Version 1.70 (created on January 4, 2023)
Approval number 20211013

LONG- VS. SHORT-ACTING LOOP DIURETICS AND NEUROHORMONAL AGENTS ON PATIENTS' QUALITY-OF-LIFE AMONG PATIENTS WITH HEART FAILURE (LAQUA-HF TRIAL)

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1 RESEARCH OBJECTIVE

ABOUT THE ILLNESS CALLED HEART FAILURE

Heart failure is an illness characterized by a sick heart causing shortness of breath and swelling, eventually endangering life. The number of patients with this condition is constantly increasing, and in Japan, hospitalization due to heart failure has reached 280,000 cases a year. Treatment in the period when symptoms of heart failure suddenly appear, the acute phase, is making considerable progress, and the number of patients who pass away during this period has diminished. However, often patients relapse and are re-hospitalized in the subsequent chronic phase, and in fact, the overall number of patients with heart failure is not decreasing.

ABOUT TREATMENT WITH MEDICATION FOR HEART FAILURE

In the treatment of heart failure, medicines called loop diuretics, which excrete water out of the body as urine, play a significant role. Based on their acting time, they are divided into short-acting types (e.g., furosemide) and long-acting types (e.g., torsemide), but while these medicines are widely used, there is no clear rule with regard to their use in the chronic phase, and scientific evidence is lacking.

In addition, new neurohormonal agents called neprilysin inhibitors, which relieve heart and kidney burdens by reducing blood pressure; and dapagliflozin, which protects the heart by excreting excessive sugar into the urine, have been used as new treatments for heart failure since 2020. However, their priority of use, and efficacy in the Japanese population, have not been clarified.

Shiraishi Y, *et al. BMJ Open* 2024; 14:e076519. doi: 10.1136/bmjopen-2023-076519

RESEARCH OBJECTIVE

This research is conducted to comparatively examine how the combination treatment of long-acting loop diuretics (torsemide) or short-acting loop diuretics (furosemide), and angiotensin receptor neprilysin inhibitors (ARNI) or dapagliflozin for patients with heart failure, improve your symptoms and quality of life. It is expected that the outcomes will lead to the discovery of treatments that will improve the symptoms and quality of life of patients with heart failure. This research that we are requesting you to participate in is a clinical study conducted by a pharmaceutical company to investigate the safety and usefulness of new medicines, and obtain the approval of the Ministry of Health, Labor and Welfare, by targeting medicines that have already been approved by them. As such, it is not a so-called “trial.” In addition, its implementation has already been approved by the head of each institution.

2 VOLUNTARINESS OF RESEARCH COOPERATION AND FREEDOM OF WITHDRAWAL

ABOUT CONSENT

This explanatory document provides information on the contents of this study and on participation. If you have read the contents carefully and would like to cooperate in this research free willingly, please sign the consent form. You may also consult your family and friends and reply to us at a later date. This research will be conducted within the scope of normal insurance medical treatment. If you choose not to participate in this research, we will provide you with the best heart failure treatment at our disposal, including other medicines. Even if you do not consent, or withdraw your consent halfway, you will not be subject to unfavorable treatment because of this.

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ABOUT WITHDRAWAL OF CONSENT

Even after you have consented to participate in this research, if you change your mind, you can withdraw your consent regardless of the reason. If you withdraw your consent, we will discard your information and samples related to this research. However, if you apply for withdrawal after the publication of the research results, the effect of such withdrawal will be effectively nullified. In addition, in a case of withdrawal of consent, in an effort to give maximum respect to your will, we will adopt the most appropriate method out of these options, according to the circumstance.

- **Full withdrawal of consent:** Withdrawing the consent to participate in the research, and refusing subsequent research treatments, research-related outpatient visits and tests, and research use of data obtained before the withdrawal of consent.

- **Withdrawal of consent:** Withdrawing the consent to participate in this research, and refusing subsequent research treatments, as well as research-related outpatient visits and tests. However, the research use of data obtained before the withdrawal of consent is allowed.

- **Refusal of research treatment:** Refusing the continuation of subsequent research treatments (medicine taking, questionnaire, etc.) However, research-related outpatient visits and tests will be continued as much as possible thereafter, and the research use of data obtained before the refusal of research treatments is also allowed.

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3 RESEARCH METHODS/RESEARCH COOPERATION MATTERS

1. Consent Acquisition

We are calling out to individuals who meet the conditions required for this research to participate in the study. If you agree to participate in this research, please provide your written consent.

2. Randomization

If you consent to participate in this research, based on the information entered into the computer, a program will randomly determine your treatment, and the treatment will be provided after you have been allocated into one of the four groups to be described later. Thus, neither you nor your attending physician can choose which treatment you will be assigned. In addition, it is possible that you may not be able to receive the interventional treatment that you want. Medicines that you will take are by the usage and dose approved by the Ministry of Health, Labor and Welfare, and you will purchase them by yourself at hospital pharmacies or out-of-hospital pharmacies, just like the medicines you normally take.

3. Dose adjustment period

In this research, during the dose adjustment period, the dose of antihypertensives that you are currently using will be adjusted before the start of the treatment following group division four to six weeks after consent acquisition.

4. Treatment following group division

After the dose adjustment period, treatment will be provided after you have been allocated into one of the following four groups.

A: ARNI + long-acting diuretic (torsemide) group.
B: ARNI + short-acting diuretic (furosemide) group.
C: Dapagliflozin + long-acting diuretic (torasemide) group.
D: Dapagliflozin + short-acting diuretic (furosemide) group.

Treatment following group division is scheduled to last about 26 weeks (±3 weeks). Within this treatment period, you will need to visit the hospital every six weeks, for a total of five times. However, regardless as to whether you participate or do not participate in this research, the burden of outpatient visits remains unchanged. As per the schedule to be described later, you will need to undergo medical examinations by doctors, blood tests, and physiological tests, as well as respond to a questionnaire by yourself. The time required to answer it is estimated to be approximately five minutes each time. If you are unable to come to the hospital, postal surveys are possible, but in that case, please allow us to confirm your consent to postal surveys via a phone call in advance.

In addition, some of you may be requested to wear an activity tracker for the purpose of analyzing physical activity level, and sleep quality in the future. These are optional items. Furthermore, for future research, blood collections of 15 mL/time (twice in total) will be carried out in terms of regular medical treatment. Blood will be collected at the start of the experiment, and at the end of the experiment, and stored in a freezer for research use following anonymization.

5. Follow-up period

After the end of the treatment following group division, treatment in accordance with normal insurance medical treatment will be provided. In addition, one year, and two years after the start of the research, we will confirm and conduct telephone surveys on the contents of your medical records regarding information related to your physical condition, medication status, and subsequent course.

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REGARDING RESEARCH DISCONTINUATION

Individual discontinuation of research participation

Even after you have consented to participate in this study, if you suffer from a serious illness, and your attending physician deems it undesirable for you to continue participating in this research, your participation may be discontinued. If your research participation is discontinued, your data up to the time point of research discontinuation will be used for this research. In addition, even after the discontinuation of research participation, if deemed necessary by your attending physician, you may be required to undergo further tests.

Discontinuation of the entire research

In addition, in the acquisition of critical information related to the quality, safety, and effectiveness of medicines used in this research, and research-related medical materials; or in the occurrence of other events deemed to be significantly damaging, such as questions regarding the appropriateness of conducting this research, or regarding the reliability of the results, the entire research may be discontinued.

4 ADVANTAGES AND DISADVANTAGES INCURRED ON RESEARCH SUBJECTS

EXPECTED ADVANTAGES

By participating in this research, your attending physician can more easily understand your health-related quality of life via the questionnaires. In addition, there will be a social benefit in that, as this research progresses, new knowledge useful for the future treatment of heart failure is expected to be discovered, leading to more appropriate treatments for patients who develop this illness in the future.

EXPECTED DISADVANTAGES

The medicines used in this research are commonly used and already approved by the Ministry of Health, Labor, and Welfare. This research will be conducted within the scope of the medicines' approved indications, and the treatments to be provided are commonly performed treatments. However, as stated on the package inserts of the medicines, the medicines used in this research have reported side effects, as mentioned above. If health hazards, such as side effects, occur even though you have followed the instructions and used the treatments and medicines correctly, they will be handled exactly like the health hazards and medical accidents that would have occurred if you had not participated in this research, and you will be covered by the relief system of public institutions, so please consult your attending physician in such cases.

5 PERSONAL INFORMATION PROTECTION

When handling your data in this research, your personal information, such as your name and address, will be deleted, and individuals will be identified by research-specific numbers. In addition, personal information will be strictly managed to prevent external leaks by setting passwords or locking it up. While this research will be conducted jointly with external medical institutions,

so that your data will be shared with these institutions, the correspondence table matching personal information and research-specific numbers will be in the possession only of the medical institution that attended to you. Therefore, external medical institutions will not be able to identify you personally. In addition, in order to investigate whether this research is being properly conducted, the person in charge of monitoring may directly check your medical records.

Research results will be published in medical journals and conferences. However, information that may identify you will not be leaked to external parties, nor made public. However, when you consent to participate in this study, you consent also to the viewing of your details by the person-in-charge of this research.

6 DISCLOSURE OF RESEARCH PLAN / METHODS OF DISCLOSING RESEARCH-RELATED INFORMATION

Before the enrolment of the first research subjects begins, the contents of the research plan will have been registered and made public in UMIN-CTR and ClinicalTrials.gov, which are clinical trial registration/publication websites. In addition, research progress will be updated as appropriate, and research completion will be reported without delay. Furthermore, if you wish, you may view the research plan and other related documents, as long as there is no hindrance to the protection of the personal information of other parties, and the originality of this research. Please feel free to contact your attending physician in this regard.

7 DISCLOSURE OF RESULTS OF COOPERATORS THEMSELVES

If you wish for the results related to yourself (questionnaires, test results) to be disclosed, we will explain them to you directly. Requests from parties other than yourself will not be entertained, except for special circumstances. In addition, throughout the

implementation period of this research, in the acquisition of new information that may influence your will to participate in this study, we will inform you immediately, and confirm whether you wish to continue participating or not.

8 PUBLICATION OF RESEARCH OUTCOMES

Information obtained in this research may be recorded and published in medical journals. However, in such cases, in order to protect your human rights and interests and that of related parties, research results will be published after confirmation that the necessary measures have been adopted. These may involve replacing information obtained from you with symbols by which you cannot be identified, so that data by means of which you may be recognized, such as your name, will not be published, and your privacy will be protected.

9 ATTRIBUTION OF INTELLECTUAL PROPERTY RIGHTS ARISING FROM THIS RESEARCH

Intellectual property rights arising from this research will not belong to you, as a participant. Outcomes, all patent rights, and intellectual property rights among others, arising from this research, belong to the principal investigator and paper presenters. In addition, there may be economic benefits related to the intellectual property rights, etc., but you shall have no right to them as well.

10 POLICIES OF HANDLING SAMPLES/INFORMATION AFTER RESEARCH COMPLETION

Samples such as blood samples will be appropriately disposed of according to the procedures of the hospitals or testing companies, after the necessary tests have been conducted in this research.

However, for future studies, some of the blood collected from you (samples) will be stored in a freezer managed by the Department of Cardiology, Keio University School of Medicine even after research completion. They will be disposed according to the procedures of Keio University School of Medicine after anonymization.

11 MATTERS RELATED TO COST BURDEN AND CONFLICT OF INTEREST

As this research will be conducted based on insurance medical treatment, costs incurred from tests and medicines will be the same as for those who are not participating in this research. In addition, in preparation for future studies, additional blood samples will be collected from individuals who can cooperate in this research, and ("About medical examination/test". Comprehensive analysis using blood samples) the costs will be covered by research funds.

12 CONTACT INFORMATION

If you have any questions or matter that you wish to discuss regarding this research, please contact your attending physician or the following consultation desk.

Research secretariat: Department of Cardiology, Keio University School of Medicine
Principal investigator: Shun Kohsaka
Telephone: 03-5843-6702

Version 1.70 (created on January 4, 2023)

Approval number (School of Medicine Ethics Committee)	20211013
Clinical trial registration number	UMIN000045229
Patient ID (Keio University Hospital)	

Consent form for research cooperation
(when obtaining consent for sample storage after research completion)

Dean of Keio University School of Medicine
Director General of Keio University Hospital
Principal Investigator

I have received explanation about this research titled: "Long- vs. Short-Acting Loop Diuretics and Neurohormonal Agents on Patients' Quality-of-Life Among Patients with Heart Failure (LAQUA-HF Trial)" using the explanatory document, (Version 1.70 [created on January 4, 2023]), and I understand the following items, and voluntarily consent to cooperate in this research.

・Items on which I have received explanation and understood (Note: Please put a check mark (✓) in the box (□) by yourself.)

□ 1 Research Objective
□ 2 Voluntariness of research cooperation and freedom of withdrawal
□ 3 Research methods/research cooperation matters
□ 4 Advantages and disadvantages incurred on research subjects
□ 5 Personal information protection
□ 6 Disclosure of research plan / Methods of Disclosing research-related information
□ 7 Disclosure of results of cooperators themselves
□ 8 Publication of research outcomes
□ 9 Attribution of intellectual property rights this research
□10 Policies of handling samples/information after research completion
□11 Matters related to cost burden and conflict of interest
□12 Contact information

To be filled by the research subject

Date of consent

Name of research subject:
<Signature, or name/stamp>