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Rationale and protocol of the LAQUA-HF trial: a factorial randomised controlled trial evaluating the effects of neurohormonal and diuretic agents on health-status reported outcomes in heart failure patients

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ABSTRACT

Introduction The current guidelines strongly recommend early initiation of multiple classes of cardioprotective drugs for patients with heart failure with reduced ejection fraction to improve prognosis and health status. However, evidence on the optimal sequencing of approved drugs is scarce, highlighting the importance of individualised treatment plans. Registry data indicate that only a portion of these patients can tolerate all four recommended classes, underscoring the need to establish the favoured sequence when using these drugs. Additionally, the choice between long-acting and short-acting loop diuretics in the present era remains uncertain. This is particularly relevant given the frequent use of angiotensin receptor-neprilysin inhibitor and sodium-glucose cotransporter 2 inhibitor, both of which potentiate natriuretic effects.

Methods and analysis In a prospective, randomised, open-label, blinded endpoint method, LAQUA-HF (Long-acting vs short-acting diuretics and neurohormonal Agents on patients' QUAlity-of-life in Heart Failure patients) will be a 2×2 factorial design, with a total of 240 patients randomised to sacubitril/valsartan versus dapagliflozin and torsemide versus furosemide in a 1:1 ratio. Most enrolment sites have participated in an ongoing observational registry for consecutive patients hospitalised for heart failure involved dedicated study coordinators, and used the same framework to enrol patients. The primary endpoint is the change in patients' health status over 6 months, defined by the Kansas City Cardiomyopathy Questionnaire. Additionally, clinical benefit at 6 months defined as a hierarchical composite endpoint will be assessed by the win ratio as the secondary endpoint.

Ethics and dissemination The medical ethics committee Keio University in Japan has approved this trial. All

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ LAQUA-HF (Long-acting vs short-acting diuretics and neurohormonal Agents on patients' QUAlity-of-life in Heart Failure patients) is a pragmatic, randomised, 2×2 factorial, comparative-effectiveness trial of sacubitril/valsartan versus dapagliflozin and torsemide versus furosemide on health-related quality of life among patients with heart failure with an ejection fraction <50%.

⇒ Enrolment sites have participated in an ongoing observational registry for consecutive patients hospitalised for heart failure involved dedicated study coordinators, and used the same framework to enrol patients that address the limited generalisability (ie, registry-based randomised controlled trial).

⇒ The primary endpoint is the change in the Kansas City Cardiomyopathy Questionnaire-Overall Summary score over 6 months, and the key secondary endpoint is a hierarchical composite endpoint at 6 months assessed by the win ratio.

⇒ Establishing a reliable strategy for the preferential use of cardioprotective drugs is crucial due to limited evidence on preferred sequencing; moreover, contemporary large-scale observational studies indicate that only a portion of patients with heart failure can tolerate all recommended classes of drugs.

⇒ Additionally, as for diuretics, a key agent for alleviating heart failure symptoms poses uncertainty regarding the preference between long-acting versus short-acting loop diuretics in the contemporary era; this is further exacerbated by the frequent concomitant use of angiotensin receptor-neprilysin inhibitor and sodium-glucose cotransporter 2 inhibitor, which potentiate natriuretic effects.

participants provide written informed consent prior to study entry. The results of this trial will be disseminated in one main paper and additional papers on secondary endpoints and subgroup analyses.

Trial registration number UMIN000045229

INTRODUCTION

Significant progress has been achieved in drug treatments for heart failure (HF) during the last decade, especially HF with reduced ejection fraction (HFrEF). The prognosis as well as health status of HFrEF patients is expected to be considerably improved with the use of guideline-directed medical therapy (GDMT), which consists of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)/angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2is), which each have a class I recommendation for use in patients with HFrEF without contraindication according to the 2022 AHA/ACC/HFSA guideline.[1] Similarly, the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF recommend the use of ARNI, as a replacement for ACEI, and SGLT2is such as dapagliflozin and empagliflozin for patients with HFrEF, both to reduce the risk of worsening HF and cardiovascular death and to improve health status.[2]

However, evidence-practice gaps still exist, especially for patients with multiple comorbidities, polypharmacy, or reluctance to undergo treatment due to cost-related concerns.[3–5] Clinicians may need to prioritise GDMTs with the greatest potential benefits. Consequently, multiple observational studies, including ours, have demonstrated that only a fraction of patients with HF can complete the full set of GDMT.[6–8] At present, there is currently a paucity of empirical evidence comparing the efficacy of available therapeutic options for HF.

Additionally, as for the alleviation of HF symptoms, the utilisation of diuretics, particularly short-acting and long-acting loop diuretics, has remained largely unchanged for many years. Recently, the TRANSFORM-HF (Torsemide Comparison with Furosemide for Management of Heart Failure) trial showed no significant mortality benefit over 12 months between furosemide and torsemide in patients hospitalised with HF.[9] It should be noted, however, that the study participants were largely recruited prior to the approval of modern GDMTs. In recent years, the use of ARNI and SGLT2i are becoming more prevalent with potentially augmenting natriuretic effects.

STUDY RATIONALE AND AVAILABLE EVIDENCE

Clinical dilemma in sequencing GDMTs

Major randomised clinical trials have shown the efficacy and safety of novel HF medications in the context of optimal medical therapy at the time. Clinical trials of ARNI and SGLT2i have also been conducted in situations where optimal background treatments such as ACEIs/ARBs, BBs, and MRAs are substantially implemented, although target doses were often not achieved. The fact provides strong evidence of the additional benefits of novel drugs to well-treated patients. In recent years, there has been a practical recommendation to combine and increase the dose of each class of drugs from the initial stage, along with prompt drug up-titration. The recent STRONG-HF (The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial supports this approach with caution for increased adverse events, such as hypotension, hyperkalemia, and renal impairment, particularly in actual clinical settings with diverse backgrounds.[10] Clinicians often face the challenge of selecting appropriate medications early in the management of HF, given the presence of various comorbidities and individual patient characteristics. As a result, patients rarely receive all evidence-based therapies, and up-titration is not frequent in clinical practice.[6 11] An independent academic web-based survey by the European Society of Cardiology has shown a wide variation in each clinician's preference of drug choice for HFrEF.[12]

The hallmark randomised clinical trials have provided some evidence regarding the interaction of these agents. The DAPA-HF and EMPEROR-reduced trials demonstrated the efficacy of SGLT2is when added to background medication for HFrEF, including ARNI.[13 14] The addition of SGLT2is to the treatment of HFrEF patients resulted in a lower risk of cardiovascular death and HF hospitalisation and an improvement in health status, regardless of the background use of ARNI (ie, 11%–20% were treated with ARNI at baseline).[15] Furthermore, the EMPULSE trial, which enrolled patients hospitalised for acute HF, revealed that approximately 15% of the patients received ARNI as background drug therapy.[16] On the other hand, the PARADIGM-HF trial evaluating the superiority of ARNI over enalapril did not include patients treated with SGLT2is.[17] In the absence of direct or incremental comparative studies between ARNI and SGLT2is, further research is needed to fully understand their optimal sequencing in the treatment of HF.

Hence, pragmatic trials designed to test sequencing of GDMTs may guide clinicians to initiate drugs without restricted by the historical background of clinical trials. For instance, the Cardiac Insufficiency Bisoprolol Study (CIBIS) III trial assessed whether initiating therapy with an ACEI or beta-blocker is preferable in patients with HFrEF.[18] Similar approaches can be utilised for new therapies: ARNI and SGLT2i. Importantly, sequencing trials could also combine clinical and echocardiographic endpoints as well as those assessing evaluating adherence, tolerability of additional GDMT, and compliance.

Usage of diuretics in the contemporary HF patients

Short-acting loop diuretics, such as furosemide, are commonly used for HF management but have been shown to activate the renin–angiotensin–aldosterone system and sympathetic nervous system,[19] leading to adverse

outcomes, particularly at higher doses.[20–22] In contrast, long-acting loop diuretics such as torsemide have a less impact on the renin–angiotensin–aldosterone system and sympathetic nervous system, stable bioavailability, and are less likely to cause hypokalemia.[23 24] This trend is evident across international guidelines for HF, which do not currently endorse any particular preference for either medication. As mentioned previously, the TRANSFORM-HF trial was conducted to compare the efficacy of torsemide with furosemide in patients hospitalised with HF and showed no significant between-difference in all-cause mortality over 12 months.[9] It is noteworthy, however, that most participants were younger with a mean age of 64–65 years, and those who received ARNI (18%) and SGLT2is (6%) were less frequently than the current usual care. Furthermore, the proportion of Asian patients was very small, accounting for approximately 2% of the study population (most of them were Black/African American and White races).[9] In the TRANSFORM-HF trial, the amount of loop diuretics used were relatively high (approximately 80 mg per day of furosemide equivalent), which might have markedly activated both the renin–angiotensin–aldosterone system and sympathetic nervous system, potentially offsetting the overall benefit of torsemide with the long-acting mechanism. Traditionally, the dosages of loop diuretics employed in Japan and other East Asian countries tend to be lower than those commonly used in Western countries, and the situation is different from the TRANSFORM-HF and clinical practice in other regions. These considerations represent a critical challenge in developed countries with ageing, multimorbid, and non-Black/African American and non-White patients.

In addition, it remains unclear whether long-acting or short-acting loop diuretics are preferable for patients with HFrEF due to the potential synergistic natriuretic effects by ARNI and SGLT2i. The PARADIGM-HF trial revealed a reduced requirement for diuretics in the ARNI-treated group.[25] Similarly, the randomised, double-blind, placebo-controlled, crossover design RECEDE-CHF (Renal and Cardiovascular Effect of Sodium-Glucose Co-Transporter 2 Inhibition in Combination With Loop Diuretics in Diabetic Patients With Chronic Heart Failure) trial reported a significant increase in 24-hour urinary volume but no change in urinary sodium levels after 6 weeks of the combination therapy of loop diuretics and empagliflozin in patients with HFrEF and type 2 diabetes mellitus.[26] In light of these observations, there is a need for clinical studies to investigate the effect of combining long-acting or short-acting loop diuretics with ARNI/SGLT2is.

Importance of setting primary treatment goal in patients' health status

The primary objectives in the management for HF patients are twofold: to minimise disease progression, and to improve patients' health status, their symptoms, physical function, and quality of life (QoL). Patient-reported outcomes (PROs) can not only capture patients' health status directly, without being influenced by a physician's interpretation, but it also predicts their prognosis. The US Food and Drug Administration has encouraged that an effect on symptoms or physical function, as assessed by PRO, can serve as a basis for approving new drugs and devices to treat HF.[27–29] Beyond their role as outcomes in clinical trials, PROs are increasingly being utilised in patient-centred clinical practice, responding to the growing call for PROs to be an integral part of quality assessment and improvement.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a PRO designed specifically for HF and includes 23 items that quantify seven different domains, including physical limitations, symptoms (frequency, severity, and change over time), self-efficacy and knowledge, social interference, and QoL, within a 2 week recall period. Furthermore, the short version of the original KCCQ is now available, a 12-item instrument (KCCQ-12). Both versions have been validated across a wide spectrum of HF patients.[30]

Design of the LAQUA-HF trial

Objectives

The primary objective of the LAQUA-HF (Long-acting vs short-acting diuretics and neurohormonal Agents on patients' QUAlity-of-life in Heart Failure patients) trial is to determine the superiority of sacubitril/valsartan versus dapagliflozin or torsemide versus furosemide in improving patients' health status, defined by KCCQ for 6 months among patients with HFrEF who receive standard background therapies (ie, ACEI/ARB, beta-blocker, and MRA) (Box 1). Secondary objectives include determining whether sacubitril/valsartan is superior to dapagliflozin or torsemide is superior to furosemide in clinical benefits at 6 months, defined as hierarchical composite outcomes of time to all-cause death, total number of worsening heart failure events (HFEs), time to first HFEs, and non-improvement in KCCQ-OSS of ≥5 points from baseline to 6 months, assessed by the win ratio. HFEs includes HF hospitalisation, urgent HF visits, and unplanned outpatient HF visits. An event is considered an HFE only if worsening signs and symptoms of HF were present and an intensification of therapy was performed. In addition, exploratory objectives include the impact of these drugs on omics information and their effect on physical activity and sleep conditions measured by a wearable device. Furthermore, the patients will be extendedly followed up during 2 years after 6 month-intervention period to capture treatment changes and also subsequent clinical outcomes after the trial participation.

Study design

LAQUA-HF is a 2×2 factorial comparative-effectiveness trial with a prospective, randomised, open-label, blinded endpoint method (figure 1). Enrollment occurs entirely within Japan and the trial is projected to randomise up to 240 patients across 13 sites (online supplemental table S1). The LAQUA-HF trial organisation includes a:

Box 1 Primary, key secondary, and exploratory outcomes

Primary outcome
⇒ Change in KCCQ-OSS from baseline to 6 months after treatment initiation.

Key secondary outcomes
⇒ A hierarchical composite endpoint consisting of the time to all-cause death, total number of worsening HFEs, the time to first HFEs within 6 months, and non-improvement in KCCQ-OSS of ≥5 points from baseline to 6 months, assessed by the win ratio. HFEs includes HF hospitalisation, urgent HF visits, and unplanned outpatient HF visits. An event is considered an HFE only if worsening signs and symptoms of HF were present and an intensification of therapy was performed.
⇒ A composite of all-cause death and non-improvement in KCCQ-OSS ≥5 points from baseline to 6 months.
⇒ Incidence of all-cause death, cardiovascular death, HF hospitalisation, and urgent HF visits for worsening signs and symptoms of HF and an intensification of therapy from baseline to 6 months and 24 months.
⇒ Change in KCCQ-CSS and KCCQ-TSS from baseline to 6 months after treatment initiation.
⇒ Change in NT-proBNP from baseline to 6 months after treatment initiation.
⇒ Change in LVEF from baseline to 6 months after treatment initiation.
⇒ Change in eGFR from baseline to 6 months after treatment initiation.

Exploratory outcomes
⇒ Change in daily physical activity and sleep conditions assessed by a wearable device.
⇒ Change in the circulating levels of intracellular transcriptomes, proteomes, and metabolomes of biosamples.

CSS, clinical summary score; eGFR, estimated glomerular filtration ratio; HFE, heart failure event; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OSS, overall summary score; TSS, total symptom score.

(1) steering/executive committee; (2) clinical coordinated centre; (3) data coordinating centre; and (4) data and safety monitoring and clinical events adjudication committee (DMCEC). The independent DMCEC meets approximately every 6 months to monitor enrollment, patient characteristics, trial processes and adherence to randomised therapy, and accruing endpoint data. DMCEC consists of three judges who are blinded to the treatment arm. The members of the committee are listed in online supplemental table S2.

LAQUA-HF also utilises state-of-the-art modalities commonly employed in clinical trials, including pragmatic, registry-based, and patient-oriented approaches. The specifics of each modality are outlined in box 2.

Inclusion and exclusion criteria

Adult patients with HF in the ambulatory setting who has standard medication regimens, including ACEI/ARB, BB, and MRA, and daily loop diuretics with anticipated long-term need, are eligible, provided they have: (1) a recently documented left ventricular ejection fraction (LVEF) 45% or less; (2) the New York Heart Failure (NYHA) functional classification II to IV; and (3) an elevated natriuretic peptide level at screening as measured by the local laboratory (Box 3). During the study period, it became possible to use dapagliflozin regardless of LVEF based on the results of the DELIVER trial and from January 2023,[31] the above eligibility criteria was expanded to LVEF<50%. There are no criteria regarding comorbidities, with the exception that patients with systolic blood pressure<100 mm Hg, patients with a serum potassium level of >5.4 mEq/L, and patients with end-stage renal disease requiring dialysis and severe renal impairment of estimated glomerular filtration ratio of <30 mL/min/1.73 m^2 are excluded (given that sacubitril/valsartan are not recommended used in this patient population).

Statistical consideration

This study is designed to evaluate two efficacy hypotheses: (1) sacubitril/valsartan is superior to dapagliflozin for the change in KCCQ-OSS after 6 months, and (2) torsemide is superior to furosemide for the change in KCCQ-OSS after 6 months.

Based on previous reports, we hypothesised that sacubitril/valsartan would significantly increase KCCQ-OSS by six points after 6 months compared with dapagliflozin;[32–34] a change of five points in KCCQ-OSS is considered the minimum clinically meaningful difference.[35] The change in KCCQ-OSS within 6 months after intervention converges a SD of 15–20 points,[32 36] and we hypothesised that the SD of the change in KCCQ-OSS would be 15 based on the results of a pilot study conducted at a single institution of the Department of Cardiology at Keio University. For the first hypothesis, the required number of cases was calculated to be 220 under the conditions of a two-sided test, type I error (α): 5%, and statistical power: 80%. The second hypothesis assumed that torsemide would significantly increase the KCCQ-OSS by five points after 6 months compared with furosemide, and when superiority was tested in 220 patients for two-sided, type I error (α) was 5%, the statistical power was 70%. Since approximately 10% of patients will drop out due to a loss to follow-up, that is, adverse events and deaths, during the run-in phase and whole study period,[17] and finally we determined the enrolment of 240 patients (120 per trial group).

The primary outcome—change in the KCCQ-OSS—will be assessed with a mixed-effects model for repeated-measures that included treatment (sacubitril/valsartan or dapagliflozin/torsemide or furosemide), time, time-by-study intervention interaction and baseline KCCQ-OSS, using an unstructured covariance matrix. Least squares mean differences and 95% CIs will be estimated at 6 months for treatment groups. This will be repeated for key prespecified subgroups: age, sex, body mass index, diabetes mellitus, renal dysfunction, atrial fibrillation, baseline LVEF, NT-proBNP, KCCQ, and physical frailty. The distribution of patients with different clinical magnitudes of change will be calculated to support the clinical interpretation of the mean differences in scores. The secondary outcome analysis will be performed using a win

LAQUA-HF trial

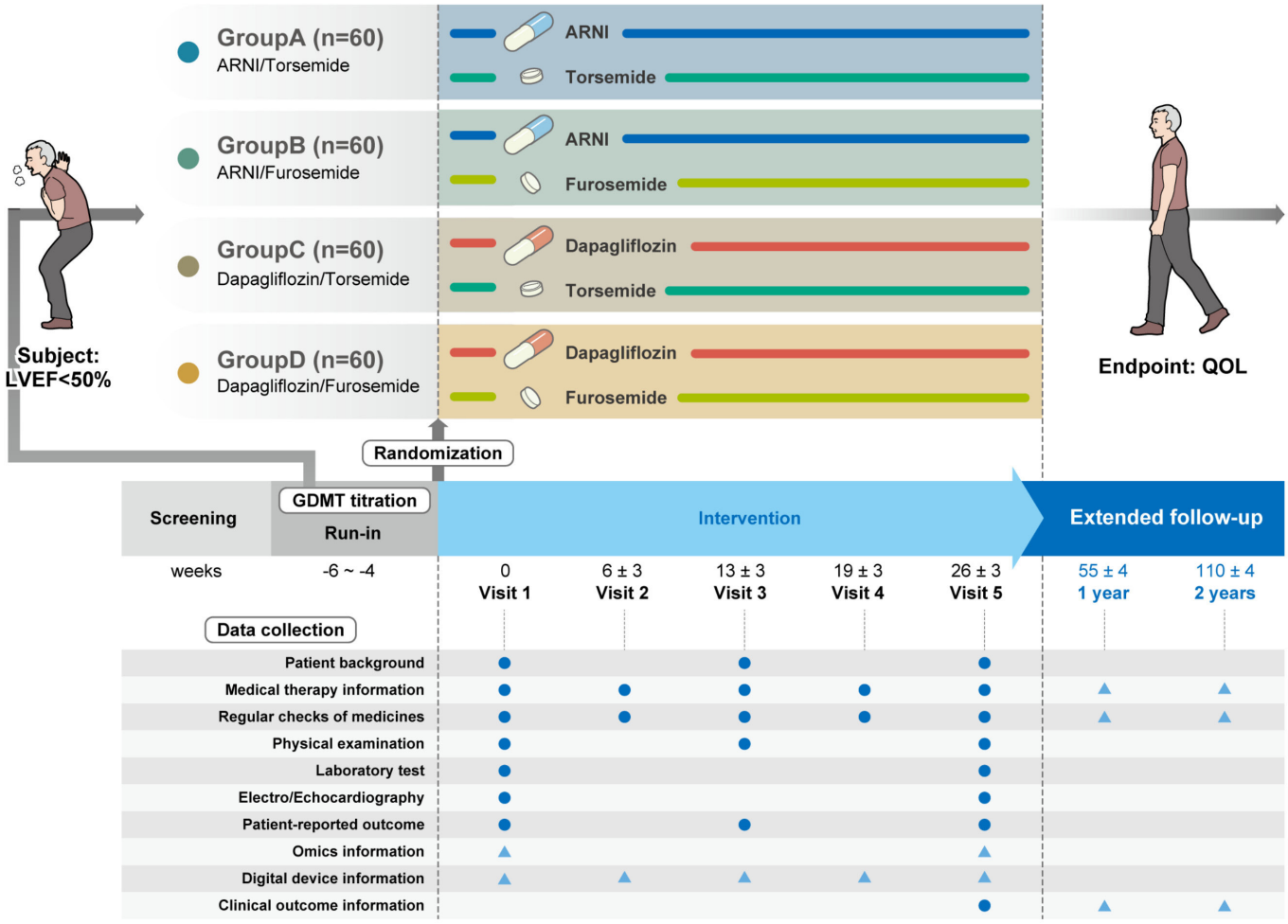

Figure 1 Overview of the study flow. ARNI, angiotensin receptor-neprilysin inhibitor; GDMT, guideline-directed medical therapy; LAQUA-HF, Long-acting versus short-acting diuretics and neurohormonal Agents on patients' QUAlity-of-life in Heart Failure patients; LVEF, left ventricular ejection fraction; QoL, quality of life.

ratio. The win ratio is calculated by forming all possible pairs of one patient from the treatment group (eg, sacubitril/valsartan) and one patient from the opposite (eg, dapagliflozin), then dividing the total number of wins in the treatment group divided by the total number of losses. The hierarchy of the secondary endpoint is predefined as the time to all-cause death, the total number of worsening HFEs, the time to first HFEs within 6 months, and non-improvement in KCCQ-OSS of ≥5 points from baseline to 6 months in order. The win ratio will be presented with a calculated 95% CI. We will also repeat these processes for the second hypothesis (torsemide vs furosemide).

All primary and secondary efficacy endpoints will be evaluated using the intention to treat data set, including all randomised patients. Patients with no evaluable follow-up data for a particular outcome (eg, KCCQ) will be excluded from these analyses. The per-protocol data set includes all patients in the intention-to-treat data set, excluding cases with protocol violations. We will use the per-protocol data set for sensitivity analysis. The safety analysis set included all patients who received at least one dose of study medication and will be used for all safety analyses.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics and dissemination

The trial was authorised by the Institutional Review Board of Keio University School of Medicine (permission number; 20211013). The trial has been registered at UMIN Clinical Trial Registry, and is being conducted in accordance with the Declaration of Helsinki. All participants provide written informed consent prior to study entry (online supplemental material). Patient enrolment began in January 2022, when the first patient was randomised, and has already been completed in June

Box 2 Specific features of the LAQUA-HF trial

Pragmatic design

Patients with HF and in both inpatient (ie, acute HF) and outpatient settings (ie, chronic stable HF) will be randomised in a 1:1 ratio to sacubitril/valsartan or dapagliflozin, and torsemide or furosemide, respectively. Titrating of sacubitril/valsartan, and dosing and frequency of the randomised diuretics during the intervention period will be at the discretion of the patient's usual outpatient clinicians. Patients will be assessed by the patient's usual outpatient clinicians at every 6–7 week following randomisation up to 6 months. Safety and tolerability will be assessed at each visit by full physical examination, and laboratory assessments of NT-proBNP, kidney function, electrolytes, and haemoglobin measures. After randomisation, up-titration to full optimal doses of sacubitril/valsartan should be performed given adequate safety. Biomarker results and clinical assessment will guide the safety of up-titration of sacubitril/valsartan or dosing of loop diuretics.

Registry-based

Most study sites have participated in an HF observational study during the last decade (West Tokyo Heart Failure (WET-HF) registry), which required consecutive registration of hospitalised patients and involved dedicated study coordinators.[55 56] In brief, WET-HF is an ongoing, prospective, multicentre, all-comer hospitalised HF cohort registry. Individuals hospitalised with HF were diagnosed by cardiologists at each institution, based on both signs and symptoms of HF (eg, the universal definition of HF)[57] and levels of plasma BNP or N-terminal proBNP (≥100 or ≥300 pg/mL). WET-HF has provided insights on the national current status of clinical outcomes in patients with HF,[58] as well as in international collaborative projects.[41 59]

Patient-oriented

LAQUA-HF trail will use KCCQ as a primary outcome of interest. As previously stated, KCCQ has received federal certification as a clinical outcome assessment tool, providing standardised assessment of patients' history over time and share consistent insights on patients' well-being regardless of their healthcare systems or country of residence. In addition, the cross-sectional assessment of KCCQ has shown its prognostic ability for the occurrence of clinical adverse events in multiple studies, making it excellent surrogate for long-term prognosis.[60–62] Additionally, longitudinal changes in KCCQ scores have demonstrated a prognostic value,[63 64] further supporting its suitability as the primary outcome measure in the LAQUA-HF trial.

BNP, B-type natriuretic peptide; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAQUA-HF, Long-acting vs short-acting diuretics and neurohormonal Agents on patients' QUAlity-of-life in Heart Failure patients; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

2023, with expected follow-up completion by the end of January 2024.

Study findings will be disseminated through publications in peer-reviewed journals, presentations at both national and international academic/medical conferences, and a webinar to patients with HF and health professionals. Data are available on reasonable request to the corresponding author. Authorship of articles will be determined by discussion within the research team, adhering to authorship guidelines.

Box 3 Eligibility criteria for the LAQUA-HF trial

Main inclusion criteria

1. Patient with the NYHA functional class II, III, or IV in the outpatient setting.
2. An LVEF<45% within previous 12 months by any method (with most recent value used to determine eligibility).*

*Expanded to LVEF<50% after January 2023.

3. An elevated natriuretic peptide level (either BNP or NT-proBNP) as measured by local laboratory.

If the patient has a history of hospitalisation for heart failure (HF) within 1 year at screening, BNP≥100 pg/mL or NT-proBNP≥300 pg/mL in sinus rhythm, and BNP≥150 pg/mL or NT-proBNP≥450 pg/mL in atrial fibrillation.

If the patient has no history of hospitalisation for HF within 1 year at screening, BNP≥150 pg/mL or NT-proBNP≥600 pg/mL in sinus rhythm, and BNP≥225 pg/mL or NT-proBNP≥900 pg/mL in atrial fibrillation.

4. Age of ≥20 years.

Main exclusion criteria

1. Systolic blood pressure<100 mm Hg at the time of screening.
2. eGFR<30 mL/min/1.73 m^2 at the time of screening.
3. Serum potassium level≥5.4 mEq/L or already taking potassium binders at the time of screening.
4. Pregnant or nursing women.
5. Known hypersensitivity to furosemide, torsemide, or related agents.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration ratio; LAQUA-HF, Long-acting versus short-acting diuretics and neurohormonal Agents on QUAlity-of-life in Heart Failure patients; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

DISCUSSION

LAQUA-HF is a distinctive multicentre randomised controlled trial designed to examine the health status of patients with HF after the introduction of sacubitril/valsartan versus dapagliflozin, as well as long-acting (torsemide) versus short-acting loop diuretics (furosemide), in synchronisation with the registration of consecutive hospitalised HF patients. The innovative design of this study allows for testing of clinical benefits that include patients' health status defined by an internationally validated HF-specific PRO. This study will address several important scientific gaps in the knowledge by assessing two promising agents that have the potential to improve the prognosis and health status of patients with HF, in parallel with testing the efficacy of two classical diuretics. First, strong evidence supports the use of GDMT for HFrEF patients, yet there is limited knowledge on how clinicians can prioritise these drugs. Second, prior large-scale observational studies suggest that torsemide is superior to furosemide in patients with HF, but there are confounding issues that can only be resolved by a randomisation strategy. Finally, LAQUA-HF includes important features of modern clinical trial design, such as being pragmatic, registry-based, and patient-oriented data.

LAQUA-HF has several strengths, including the unique ability to directly compare different types of

cardioprotective agents, such as ARNI versus SGLT2i, which is unprecedented in the history of clinical trials for HF. Except for the previously mentioned CIBIS III trial, there are no other trials that have directly compared various classes of GDMTs. The STRONG-HF trial demonstrated that rapid escalation of GDMTs, coupled with close monitoring and prompt follow-up, resulted in a significant reduction in the composite outcome of all-cause death and HF rehospitalisation in hospitalised HF patients during a 6 month period.[10] However, the trial did not specify a particular sequence for adjusting the dosage of each drug, and the use of SGLT2is was infrequent. These findings highlight the need for individualised adjustment of GDMT, as well as the type of diuretics, used in clinical practice. Furthermore, because of the large discrepancy in patient characteristics between clinical trials and observational studies, we planned a pragmatic trial incorporating a multicentre HF registry that enrolled hospitalised HF patients consecutively.

Assessment of HF practices in Japan

There have been substantial differences in clinical characteristics, treatment patterns, and outcomes in HF patients between Asian and Western countries. International registries have highlighted their marked differences between Asian and Western countries (online supplemental table S3).[37–40] The international collaborative study with the WET-HF registry and the Hull Lifelab registry demonstrated that the patients in the Japanese cohort had lower prevalence of ischaemic heart disease and chronic lung disease, lower body mass index, and longer length of hospital stay than those in the UK.[41] British patients had substantially higher mortality even after adjusting for plasma NT-pro BNP and other prognostic indicators.[41]

Regional variations in outcomes have also been observed in clinical trial settings; for example, the PARADIGM-HF trial demonstrated a higher rate of cardiovascular death in Asia compared with Western countries.[42] Even within Asia, interregional variations in outcomes persist, potentially due to insufficient medical treatment.[43 44] Despite enrolling in the PARADIGM-HF trial, Asian HFrEF patients exhibited a lower rate of GDMT implementation.[42] While differences in genetic backgrounds, healthcare systems, and willingness of individual centres to randomise eligible patients may contribute to the variation between Asia and Western countries, the underlying mechanism is multifactorial and complex and hard to be explained.

Investigation of HF agents in Asian countries, including Japan, is pertinent, since the Asian population has experienced explosive growth over the past century, with 4.4 billion people currently residing in Asia, comprising 60% of the world's population.[45] The concomitant rise in population growth, urbanisation, and adaptation of Westernised lifestyles has resulted in an alarming surge in the prevalence of obesity, hypertension, and diabetes mellitus. These comorbidities increase the susceptibility of HF and contribute to a potential 'HF pandemic' in the region, with far-reaching health, social and economic consequences.[45 46] Additionally, Japan and other developed countries are facing a progressive ageing trend, which further contributes to the recent rise of HF cases.[46] Collectively, these findings highlight the need for a more practical approach for clinicians to apply the findings in their region and optimise medical care.

Need of pragmatic investigation in HF management

Randomised controlled trials are crucial for guiding clinical practice, but they typically enrol a homogeneous patient population who meet strict entry criteria, and may not represent the diverse patient population encountered in real-world settings.[47] Consequently, there is uncertainty about the benefits and risks of HFrEF therapies in understudied population, including older adults, frailty, sarcopenia, and cachexia patients.[48] In addition, there is a lack of representation of Asian patients in clinical trials evaluating the safety and efficacy of ARNI and SGLT2i with only 13%–23% of participants being Asian.[13 14 17 31 49 50] Because of these concerns about real-world applicability, the pragmatic trials are attracting increasing attention.[51]

Apart from the strict eligibility criteria mentioned earlier, the exorbitant financial costs of HF trials have been a major concern. The cost of HF trials is approximately 10–20 times higher than that of other trials and can amount to several hundred million dollars.[52 53] To overcome these issues and address research questions in real-world settings, pragmatic registry-based randomised controlled trials have been gaining attention.[54] The feasibility of such trials has been demonstrated in the recent TRANSFORM-HF trial.[9] Furthermore, the ongoing SPIRRIT-HFpEF (Spironolactone Initiation Registry Randomised Interventional Trial in Heart Failure with preserved Ejection Fraction) trial, which is based on the integrated platform from the Swedish Heart Failure Registry, aims to evaluate the effectiveness of MRAs among patients with HF with preserved ejection fraction. Following these trials, we plan to conduct the LAQUA-HF trial in the registry settings to address the limited generalisability in traditional trials and research questions in real-world clinical settings, such as comparing the efficacy between ARNI and SGLT2i. Furthermore, we anticipate that the cost of this trial will be relatively low.

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Rationale and Protocol of the LAQUA-HF Trial: A Factorial Randomized Controlled Trial Evaluating the Effects of Neurohormonal and Diuretic Agents on Health-Status Reported Outcomes in Heart Failure Patients

Supplementary Appendix

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Table S3. Patient backgrounds of observational studies between Asian and Western countries.

	WET-HF cohort 1 (2006–2017)	WET-HF cohort 2 (2018–2023)	REPORT-HF						
			Western Pacific	Southeast Asia	Central and South America	North America	Western Europe	Eastern Europe	Eastern Mediterranean region and Africa
Number, n	4000	3641	3298	2292	2525	1565	3489	2761	2172
Age, year	77 (67–84)	79 (70–86)	67 (56–77)	61 (53–70)	67 (57–77)	63 (54–73)	75 (65–81)	68 (60–77)	64 (55–73)
Male, %	60	58	61	61	60	59	64	58	62
BMI, kg/m^2	23 (20–26)	23 (20–26)	24 (21–27)	23 (20–26)	25 (22–30)	29 (24–36)	27 (24–32)	27 (24–31)	27 (24–31)
Obesity (BMI ≥30), %	7	9	8	4	10	49	20	19	12
Race									
White	0	0	3	0	40	50	98	99	64
Black	0	0	<1	<1	4	45	<1	0	2
Asian	100	100	97	100	<1	2	1	<1	5
Native American	0	0	0	0	14	<1	<1	0	0
Pacific Islander	0	0	0	0	<1	<1	<1	0	0
Other	0	0	<1	<1	42	4	1	1	30
Prior HF hospitalization, %	30	30	53	21	60	80	62	67	62
NYHA classification at admission, %									
I	0	0	5	5	6	1	5	2	7
II	18	16	19	14	22	9	17	17	25
III	36	46	31	18	29	17	26	35	32

	WET-HF cohort 1 (2006–2017)	WET-HF cohort 2 (2018–2023)	REPORT-HF						
			Western Pacific	Southeast Asia	Central and South America	North America	Western Europe	Eastern Europe	Eastern Mediterranean region and Africa
IV	41	38	13	18	10	4	6	12	17
Missing	5	0	33	46	34	69	46	34	19
LVEF, %									
≤40%	43	41	50	59	56	56	55	36	58
41-49%	15	15	19	18	14	10	17	20	18
≥50%	41	38	31	23	30	34	28	43	24
Missing	1	4	8	10	12	1	10	7	9
Etiology of HF, %									
Ischemic	29	25	44	37	31	27	40	45	48
Cardiomyopathy	14*	10*	23	23	17	30	18	12	15
Valvular	26	25	11	7	16	7	18	14	13
Others/Unknown	30	40	9	9	20	14	4	11	6
Missing	0	0	13	15	16	22	20	8	18
Comorbidities, %									
Hypertension	69	65	55	47	68	77	63	80	60
Diabetes	33	31	32	42	37	42	37	33	47
Atrial fibrillation	47	41	25	8	31	38	46	47	21
CKD$	69	74	15	10	17	34	26	23	18
Anemia†	58	57	38	54	40	67	52	35	52

	WET-HF cohort 1 (2006–2017)	WET-HF cohort 2 (2018–2023)	REPORT-HF						
			Western Pacific	Southeast Asia	Central and South America	North America	Western Europe	Eastern Europe	Eastern Mediterranean region and Africa
Medications, %, ‡									
ACEI or ARB	68	71	73	56	73	63	74	75	73
Diuretics (any)	78	88	81	85	80	90	93	93	91
Loop diuretics	78	86	78	84	80	89	92	92	90
Thiazide diuretics	6	3	3	1	2	1	4	8	2
Beta-blocker	86	88	71	50	83	85	89	87	75
MRA	44	56	71	38	73	44	63	72	50
Length of stay, days	16 (11–24)	17 (12–27)	9 (7–14)	6 (4–8)	8 (5–14)	6 (4–10)	9 (6–13)	9 (6–13)	6 (4–10)
1-year post-discharge mortality, %	11	11	17	21	23	21	20	16	22

Values are median (IQR), or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association. * Dilated non-ischemic cardiomyopathy; $ eGFR (estimated glomerular filtration rate) at admission < 60 mL/min/1.73m^2; † hemoglobin at discharge < 13 g/dL for men and < 12 g/dL for women; ‡ at the time of discharge among patients with LVEF ≤ 40%.

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

Principal investigator
Department of Cardiology, Keio University School of Medicine
Shun Kohsaka, MD, PhD

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.

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

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.

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

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.

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

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>