# COMPARATIVE EFFECTS OF SINGLE VERSUS TWICE-DAILY RAMIPRIL DOSING ON RENAL FUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND HEART FAILURE WITH REDUCED EJECTION FRACTION

**(Evaluation Of Plasma Renin Activity, Malondialdehyde, Interleukin-6, Albuminuria, And Cystatin C)**


**Authored by :**

**EVI LILIEK WULANDARI**

**NIM : T502208008**

**Doctoral Program in Medical Science**

**Faculty of Medicine**

**UNIVERSITAS SEBELAS MARET**


**2025**

## Study Protocol and Statistical Analysis Plan

### A. Study Protocol

This research is a clinical, double-blind, Randomized Controlled Trial. Research subjects will be assigned to either the single-dose or divided-dose group through simple randomization. The target population for this study is outpatients with Chronic Kidney Disease (CKD) and low ejection fraction heart failure at the Internal Medicine polyclinic of Sebelas Maret University Hospital.

Patients who willing to participate in the study will be randomized into Group I or Group II using a simple random sampling method with consecutive sampling for sample collection and a simple random test to determine entry into Group I or Group II. Patients from the Internal Medicine Polyclinic diagnosed with CKD stages 3-5 accompanied by low ejection fraction heart failure who meet the inclusion and exclusion criteria will undergo blood and urine sample collection, as well as physical examination. Then, simple randomization will be performed, and they will be divided into two groups: Group I (Ramipril 10mg/24 hours) and Group II (Ramipril 5mg/12 hours). Simple randomization is done by drawing one of 80 sealed envelopes, each containing either number I or II, with 40 envelopes for each number. Each number will then be given a package of ramipril capsules prepared by the Pharmacy Installation of UNS Hospital from day one to day 30. Patients will continue to take their routine heart failure medication and other medications for comorbidities. In the second week, patients will undergo blood electrolyte examinations at the Clinical Pathology Laboratory of UNS Hospital. On day 30, patients will have a follow-up visit to the internal medicine polyclinic for physical examination, blood tests, and urine tests.

All study subjects must meet the inclusion criteria, which are:

1. Male and female patients aged ≥ 18 years
2. Patients with a diagnosis of non-dialysis CKD stages 3–5 with low ejection fraction heart failure (ejection fraction < 40%)

Subjects with the following characteristics are required to be excluded from the study:

1. Receiving hemodialysis therapy
2. History of intolerance to ACE inhibitors
3. Refractory hyperkalemia
4. Pregnant condition
5. History of angioedema to ACE inhibitors
6. Receiving sacubitril-valsartan therapy

7. Receiving ARB therapy
8. Hypotension with blood pressure < 90/60, or shock patients

Routine heart failure therapies (spironolactone, furosemide, bisoprolol, or carvedilol) and other comorbid disease therapies will continue to be given. Contraindicated therapies include ARB (Candesartan or Valsartan) and ARNI.

Blood and urine samples obtained will be tested for Plasma Renin Activity, Malondialdehyde, Interleukin-6, Albuminuria, and Cystatin C. Physical examinations include measurements of blood pressure, pulse, respiratory rate, body temperature, weight, and height, as well as serum electrolyte, urea, and creatinine examinations.

**B. Statistical Analysis Plan**

Data normality will be tested using Shapiro Wilk. If the data distribution is normal and homogeneous, paired T-tests will be used for pre and post-tests, and independent T-tests will be used for testing the single-dose and divided-dose groups. If the data distribution is not normal and/or not homogeneous, the Mann-Whitney U test will be performed. Parameters PRA, MDA, IL-6, Albuminuria, and Cystatin C will use paired T-tests for pre and post, and then independent T-tests for testing the single-dose and divided-dose groups if the data are normally distributed and homogeneous. Multivariate analysis will be conducted to analyze confounding variables in the samples. Testing will be performed using SPSS version 29.0.2.0 for Windows

**INFORMED CONSENT**

I am Evi Liliek Wulandari, a researcher from FK UNS/RS UNS Department of Internal Medicine, hereby ask you to voluntarily participate in a study titled "DIFFERENCE IN THE EFFECT OF SINGLE AND DIVIDED DOSES OF RAMIPRIL ON RENAL FUNCTION IN CHRONIC KIDNEY DISEASE PATIENTS WITH LOW EJECTION FRACTION HEART FAILURE" with the following explanations:

1. The purpose of this study is to analyze and explain the difference in the effect of single and divided doses of ramipril on renal function in chronic kidney disease patients with low ejection fraction heart failure (HFrEF), using blood and urine tests before drug administration and on the 30th day of drug administration.
2. You are involved in this study because you meet the research criteria, which is having chronic kidney disease accompanied by low ejection fraction heart failure. Your involvement in this research is voluntary.
3. If you do not agree to this method, you can withdraw or choose not to participate in this study at all. For this, you will not be subjected to any sanctions.
4. This study will last for 30 days (duration of sample collection/study duration) with blood serum and urine samples.
5. You will be given compensation in the form of a package/gift for your lost time or other inconveniences, such as blood and urine sample collection.
6. After the study is completed, you will be given information about the general research results through a written report per individual.
7. You will receive information about your health condition during data/sample collection from the researcher.
8. You will receive information if hyperkalemia and worsening conditions are found during this study.
9. You will also be informed of other data related to your condition that may be found during sample/data collection.
10. The sample collection procedure involves taking blood and urine samples, which may cause pain and discomfort.
11. The benefits you gain from your participation are a more thorough examination of kidney function and therapy for the slowdown of chronic kidney disease progression and improvement of heart failure.
12. This research is conducted with the hope of providing benefits for chronic kidney disease patients with low ejection fraction heart failure, the general public, the government, and for the development of science.
13. After this study is completed, you can continue further treatment/health services at the Internal Medicine Polyclinic of UNS Hospital, still using BPJS insurance.
14. After receiving treatment or health procedures as a result of the research, you must wait until the treatment or health procedure is legally authorized.
15. While waiting for legal authorization, you can use standard therapy.
16. You will be given information if new information is obtained from this research or from other sources.
17. All data in this study will be stored by the researcher (research team) in softfile and hardfile format during the study until the research results are released.

18. All information you provide in this study will not be disseminated, thus ensuring its confidentiality.
19. This research is a private study, and no sponsors are funding this research.
20. The researcher is solely responsible for this study.
21. During the study, the researcher will be responsible for the risk of pain or discomfort during blood collection.
22. If risks related to the research occur, you can receive free healthcare services in the form of inpatient care at UNS Hospital. However, if risks unrelated to the research are found, it is not the responsibility of the researcher.
23. If disability or death occurs as a result of this study, compensation in the form of money will be provided by the researcher to the patient's family.
24. This research does not involve elements that are harmful to individuals/subjects, so there is no legal guarantee for such matters.
25. This research has received ethical approval from KEPK RS UNS.
26. You will be informed if there is a violation of the implementation of this research protocol; and if a violation occurs, the lead researcher will provide security guarantees for the subject.
27. You will receive an explanation of the research design and the treatments that will be carried out until the study is completed.
28. All important information will be disclosed during the study, and you have the right to withdraw data/information during the study.
29. Genetic test results and family genetic information will be kept confidential by the researcher and will not be disclosed without your permission.
30. The research will use your medical records and laboratory results only if you give permission.
31. This research uses your blood and urine samples. The researcher will only use these samples for the purpose of this research, and any remaining samples will be destroyed to prevent misuse.
32. This research involves you (women of childbearing age), and you have the right to continue participating in this study or withdraw if risks occur.
33. This research does not involve you (pregnant/nursing women), and you have the right not to continue participating in this study or to withdraw.
34. This research does not involve you as a disaster victim for research purposes and is not related to humanitarian aid that may be provided by other parties.
35. This research is conducted offline and online with the help of the WhatsApp application as a means of reminding medication adherence. The researcher will monitor daily reporting and prevent your data from leaking.

I hope you are willing to be a respondent in this study where you will complete a questionnaire related to the research.

Researcher

Evi Liliek Wulandari

**INFORMED CONSENT**

**(AGREEMENT AS A RESEARCH SUBJECT)**

I, the undersigned:

Name : _____

Age : _____

Gender : _____

Religion/Occupation : _____

Address / Phone Number : _____

Have received a detailed and clear explanation regarding the study titled "DIFFERENCE IN THE EFFECT OF SINGLE AND DIVIDED DOSES OF RAMIPRIL ON RENAL FUNCTION IN CHRONIC KIDNEY DISEASE PATIENTS WITH LOW EJECTION FRACTION HEART FAILURE". I have also received information regarding:

1. Treatment to be given to research subjects
2. Benefits as a research subject
3. Possible hazards
4. Research procedures
5. Right to safety and privacy
6. Results of sample collection

I also have the right to ask questions about anything related to the research. Therefore, I willingly agree/do not agree*) voluntarily to be a research subject with full awareness and without any coercion.

Thus, I make this statement truthfully and without pressure from any party.

....., ..... 2025

| The undersigned, | Witness | Researcher |
|---|---|---|
| (.....) | (.....) | (Evi Liliek Wulandari) |

**) Cross out what is not needed*