patient from the study without re-challenge. If the tolerability issues are not alleviated despite down-titration by one dose level, the investigator may lower the study drug dose further to the next lower level for 1 to 4 weeks, up to temporary withdrawal of the study drug. Again, once stable, the patient should be rechallenged with up-titration to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to the target study drug dose level (dose level 3).

In some instances, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up-titration to the target dose of study medication (level 3). In this case it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those who temporarily discontinue it as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level (Figure 1) per his/her medical judgment. If

he/she may withdraw the patient from the study without re-challenge. If the tolerability issues are not alleviated despite down-titration by one dose level, the investigator may lower the study drug dose further to the next lower level for 1 to 4 weeks, up to temporary withdrawal of the study drug. Again, once stable, the patient should be rechallenged with up-titration to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to the target study drug dose level (dose level 3).

In some instances, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up-titration to the target dose of study medication (level 3). In this case it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those who temporarily discontinue it as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level (Figure 1) per his/her medical judgment. If tolerated based on the safety and tolerability criteria in Appendices 2, 3, and 4, the patient should be up-titrated up to dose level 3 every 1 to 4 weeks, as per the investigator's judgment. Patients re-started on the study drug will retain their original randomization and study identification numbers. Should the patient not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or discontinue the study medication again and a new attempt to up-titrate or reintroduce the study drug could be considered by the investigator as soon as medically justified in his/her medical judgment.

Study visits should occur as close as possible to the time points indicated in Table 7-1. The timeframe between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in Table 7-1.

Any changes in the study drug dose level, including temporary/permanent withdrawal or restart of the study drug, must be recorded on the Dosage Administration Record electronic case report form.

In case of pregnancy discovered during the screening period, the patient will be withdrawn from the study immediately.

In case of pregnancy discovered during the follow-up period, the patient should be instructed to stop taking the study drug immediately.

Study drug intake should be resumed as soon as possible after the completion of the pregnancy and lactation period. Meanwhile, the patient should continue to attend scheduled study visits.

See Section 8.3 for further details on pregnancies and reporting guidelines.

6.4.4 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in Appendices 2, 3, and 4, respectively. Patients may receive other ACEIs and/or ARBs during the study ONLY if the study medication has been discontinued either temporarily or permanently.

6.4.5 Other concomitant treatment

The investigator should instruct the patient to notify the study site staff of any changes in concomitant medications (new medications or changes in dose regimens of existing medications). All concomitant medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with the study medication must be listed on the Concomitant Medications/Significant Non-Drug Therapies electronic case report form.

ACEIs and ARBs
Patients pre-study ACEIs/ARBs will be replaced with the study medications.
The concomitant use of other ACEIs or ARBs is strictly prohibited while the patient is receiving study medication, regardless of study period (Outpatient dose titration and follow-up). If the investigator believes that addition of an ACEI or ARB is necessary, then study drug must be discontinued. If not already treated with an aldosterone antagonist, consideration should be given to adding this therapy rather than an ACEI or ARB.

Secondary prevention drugs for coronary heart disease and other cardiovascular medications
The patient should be on an optimal medical regimen of background AMI medications. Medications after PCI also include: dual antiplatelet, statins, beta blockers and so on. The use of mineralocorticoid receptor antagonist (MRA), diuretics and inotropes according to the patient's condition. Every effort should be made to keep the dose level of these background, life-saving AMI medications stable throughout the entire study. However, if the patient s condition warrants a change in any of these medications, it is allowed at the discretion of the study investigator.

Diuretics may be used and may be adjusted throughout the length of the study at the discretion of the investigator.

If a patient experiences any adverse events that may be contributed to the study drug, other Secondary prevention drugs for coronary heart disease, or other CV medications, the investigator should adjust non-life saving medications (e.g., CCBs, nitrates, a-blockers, and diuretics) first in an attempt to alleviate the adverse events.

Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements, aldosterone antagonists, renin inhibitors, and any other medications known to raise potassium levels should be used with caution while the patient is receiving the study medication due to the increased possibility of occurrence of hyperkalemia. The investigator is encouraged to assess patients' potassium levels regularly, especially in those who are receiving these medications.

6.4.6 Study drug discontinuation and premature patient withdrawal

The emergence of the following circumstances will require study drug discontinuation:

- Withdrawal of informed consent
- Pregnancy (Section 8.3)
- Investigator thinks that continuation would be detrimental to the patient's well-being
- Suspected occurrence of angioedema during the outpatient dose titration and follow-up period

Study medication may be discontinued at the investigator's discretion if any of the following occurs:

- Any severe suspected drug related adverse event
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and constitute a reason for interruption of study medication.
- Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued, or, if appropriate, have potentially contributing agents adjusted. Please refer to Appendices 2, 3, and 4 for treatment guidelines for hyperkalemia, hypotension, or renal dysfunction, respectively.

In the case of study drug discontinuation, the patient should continue to complete all scheduled study visits and procedures. If the patient refuses, he/she should be contacted by telephone in place of protocol-specified visits unless the patient expressly refuses such contacts.

The investigator must also record the discontinuation of the drug administration form of the electronic case report form.

6.4.7 Study completion and post-study treatment

At the end of study visit, patients will decide for themselves whether to continue the drug study. There is no extension study planned after all assessments of the end-of-study visit are completed.

The investigator also must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

7 Visit schedule and assessments

All patients, including those who discontinue the study medication before completing the study, should continue attending the scheduled visits as outlined in Table 7-1 until the study ends. At that point all patients will return to the study sites as soon as possible to undergo the end of study visit assessments. If any patient refuses to return for these assessments or is unable to do so, every effort should be made to contact him/her or a knowledgeable informant by telephone to ask if any of the secondary and safety endpoints have occurred at the foreseen visit dates for the remaining duration of the study. Documentation of attempts to contact the patient should be recorded in the patient's record.

All data obtained from the assessments listed in Table 7-1 and described in detail in the subsections below must be supported in the patient s source documentation (e.g., medical charts or patient notes).

Table 7-1 indicates which data remain in source documents only (S), or may be entered directly into the database (D; i.e., these data are considered source documentation and do not require separate source documentation), or are entered into the database from separate source documents (DS). Assessments that generate data for database entry and are recorded on electronic case report forms are listed using the electronic case report form name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

There is a short washout periods (approximately 36 hours for each) during the randomization period to minimize the potential risk of angioedema due to overlapping ACE-NEP inhibition at Visit 2 (Section 7.5.7): after randomization at Visit 2.

For example, if a patient's Visit 2 is on Wednesday, he/she must not take any doses of the enalapril medication after the Tuesday evening dose. The patient will then start to take the first dose of the sacubitril/valsartan medication on Thursday morning.

Table 7-1 Assessment schedule

phase		screening	Randomization	Outpatient dose titration period				Follow-up period				
Visit	**D/S***	**1**	**2**	**3a**	**3b**	**3c**	**3d**	**4a**	**4b**	**4c**	**4d**	**4e**
Weeks (w)		**-2 to -1w**	**-1W to -0**	**2w**	**4w**	**6w**	**8w**	**10w**	**12w**	**16w**	**20w**	**24w(EOS)**
Informed consent form	S	x										
Inclusion/Exclusion criteria[1]	DS	x 2	(x)									
Demography/Medical history (including smoking history)	DS	x										
Cardiovascular disease History	DS	x										
Diabetes mellitus History	DS	x										
Physical Exam[2]	S	x	x	(x)	x	x	x	x	x	x	x	x
Height (H) / Weight (W)	DS	H / W	W	W	W	W	W	W	W	W	W	W
Vital signs	DS	x	x	x	x	x	x	x	x	x	x	x
Waist/hip circumference	DS		x									
Onset to balloon, h	DS	x										
KILLIP Classification	DS	x										
TIMI flow grade	DS	x										
Coronary heart disease and CV Medications	DS	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications	DS	x	x	x	x	x	x	x	x	x	x	x
Endpoint information	DS	x	x	x	x	x	x	x	x	x	x	x
AEs / SAEs	DS	x	(x)	x	x	x	x	x	x	x	x	x

Pregnancy tests[3]	DS	x						x				
Echocardiography	DS	x							x			x
Plasma NT-proBNP	DS	x	x		x				x			x
Complete laboratory assessments	DS	x	x	x	x	x	x		x			x
12-lead ECG evaluation	DS	x	x	x	x	x	x		x			x
Screening log	DS	x										
Randomization	DS		x									
Outpatient dose titration	DS			x	x	x	x					
Urinalysis	S	x	x		x		x		x			x
End of study information	DS											x

* D: to be documented in the clinical database, S: in the source data and DS: in the database from separate source documentation.

[1] During the screening, patient safety will be monitored to ensure eligibility to continue to the next phase. Reason for not qualifying for randomization must be documented in detail in the electronic case report forms.

[2] Complete physical examination required at each Visits.

[3] Women of childbearing potential only. At Visit 1 and in case of a positive urine pregnancy result, a confirmatory serum pregnancy test has to be performed at the central laboratory. The pregnancy test will be performed again at Visit 4.

7.1 Information to be collected on screening failures

Patients may discontinue from the study prior to randomization, prior to any study medication being administered.
If a patient discontinues before entering in the randomization period, only the demographic information and Screening Log entry with the reason for discontinuation should be completed on the electronic case report form. It is not necessary to complete all the required evaluations at the time of discontinuation unless medically indicated.
All required evaluations must be performed and clearly documented in the appropriate electronic case report forms of patients who entered the randomization and received study medication. This information must include demographics, reason for discontinuation, and adverse events and safety data (e.g., hyperkalemia, hypotension, renal dysfunction, and other adverse events).

Re-screening

If a patient is not eligible to enter into the randomization period and screen-fails, the investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and may potentially be eligible. In this case, a completely new patient number will be allocated to the subject and he/she will need to re-perform all Visit 1 procedures.

7.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex and source of patient referral. Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnoses and not symptoms will be recorded.

7.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver. This information should be captured in the source document at each visit. Patient compliance should be at least 80% during the Outpatient dose titration and follow-up period. The investigator and/or study personnel will counsel the patient if compliance is below 80%. Study

drug accountability will also be determined by the site monitor while performing routine outpatient visits and at the completion of the study.

7.4 Efficacy

7.4.1 Primary and secondary efficacy outcomes

The primary outcomes are:

- NT-proBNP
- LVEF
- LVEDV
- LVESV

The secondary composite outcome consists of the following components:

- Death
- Reinfarction
- hospitalization for heart failure or outpatient heart failure
- arrhythmia
- stroke

7.4.2 Endpoint Committee

All of the following events, which could potentially fulfill the criteria for the secondary or other endpoints will be assessed during the study, and reported to the Endpoint Adjudication Committee for adjudication or assessment:

- All death events
- All Reinfarction
- Unplanned hospitalization for heart failure or outpatient heart failure
- All arrhythmia
- Stroke
- Renal dysfunction
- Others

The Endpoint Adjudication Committee will be responsible for classifying all death events and for determining whether pre-specified endpoint criteria were met for the other events. if the investigator suspects an endpoint may have occurred, it is best to report the event to the Endpoint Adjudication Committee for the final determination.

guidelines for AE and SAE as outlined in Section 8.1 and Section 8.2 must be followed, independent from the circumstance that an event is also reported as a suspected study endpoint.

7.4.3 Endpoint Definitions

Death includes death classified in any of the following categories:
1. Fatal Myocardial Infarction (MI):
a. Death occurring within 14 days after a documented MI, in which there is no conclusive evidence of any other cause of death. Subjects who are being treated for a MI and who die as a result of complications of the MI (eg, sudden death, pump failure, or cardiogenic shock) will be classified as having had a MI-related death.
b. Autopsy evidence of a recent infarct with no conclusive evidence of any other cause of death.
c. An abrupt death that has characteristics suggestive of an acute infarct but does not meet the definition of a MI. Suggestive characteristics are:
-presentation with acute ischemic symptoms
AND one of the following:
- ECG changes indicative of an acute injury
- abnormal cardiac biomarkers
-other evidence (eg, echocardiography, ventriculography, or scintigraphy) of new ventricular wall motion abnormality
2. Heart Failure:
Death occurring in the context of clinically worsening symptoms and/or signs of heart failure (HF) without evidence of another cause of death.
Death occurring as a complication of the implantation of a ventricular assist device, cardiac transplant, or other surgery primarily for refractory HF.
Death occurring after referral to hospice specifically for progressive HF.
3. Sudden Death:
Death occurring unexpectedly in an otherwise stable subject. Further subclassification of sudden death will be as follows:
a. death witnessed or subject last seen alive <1 hour previously or
b. subject last seen alive ≥1 hr and < 24 hrs previously
4. Presumed Sudden Death
Death occurring unexpectedly in an otherwise stable subject last seen alive ≥24 hours previously, with circumstances suggestive of sudden death.
5. Presumed Cardiovascular Death:
Death likely due to a cardiovascular cause in which the available clinical data is insufficient to support a more specific cause of death.
6. Fatal Stroke:
Death occurring as a result of a documented stroke. Where possible, the stroke will be further classified as ischemic (non-hemorrhagic), ischemic (non-hemorrhagic) with hemorrhagic conversion, hemorrhagic, or unknown.
7. Fatal Pulmonary Embolism:
Death occurring as a direct result of a documented pulmonary embolism.
8. Cardiovascular Procedure-Related Death:

Death occurring during a cardiovascular procedure or as a result of complications related to a cardiovascular procedure (e.g. percutaneous coronary intervention), usually within 14 days.
9. Other Cardiovascular Death:
Death resulting from a specifically documented cardiovascular cause other than those listed above.

Heart failure hospitalization also includes the development of new symptomatic heart failure during an ongoing hospitalization including the index AMI hospitalization.

Outpatient heart failure is defined as:
- An urgent/unscheduled visit to an ED, acute/urgent care facility or outpatient clinic or a non-urgent office/practice or study visit for a primary diagnosis of HF that does not require an overnight hospital stay.
- Patients must exhibit at least one documented new HF symptom with objective evidence of clinical HF consisting of at least 2 physical examination findings or one physical examination findings and at least one laboratory criterion.
- The event requires initiation or intensification of treatment specifically for HF. Such treatment can include administration of intravenous agent (e.g., diuretic, vasodilator, vasopressor, or inotrope) or mechanical or circulatory intervention for HF, OR initiation of oral loop diuretic treatment, or intensification of oral maintenance loop diuretics for the diagnosis of HF, over a sustained period (i.e., initiation or doubling of total daily dose through a period of $\geq$ 4 weeks), which is confirmed at a subsequent outpatient visit.

7.4.4 Biomarkers

Biomarker measurements will be obtained from serum and plasma in a subset of patients at selected sites before surgery and at Visits 1, 2, 3 and 4 to determine effects of treatments on biomarkers of STEMI after PCI.

Biomarkers studied include:

NT-proBNP
Details on sample collection, handling and shipment of biomarker samples will be provided to investigators in the laboratory manual.

7.4.5 Cardiac ultrasonic parameters

Professionals use Philips IE33 ultrasound system (Philips Medical System, Bothell, Washington, USA) for echocardiographic measurements after PCI and 12 and 24 weeks after discharge. Use the biplane Simpson method to measure LVEDV, LVESV and LVEF in the apical four-chamber heart and two-chamber heart views according to

the recommendations issued by the American Society of Echocardiography and the European Cardiovascular Imaging Association[15].

7.5 Safety

7.5.1 Physical examination

A complete physical examination will be performed at Visits 1, 2, 3, and 4. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (BP and pulse). A short physical exam will be at all visits starting from Visit 2, except where a complete physical exam is required (see above).

Information about the all physical examinations must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's electronic case report form. Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the adverse event screen of the patient's electronic case report form.

7.5.2 Vital signs

Vital signs will be assessed at every visit. This will include BP and pulse measurements. BP will be measured by using a standard sphygmomanometer with an appropriate size cuff and the non-dominant arm in the sitting position after 5 minutes of rest.

7.5.3 Height, weight, and waist/hip circumference

Height in centimeters (cm) will be measured at Visit 1.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing without shoes) will be measured at all visits, until the end of study visit.

Waist/hip circumference (to the nearest centimeter [cm] in indoor clothing) will be measured at Visit 2 and at the end of study visit.

7.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all collected specimens. Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

Complete laboratory evaluations (hematology, blood chemistry, and urine; Table 7-2) for the assessment of safety in this study will be performed at Visits 1, 2, 3, and 4.

Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator in the Comments screen of the patient's electronic case report form and additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the adverse events screen of the patient's electronic case report form. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an adverse event, then the procedure for rapid notification of serious adverse event must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator.

Table 7-2 Routine laboratory examinations

Hematology*	**Biochemistry***	**Urine measurements**
Red Blood Cells count White Blood Cells count Platelet Count Hemoglobin Hematocrit WBC Differential	Sodium Potassium Chloride Calcium Blood urea nitrogen (BUN) Creatinine Total Bilirubin Aspartate amino-transferase (AST) Alanine amino-transferase (ALT) Alkaline phosphatase Total protein Albumin Uric Acid Serum Pregnancy Testa Lipid profile (total cholesterol, LDL, HDL, and triglycerides) Hemoglobin A1C	UACR (to calculate urinary albumin/creatinine ratio) Urinalysis

	High Sensitivity Cardiac Troponin I (Hs-cTnI)	

* List of laboratory assessments performed at Visits 1, 2, 3, 4.
a. At Visit 1 and in case of positive urine pregnancy test only.

7.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Visits 1, 2, 3, and 4(Table 7-2).

7.5.4.2 Clinical chemistry

Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium, hemoglobin A1C, High Sensitivity Cardiac Troponin I (Hs-cTnI), total protein, albumin, uric acid, and lipid profile will be measured at Visits 1, 2, 3, and 4. Fractionated bilirubin will be performed for all patients whose total bilirubin value is > 2x ULN.

7.5.4.3 Potassium and eGFR assessments

In addition to the central laboratory assessments, potassium and eGFR, may be measured locally during the screening period (Visit 1), up to the randomization visit (Visit 2) to determine eligibility of the patient into the trial. potassium and eGFR measurements may also be performed during the outpatient dose titration and follow-up period, mainly at the unscheduled visits, to monitor the tolerability to study medication dose administered and adjust medication dose if needed.

7.5.4.4 Urinalysis

Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visits 1, 2,3 and 4.

7.5.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at screening (Visit 1), randomization (Visit 2), Visit 3 and Visit 4. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the electronic case report form. Each ECG tracing should be labeled with the patient initials, patient number, and date and kept in the source documents. Only clinically significant abnormalities should be reported on this page. Clinically significant abnormalities should also be recorded on the relevant medical history/current medical conditions or adverse event electronic case report form page.

7.5.6 Pregnancy and assessments of fertility

All female patients of childbearing potential will have a serum pregnancy test performed at visit 1 and Visit 4. In case of a positive urine pregnancy result a confirmatory serum pregnancy test will be performed at the central laboratory. See Section 6.4.3 and Section 8.3 for details on pregnancies.

7.5.7 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. Although, the mechanism is not fully understood, bradykinin has been implicated as the putative mediator. Therefore, medications that raise the levels of endogenous bradykinin by inhibiting the enzymes responsible for its breakdown, such as ACE, aminopeptidase P, and NEP, may result in this potentially dangerous side effect.

Simultaneous inhibition of multiple breakdown pathways of bradykinin is thought to significantly increase the risk of occurrence of angioedema [16]. Section 4.2.2 details how to avoid the simultaneous inhibition of the ACE and NEP pathways by overlapping exposure to sacubitril/valsartan and enalapril at Visit 2 (randomization). The method outlined in Section 4.2.2 is expected to provide at least 36 hours free of significant simultaneous inhibition of NEP and ACE, thereby minimizing the potential risk of occurrence of angioedema. This 36-hour washout period is expected to present minimal risk to patients.

The procedure for reporting angioedema-like events is outlined in Section 8.5.

8 Safety monitoring

8.1 Adverse events

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.
All AEs must be recorded on the Adverse Events CRF with the following information:

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

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.2.

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; patient hospitalized/patient s hospitalization prolonged. The action taken to treat the AE should be recorded on the Adverse Event Case Record Form.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Drug Instructions. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation must be reported to research team within 24 hours of learning of its occurrence.
Any SAEs experienced after this 30 days period should only be reported to research team if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English. The original copy of the SAE Report Form must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

8.3 Pregnancies

In case a patient becomes pregnant, or plans to become pregnant, the study drug must be interrupted before contraception is discontinued (or, from the date the pregnancy becomes known) for the entire duration of the pregnancy and lactation period (or, for the entire duration that contraception is discontinued). To ensure patient safety, each pregnancy in a patient on study drug must be reported to research team within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the research team. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) independent of research team will be appointed to monitor the study conduct. Any major recommendation from the DMC will be communicated to the research team and must be reviewed and ratified by the research team prior to its enactment.

8.5 Reporting angioedema-like events

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by research team) to summarize the event, its treatment, and its ultimate outcome and communicate this report to research team as soon as possible. Follow-up reports must be communicated to research team as soon as new information regarding the event becomes available.

Occasionally, the investigator may be contacted by the research team regarding AEs that were reported on behalf of patients that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not. All angioedema reports will be forwarded to research team for assessment.

Submission of an angioedema report is not a substitution for the submission of a SAE report. If an angioedema-like event satisfies the definition of a SAE, the investigator must submit a SAE report (as described in Section 8.2) in addition to the Adjudication Questionnaire for an Angioedema-like Event

9 Data review and database management

9.1 monitoring

Before study initiation, at an investigator s meeting, research team will review the protocol and electronic case report forms. During the study, the monitor will visit the database regularly to check the completeness of patient records, the accuracy of entries on the electronic case report forms, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on electronic case report forms must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the case report forms. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

9.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate.

9.3 Database management and quality control

The research team reviews the data entered into the electronic case report forms by investigational staff for completeness and accuracy and instruct the investigator to

make any required corrections or additions. Obvious errors are corrected by research team.

10 Data analysis

10.1 Populations for analysis

The full analysis set (FAS) will consist of all randomized patients. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary population.

10.2 Patient demographics/other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise. Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, sex, weight, height, body mass index (BMI), Previous history of hypertension, prior history of Diabetes mellitus, Previous smoking history, Killip class, blood tests, Number of diseased vessels, vital signs, etc. BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening Visit). Continuous variables will be summarized using n, mean, standard deviation, geometric mean and 95% confidence interval. Categorical variables will be summarized using frequency and percentage.

The difference between treatment groups will be compared using the Fisher's exact test for categorical variables or using t-test or Mann–Whitney U test for continuous variables. The p-values will be provided for descriptive purposes and will not be considered to define any formal basis for determining factors to be included in statistical models.

10.3 Analysis of the primary objective

The primary objective of this study is to test if sacubitril/valsartan is superior to enalapril in reducing the concentration of NT-proBNP and improving the main cardiac ultrasound parameters in patients with acute anterior STEMI after PCI.

10.3.1 Primary efficacy variable

The primary efficacy outcomes are the changes in NT-proBNP concentrations from baseline through weeks 4, 12 and 24 and in echocardiographic parameters (LVEF, LVEDV, LVESV) from baseline through weeks 12 and 24.

10.3.2 Statistical model, and method of analysis

Analyses of the change from baseline in NT-proBNP and echocardiographic parameter was performed using an analysis-of-covariance model adjusted for baseline values. Logarithmic transformation is used for NT-proBNP, due to its skewed distribution.

10.4 Analysis of secondary objectives

10.4.1 Secondary efficacy variables

The secondary efficacy variable is a composite of death, reinfarction, outpatient HF or HF hospitalization, arrhythmia, and stroke.

10.4.2 Statistical model, and method of analysis

The secondary efficacy variables will be analyzed using Kaplan-Meier estimates and Cox proportional hazards models. The hazard ratios, 95% confidence intervals, and two-sided P values are calculated using the model to adjust the following baseline prognostic factors: Age, gender, body mass index, total cholesterol, triglycerides, history of hypertension, diabetes and Previous smoking.

10.5 Safety

The safety and tolerability assessments are listed below:

- AEs and SAEs
- hypotension
- Angioedema
- Laboratory values
- Hyperkalemia
- Renal dysfunction

The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

The incidence of treatment-emergent adverse events (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values and by the flagging of notable values in data listings.

We will use Fisher's exact test to compare rates of Safety outcomes.

10.6 Sample size calculation

The targeted sample size mainly is driven by the LVEF of the primary outcomes. Assuming that the increase in LVEF is 3%±6%, the patients are included in the ratio 1:1 when α=0.05 and the test power is 80%, and the sample size for each group is predicted to be 64 cases. Taking into account the loss to follow-up rate of 10%, it is estimated that a total of 142 patients will be needed

10.7 End of the study

The actual trial time will depend on the end of the last patient follow-up time.
As planned, it is expected to be about 18 months: a recruitment period of 12 months and a minimal follow up of 6 weeks.

11 Ethical considerations

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Research Ethics Board approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.3 Responsibilities of the investigator and REB

The protocol and the proposed informed consent form must be reviewed and approved by Ethics Committee of the Second Affiliated Hospital of Nanchang University before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to research team and investigators as required.

11.4 Publication of study protocol and results

Research team assures that the key design elements of this protocol will be posted in a publicly accessible database such as Chinese clinical trial Registry.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by research team and approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University it cannot be implemented.

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14 Appendix 1: Clinically notable laboratory values and vital signs

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase

Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

15 Appendix 2: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.3 mmol/L)

General principles

Elevation of potassium levels above the predefined values should be repeated and confirmed before any action is taken. Any patient who experiences a potassium level 5.5 mmol/L confirmed by repeated testing during the screening period should be withdrawn from the study. Any patient with a serum potassium > 5.3 mmol/L after randomization requires regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern (5.5 and < 6.0 mmol/L) or potential danger (6.0 mmol/L).

Investigators should not randomize a patient with a serum potassium 5.5 mmol/L during the screening period. Patients with elevated potassium value will be managed according to the corrective actions outlined below.

Corrective action for management of hyperkalemia

Serum potassium > 5.3 and less than or equal to 5.5 mmol/L

• Confirm potassium concentration in a non-hemolyzed sample
• Reinforce low potassium diet and restriction of food/drinks with high potassium content(e.g. orange juice, melon, bananas, low-salt substitutes etc.)
• Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
• Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
• Potassium supplements, e.g., potassium chloride
• Salt substitutes
• Non-steroidal anti-inflammatory drugs (NSAIDs)
• Cyclo-oxygenase-2 (COX-2) inhibitors
• Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
• Herbal Supplements:
• For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries
• Repeat serum potassium measurement within 3 to 5 days
• If serum potassium remains > 5.3 and ≤ 5.5 mmol/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly)
• Consider down-titration of study medication, according to investigator's medical judgment.

Serum potassium > 5.5 and < 6.0 mmol/L

• Confirm potassium concentration in a non-hemolyzed sample
• Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
• Apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mmol/L
• Repeat serum potassium measurement after 2-3 days
• If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mmol/L

• Immediately discontinue study drug
• Confirm potassium concentration in a non-hemolyzed sample
• Urgently evaluate patient and treat hyperkalemia as clinically indicated
• Apply all measures outlined for serum potassium > 5.3 and < 6.0 mmol/L

No resumption of study drug without individualized case discussion with and permission from his/her designee.

16 Appendix 3: Guidelines for the management of blood pressure Guidelines

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:

a. Correct any treatable cause, e.g. hypovolemia

b. If hypotension persists, any antihypertensive drug and non-life saving drugs should be down-titrated or stopped first before down-titration of the study drug is considered

c. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 6.4.3 should be adhered to as much as possible.

17 Appendix 4: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study medication. Moreover, renal dysfunction may develop or may deteriorate in some patients after study drug administration. These recommendations have been developed to guide the investigators in managing patients with renal dysfunction after randomization.

During the randomization period any patient who experiences a decline in eGFR > 25% or an eGFR < 30 mL/min/1.73m2 will be considered a failure and withdrawn from the study.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (Visit 5) (or if serum creatinine concentration increase to 2.5 mg/dL [221 µmol/L]), the investigator will check for potentially reversible cases of renal dysfunction such as:

- Non-steroidal anti-Inflammatory drug intake, antibiotics, or other treatments known to affect creatininemia
- Volume decrease
- Urinary infection

- Urinary tract obstruction
- Study medication

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (Visit 5) (or if serum creatinine concentration rises above 3 mg/dL (265 μmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above)

If the investigator judges that study medication has to be stopped, he/she will have to contact his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

Investigator approval signatures for:

Angiotensin–Neprilysin Inhibition (Sacubitril/Valsartan) versus Enalapril in patients with acute anterior wall ST-elevation myocardial infarction after emergency PCI: a prospective randomized trial

Clinical Study Protocol
Version number: 01

Investigator signature
I have read the protocol and agree to conduct this trial in accordance with all stipulations of the protocol, with applicable laws and regulations in accordance with the ethical principles outlined in the Declaration of Helsinki.

Investigator	Signature	Date
		2019.1.2

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