BMJ Open

Protocol of the randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor-neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-095105
Article Type:	Protocol
Date Submitted by the Author:	15-Oct-2024
Complete List of Authors:	Kitahara, Hideki; Chiba University Graduate School of Medicine School of Medicine, Cardiovascular Medicine Okita, Shogo; Chiba University Graduate School of Medicine, Department of Cardiovascular Medicine Sugawara, Takeshi; Chiba University Hospital, Ophthalmology Yaginuma, Hiroaki; Chiba University Graduate School of Medicine, Department of Cardiovascular Medicine Goto, Hiroki; Chiba University Graduate School of Medicine, Department of Cardiovascular Medicine Yamamoto, Hiroaki; Chiba University Graduate School of Medicine, Department of Cardiovascular Surgery Kanda, Tomoyoshi; Chiba University Graduate School of Medicine, Department of Cardiovascular Surgery Matsuura, Kaoru; Chiba University Graduate School of Medicine, Department of Cardiovascular Surgery Inaba, Yosuke; Chiba University Hospital Clinical Research Center Hanaoka, Hideki; Chiba University Hospital, Clinical Research Center Matsumiya, Goro; Chiba University Graduate School of Medicine, Department of Cardiovascular Surgery Kobayashi, Yoshio; Chiba University Graduate School of Medicine, Department of Cardiovascular Medicine
Keywords:	Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, Heart failure < CARDIOLOGY

Protocol of the randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor-neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Hideki Kitahara[1)], Shogo Okita[1)], Takeshi Sugawara[2)], Hiroaki Yaginuma[1)], Hiroki Goto[1)], Hiroaki Yamamoto[3)], Tomoyoshi Kanda[3)], Kaoru Matsuura[3)], Yosuke Inaba[2)], Hideki Hanaoka[2)], Goro Matsumiya[3)], Yoshio Kobayashi[1)]

Author affiliations:

1) Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan.

2) Clinical Research Center, Chiba University Hospital, Chiba, Japan.

3) Department of Cardiovascular Surgery, Chiba University Graduate School of Medicine, Chiba, Japan.

Running title: *Kitahara et al.; Efficacy of ARNI in patients undergoing TAVI*

Address for correspondence:

Hideki Kitahara, MD, PhD

Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine

1-8-1 Inohana, Chuo-ku, Chiba, Chiba 260-8677, Japan

Phone: +81-43-226-2340

Fax: +81-43-226-2340

E-mail: hidekitahara0306@gmail.com

Word count: 4,015 words

ABSTRACT

Introduction: There are a substantial number of patients developing heart failure after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS), even though AS has been successfully treated. The purpose of this randomized controlled trial was to determine whether the addition of an angiotensin receptor neprilysin inhibitor (ARNI) is superior to conventional medications in lowering NT-proBNP levels in patients undergoing TAVI for AS.

Methods and analysis: The study design is a prospective, single-center, open-label, randomized, parallel-group, two-arm study, in which participants will be randomized 1:1 to receive either conventional medications plus ARNI or conventional medications only. In the ARNI group, if a patient was on ACE-I or ARB before TAVI, it will be switched to ARNI 100 mg/day (50 mg twice daily) on the first postoperative day. If not, candesartan 4 mg/day will be started 1-2 days before TAVI, and switched to ARNI 100 mg/day on the first postoperative day. As the patient has tolerability to ARNI, dosage will be increased stepwise to 400 mg/day 2-4 weeks apart. ARNI will be continued until at least 6 months follow-up. In the control group, the patient will receive conventional medications. The primary endpoint is the serum NT-proBNP value at 6 months follow-up after TAVI. Each group includes 42 patients (84 total patients).

Ethics and dissemination: Ethics Review Board approval was obtained. The study is ongoing. Findings from this study will be disseminated through peer-reviewed publications and conference presentations.

Trial registration: This trial has been registered on the Japan Registry of Clinical Trials jRCT1031220344 (https://jrct.niph.go.jp/latest-detail/ jRCT1031220344).

Keywords: aortic stenosis, transcatheter aortic valve implantation, angiotensin receptor-neprilysin inhibitor

INTRODUCTION

Since previous pivotal trials have shown that transcatheter aortic valve implantation (TAVI) has a similar or better short- and long-term prognosis compared with surgical aortic valve replacement (SAVR) for aortic stenosis (AS),[1,2] the indications for TAVI have expanded, with the number of cases increasing in recent years. On the other hand, many studies investigating clinical outcomes after TAVI have reported that the most common cause of rehospitalization is heart failure, with incidence ranging from 12.8% to 24.1%.[3-6] In some cases, functional problems with the TAVI valve, such as severe patient-prosthesis mismatch (PPM) and paravalvular leak (PVL), are known to cause heart failure after TAVI.[5,7] However, most of these patients develop heart failure despite no obvious problem with TAVI valve function and preserved left ventricular ejection fraction (LVEF) on echocardiography, known as "heart failure with preserved ejection fraction (HFpEF)", mainly due to left ventricular diastolic dysfunction. Even if AS is successfully treated by TAVI, HFpEF can possibly be caused by various factors, such as advanced age, residual left ventricular hypertrophy, concomitant chronic kidney disease, arrhythmia as represented by atrial fibrillation, increased afterload by hypertension and peripheral vascular resistance.[3-5] Since there is no established method to prevent HFpEF after TAVI, it is considered necessary to explore effective medications for HFpEF to improve long-term prognosis after TAVI.

Based on the results of previous large-scale randomized controlled trials,[8] administration of angiotensin receptor-neprilysin inhibitor (ARNI) is recommended as one of the important options for treatment of heart failure with reduced ejection fraction (HFrEF) in the guidelines for treatment of heart failure.[9,10] On the other hand, in the PARAGON-HF trial comparing ARNI and valsartan in patients with HFpEF, although there was no statistically significant difference in the composite primary endpoint (heart failure and cardiovascular death), ARNI was associated with a significantly lower rate of the primary endpoint in women

or patients with LVEF ≤57% in prespecified subgroup analyses.[11] Therefore, ARNI is listed as a medication that may be considered for patients with HFpEF in the guidelines (class of recommendation is IIb).[9,10] However, there are no data on the efficacy of ARNI for prevention of heart failure after TAVI. Thus, the purpose of this randomized controlled trial is to clarify whether the addition of ARNI is superior to conventional medications in lowering N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, as a diagnostic biomarker for heart failure, in patients undergoing TAVI for severe AS.

METHODS

Study design

In this phase IV, prospective, single-center, open-label, randomized, parallel-group, two-arm study, participants will be randomized 1:1 to receive either conventional medications plus ARNI or conventional medications only.

Eligibility criteria

Eligible patients are those who meet all inclusion criteria mentioned below and none of the listed exclusion criteria. Inclusion criteria are: 1) patients with AS and symptoms of heart failure requiring TAVI based on the guidelines for management of valvular heart disease;[12,13] 2) patients scheduled for TAVI at Chiba University Hospital; 3) patients aged 70 years or older at the time of enrollment; and 4) patients who have provided written informed consent to participate in this study (if the patient cannot provide a signature, a family member / designate may sign on their behalf). Exclusion criteria include any of the following: 1) acute heart failure (NYHA class IV); 2) systolic blood pressure <110 mmHg; 3) severe hepatic dysfunction (Child-Pugh class C); 4) severe renal dysfunction (serum creatinine > 3.0mg/dL); 5)

hemodialysis; 6) hyperkalemia (serum K >5.5 mEq/L); 7) bilateral renal artery stenosis; 8) history of angioedema; 9) patient with diabetes on aliskiren fumarate; 10) a patient without written informed consent; and 11) a patient whom the investigator considers to be ineligible as a subject.

Recruitment

Recruitment of this study started in September 2022 and will end in January 2025, or until a total of 84 participants have been recruited. This study is being conducted at Chiba University Hospital.

Sample size calculation

The target sample size for this randomized trial is 84. This number is based on feasibility and following validity. Primary analysis of this study is to test the superiority of the ARNI group (conventional medications plus ARNI) over the control group (conventional medications only) in lowering NT-proBNP levels in patients with AS undergoing TAVI. In the PARAGON-HF study, comparing ARNI and valsartan in patients with HFpEF, the NT-proBNP levels after 48 weeks were approximately 600 pg/ml in the ARNI group and 700 pg/ml in the control group (valsartan group).[14] Since it is unlikely that the NT-proBNP level in the control group (conventional medications) in this study would be lower than that with valsartan, the NT-proBNP level after 6 months in this study was estimated to be 600 pg/ml in the ARNI group and 700 pg/ml in the control group. Assuming a standard deviation of 150 pg/ml, an overall significance level of 5% ($\alpha = 0.05$), and a target power of 80% ($1-\beta = 0.8$), the minimum number of patients required is calculated to be 37 in each group (74 in total). Considering approximately 10% of discontinuation or dropout, the total sample size of 84 patients is required for this study.

Registration and assignment methods

1) In principle, registration should be conducted within 7 days of obtaining consent. 2) The principal investigator or subinvestigators will obtain written consent and confirm that participants meet the selection criteria and do not violate the exclusion criteria as a result of the screening test. Participants deemed eligible by the principal investigator or subinvestigators will be enrolled prior to the start of study drug administration. Participants will be enrolled in the study by faxing or bringing the case registration form (CRF) with them. 3) The principal investigator and subinvestigators will complete the CRF and bring it to the data management center at Chiba Clinical Research Center (CCRC). The data center will enter the necessary information for case registration on the data system and confirm the results of eligibility determination and assignment on the system. If the patient is found to be eligible, the investigator or subinvestigators will start the protocol treatment according to the results of the assignment. 4) Once a patient is registered, the registration will not be cancelled (deleted from the database). In case of duplicate registration, the initial registration information (registration number) will be used in all cases. In case of registration errors or duplicate registrations, the data center shall be notified immediately.

Assignment adjustment factors

Participants will be randomly assigned 1:1 to the study to receive conventional medications plus ARNI or conventional medications only. Eligible patients will be randomized to either the ARNI group or the control group at a ratio of 1:1, by employing a minimization method balancing for sex (male or female), age (<85 or ≥85 years), and LVEF (<50% or ≥50%).

Study procedures

The study outline is shown in Figure 1. A patient who meets inclusion criteria, and has provided written informed consent to participate in this study at least 2 days prior to TAVI procedure, will be randomly assigned into the ARNI group or the control group. In the ARNI group, ARNI will be initiated as follows, because ARNI must be administered by switching from angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) for adult heart failure based on the labeling information for prescription medicines by Pharmaceuticals and Medical Devices Agency in Japan. If a patient is on ACE-I preoperatively, ACE-I will be stopped one day prior to TAVI, and ARNI 100 mg daily (50 mg twice daily) will be started on the first postoperative day. If a patient is taking an ARB preoperatively, ARB will be switched to ARNI 100 mg daily (50 mg twice daily) on the first postoperative day. If a patient is not taking angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) preoperatively, candesartan 4 mg/day will be started 1-2 days before TAVI, and candesartan will be switched to ARNI 100 mg daily (50 mg twice daily) on the first postoperative day. In a patient with tolerability to ARNI, dosage will be increased stepwise to 400 mg/day (200 mg twice daily) 2-4 weeks apart. Tolerability is evaluated by a systolic blood pressure of 100 mmHg or higher and a serum potassium level of < 5.5 mEq/L. ARNI will be continued at least until 6 months follow-up. In the control group, patients will receive conventional medications without ARNI.

Blinds

Blinds are not performed.

Endpoint

The primary endpoint of the study is the serum NT-proBNP value at 6 months follow-up after TAVI. The secondary efficacy endpoints include: 1) change in NT-proBNP value at 6 months

follow-up; 2) systolic pulmonary artery pressure at 6 months follow-up; 3) edema scale at 6 months follow-up; 4) NYHA class at 6 months follow-up; 5) increase or decrease in the dose of diuretics at 6 months follow-up; 6) change in body weight at 6 months follow-up; and 7) cardiovascular events (death, admission for heart failure, myocardial infarction). The secondary safety endpoints include: 1) incidence of adverse events; 2) prevalence of patients with serum K >5.5 mEq/L; and 3) prevalence of patients with symptomatic hypotension.

Statistical analysis

The total analysis population (FAS), protocol unit population (PPS), and safety population (SP) will be analyzed; the FAS will be the primary analysis population and all 3 target populations will be analyzed. The distribution of subject background data and summary statistics for each analysis population will be calculated for each group. For nominal variables, category frequencies and proportions will be presented for each group. For continuous variables, summary statistics (number of cases, mean, standard deviation, minimum, median, maximum) will be calculated for each group. For comparisons between groups, Pearson's chi-square test is used for nominal variables, with the exception of Fisher's direct probability calculation method for cells with an expected frequency of < 5 and > 20%, Wilcoxon's rank sum test for ordinal variables, and the t-test with no correspondence for continuous variables. The significance level is set at 5% two-tailed.

For the primary endpoint, the main analysis will be performed for FAS, taking the mean value in each group for NT-proBNP levels at 6 months and testing for statistical significance by means of an unpaired t-test. For this analysis, a similar analysis will be performed for PPS as a supplementary analysis. The significance level for the hypothesis test will be 5% two-sided. For the secondary efficacy endpoints, the analyses will be performed to provide additional insight to the primary analyses. No adjustment for multiplicity will be made in the

analysis of the secondary efficacy endpoints. The significance level for hypothesis testing is 5% two-sided, and confidence intervals are calculated as two-sided 95% confidence intervals. For the secondary safety endpoints, which are the frequency of adverse events, tables will be prepared for the endpoints, and exact two-sided 95% confidence intervals of the binomial distribution will be calculated for each group to estimate proportions. If necessary, Fisher's direct probability calculation method will be used to compare between groups.

Quality control

The monitoring manager is responsible for ensuring that the human rights of the subjects are protected, the study is conducted in accordance with the protocol, and the data are accurately collected. Central monitoring will be conducted on a regular basis based on data from case report forms obtained at the data center. The monitoring manager shall prepare a report that includes a summary of important findings such as diseases, nonconformities, or other facts, and shall report the results of such monitoring to the principal investigator. The independent data monitoring committee, which consists of at least 3 expert members independent of the study, will conduct safety monitoring, including comparison of the incidence of adverse events between the study treatment and control group, and detailed examination of serious adverse events, as necessary, for the purpose of ensuring patient safety. The principal investigator will make a decision to discontinue the study as a whole if it is considered difficult to continue the study due to unforeseen adverse events, illness, or other factors.

Ethics committee

This study will be conducted in accordance with the Declaration of Helsinki (revised 2013). Ethical approval for this study has been obtained from the Chiba University Accredited Clinical Research Review Board (CRB3180015) and the study is registered in the Japan Clinical Trials

Registry (jRCT1031220344). The investigators will explain the concept of this study to patients and obtain written informed consent from all participating patients. The initial version of the protocol was approved on 08/23/2022 and patient recruitment began in 09/22/2022. The latest version 1.5 was approved 09/17/2024.

Informed consent

All participants will receive adequate information about the nature, purpose, possible risks and benefits of the trial, and on alternative therapeutic choices using informed consent approved by the IRB. A participant must be given ample time and opportunity to ask questions and to consider participation in the trial. A completed informed consent is required for enrollment in the trial. The investigators must maintain the original signed consent form and a copy of the signed consent form. To assure patient confidentiality, trial participants will be allocated a unique trial identification number for reference throughout the trial.

Dissemination

The findings of this trial will be disseminated through peer-reviewed publications and conference presentations and will also be disseminated to participants

Discussion

Although TAVI is a quite effective treatment for AS, a substantial number of patients develop heart failure after TAVI, and furthermore, heart failure after TAVI has been associated with poor prognosis.[3-6] Since patients who require TAVI are often elderly and have a variety of comorbidities, they are considered to be a population at high risk of developing HFpEF even after AS is treated. To reduce the risk of heart failure after TAVI, comprehensive treatment that includes not only relieving AS but also managing comorbidities and administrating

appropriate medications may be necessary. In addition, previous studies have indicated that cardiac fibrosis and hypertrophy persist after relief of AS, leading to poor prognosis in patients with severe AS.[15] Therefore, medications with an effect to inhibit cardiac fibrosis may improve prognosis after TAVI. Recently, the usefulness of sodium-glucose cotransporter 2 inhibitors (SGLT2-I) for heart failure, including HFpEF, has been reported, and thus, its use is strongly recommended in the guidelines.[10,16] Although SGLT2-I may be effective in preventing heart failure after TAVI, some patients possibly have difficulty to initiate SGLT2-I because of the elderly population with high frailty and risk for infections, such as urinary tract infections.[17]

While ARNI is widely used for treatment of heart failure, mainly HFrEF, it is also effective to some extent for heart failure with mildy-reduced ejection fraction and HFpEF.[11] Previous animal studies have shown that ARNI is effective in ameliorating cardiac maladaptive remodeling, as indicated by improvements in cardiac function and decreases in cardiac fibrosis, hypertrophy, and inflammation, suggesting that ARNI may also be beneficial after TAVI.[18,19] However, it has been unclear whether ARNI can actually reduce the risk of heart failure after TAVI. Therefore, this randomized study has been designed to investigate this issue. This study is designed to determine the impact of adding ARNI to conventional medications, such as antihypertensive agents and diuretics. Although most of the past studies showing the efficacy of ARNI in heart failure have compared it with ACE-I or ARB,[8,11] this study was designed to compare conventional medications plus ARNI with conventional medications only, because the efficacy of ACE-I or ARB in heart failure after TAVI has not been demonstrated. Since NT-proBNP has been used as an important parameter for evaluation of heart failure in many previous studies examining the efficacy of ARNI,[14] NT-proBNP level at follow-up is set as the primary endpoint in this study. If this study shows the usefulness of ARNI for prevention of heart failure, the next step may be to investigate whether it can reduce heart failure events in a larger-scale study.

Acknowledgments

We thank the Translational Research and Development Center, Chiba University Hospital for their cooperation in protocol development. We thank Heidi N. Bonneau, RN, MS, CCA for her editorial review of the manuscript.

Contributors

HK designed the original concept. All co-authors contributed significantly to the conception and design of the study, with specific additional contributions from each co-author within their area of expertise. The protocol was written by HK, SO and KM, and it was critically reviewed by TS, HY, HG, HY, TK, YI, HH, GM, and YK. All authors gave approval for the publication.

Funding information

This study is funded by a CREATION-Fund (of Chiba University Hospital); Clinical Research Initiation-Fund (of Chiba University Hospital).

Patient and public involvement

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

Provenance and peer review

Not commissioned; internally peer reviewed.

Open Access

Conflicts of interest:

All authors have completed the ICMJE Uniform Disclosure Form. YK received lecture fees from Novartis Pharma. All other authors report no conflict of interest related to this study.

Ethical Statement:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has received an ethical approval by Chiba University Certified Clinical Research Review Board (CRB3180015) and has been registered on the Japan Registry of Clinical Trials (jRCT1031220344). Investigators will explain the concept of the trial to the patients and obtain written informed consent from all participating patients.

References

1. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019;380:1695-705.
2. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med* 2019;380:1706-15.
3. Durand E, Doutriaux M, Bettinger N, et al. Incidence, Prognostic Impact, and Predictive Factors of Readmission for Heart Failure After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2017;10:2426-36.
4. Nazzari H, Hawkins NM, Ezekowitz J, et al. The Relationship Between Heart-Failure Hospitalization and Mortality in Patients Receiving Transcatheter Aortic Valve Replacement. *Can J Cardiol* 2019;35:413-21.
5. Auffret V, Bakhti A, Leurent G, et al. Determinants and Impact of Heart Failure Readmission Following Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv* 2020;13:e008959.
6. Heger J, Trimaille A, Kibler M, et al. Electrocardiographic Strain Pattern Is a Major Determinant of Rehospitalization for Heart Failure After Transcatheter Aortic Valve Replacement. *J Am Heart Assoc* 2021;10:e014481.
7. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. *J Am Coll Cardiol* 2018;72:2701-11.
8. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
9. Tsutsui H, Ide T, Ito H, et al. JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure. *Circ J* 2021;85:2252-91.
10. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the

Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e895-e1032.

11. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019;381:1609-20.
12. Izumi C, Eishi K, Ashihara K, et al. JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease. *Circ J* 2020;84:2037-119.
13. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143:e72-e227.
14. Cunningham JW, Vaduganathan M, Claggett BL, et al. Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 2020;8:372-81.
15. Musa TA, Treibel TA, Vassiliou VS, et al. Myocardial Scar and Mortality in Severe Aortic Stenosis. *Circulation* 2018;138:1935-47.
16. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;44:3627-39.
17. Committee ADAPP. 13. Older Adults: Standards of Care in Diabetes-2024. *Diabetes Care* 2024;47:S244-S257.
18. Burke RM, Lighthouse JK, Mickelsen DM, Small EM. Sacubitril/Valsartan Decreases Cardiac Fibrosis in Left Ventricle Pressure Overload by Restoring PKG Signaling in Cardiac Fibroblasts. *Circ Heart Fail* 2019;12:e005565.
19. Li X, Zhu Q, Wang Q, et al. Protection of Sacubitril/Valsartan against Pathological

Cardiac Remodeling by Inhibiting the NLRP3 Inflammasome after Relief of Pressure Overload in Mice. *Cardiovasc Drugs Ther* 2020;34:629-40.

Figure legend

Figure 1. Graphic outline of study design

Patients are randomly assigned to either the ARNI group with conventional medications plus ARNI or the control group with conventional medications only.

*ARNI will be initiated as follows, because ARNI must be administered by switching from ACE-I or ARB based on the labeling information for prescription medicines by PMDA in Japan. 1) If a patient is on ACE-I preoperatively, ACE-I will be stopped one day prior to TAVI, and ARNI 100 mg daily will be started on the first postoperative day. 2) If a patient is taking an ARB preoperatively, ARB will be switched to ARNI 100 mg daily on the first postoperative day. 3) If a patient is not taking ACE-I or ARB preoperatively, candesartan 4 mg/day will be started 1-2 days before TAVI, and candesartan will be switched to ARNI 100 mg daily on the first postoperative day.

ACE-I, Angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; PMDA, Pharmaceuticals and Medical Devices Agency; TAVI, transcatheter aortic valve implantation.

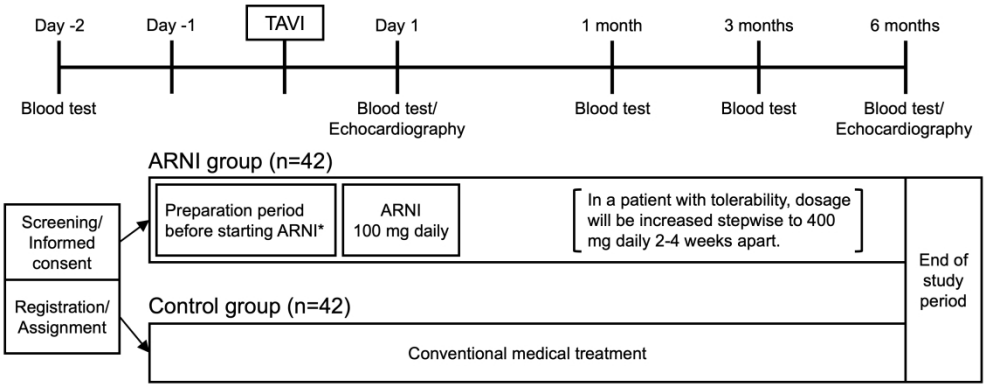


Figure 1

290x115mm (300 x 300 DPI)

BMJ Open

Protocol of the randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor-neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-095105.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Mar-2025
Complete List of Authors:	Kitahara, Hideki; Chiba University Graduate School of Medicine School of Medicine, Cardiovascular Medicine Okita, Shogo; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine Sugawara, Takeshi; Chiba University Hospital, Ophthalmology Yaginuma, Hiroaki; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine Goto, Hiroki; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine Yamamoto, Hiroaki; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Kanda, Tomoyoshi; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Matsuura, Kaoru; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Inaba, Yosuke; Chiba University Hospital, Clinical Research Center Hanaoka, Hideki; Chiba University Hospital, Clinical Research Center Matsumiya, Goro; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Kobayashi, Yoshio; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical management
Keywords:	Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, Heart failure < CARDIOLOGY

Protocol of the randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor-neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Hideki Kitahara[1)], Shogo Okita[1)], Takeshi Sugawara[2)], Hiroaki Yaginuma[1)], Hiroki Goto[1)], Hiroaki Yamamoto[3)], Tomoyoshi Kanda[3)], Kaoru Matsuura[3)], Yosuke Inaba[2)], Hideki Hanaoka[2)], Goro Matsumiya[3)], Yoshio Kobayashi[1)]

Author affiliations:

1) Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan.

2) Clinical Research Center, Chiba University Hospital, Chiba, Japan.

3) Department of Cardiovascular Surgery, Chiba University Graduate School of Medicine, Chiba, Japan.

Running title: *Kitahara et al.; Efficacy of ARNI in patients undergoing TAVI*

Address for correspondence:

Hideki Kitahara, MD, PhD

Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine

1-8-1 Inohana, Chuo-ku, Chiba, Chiba 260-8677, Japan

Phone: +81-43-226-2340

Fax: +81-43-226-2340

E-mail: hidekitahara0306@gmail.com

Word count: 4,253 words

ABSTRACT

Introduction: There are a substantial number of patients developing heart failure after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS), even though AS has been successfully treated. The purpose of this randomized controlled trial was to determine whether the addition of an angiotensin receptor neprilysin inhibitor (ARNI), Sacubitril/Valsartan, is superior to conventional medications in lowering N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients undergoing TAVI for AS.

Methods and analysis: The study design is a prospective, single-center, open-label, randomized, parallel-group, two-arm study, in which participants will be randomized 1:1 to receive either conventional medications plus ARNI or conventional medications only. In the ARNI group, if a patient was on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker before TAVI, it will be switched to ARNI 100 mg/day (50 mg twice daily) on the first postoperative day. If not, candesartan 4 mg/day will be started 1-2 days before TAVI, and switched to ARNI 100 mg/day on the first postoperative day. As the patient has tolerability to ARNI, dosage will be increased stepwise to 400 mg/day 2-4 weeks apart. ARNI will be continued until at least 6 months follow-up. In the control group, the patient will receive conventional medications. The primary endpoint is the serum NT-proBNP value at 6 months follow-up after TAVI. Each group includes 42 patients (84 total patients).

Ethics and dissemination: Ethical approval for this study has been obtained from the Chiba University Hospital Certified Clinical Research Review Board. The study is ongoing. Findings from this study will be disseminated through peer-reviewed publications and conference presentations.

Trial registration: This trial has been registered on the Japan Registry of Clinical Trials jRCT1031220344 (https://jrct.niph.go.jp/latest-detail/ jRCT1031220344).

Strengths and limitations of this study

- This randomized controlled trial is the first to investigate the efficacy of angiotensin receptor neprilysin inhibitor (ARNI) in lowering N-terminal pro-B-type natriuretic peptide levels in patients undergoing transcatheter aortic valve implantation for severe aortic stenosis.
- Potential limitations of the trial are that the primary endpoint is a surrogate marker for heart failure, and clinical outcomes or functional outcome measures cannot be assessed.
- If this study shows the potential of ARNI for prevention of heart failure development, it can serve as a platform for further evaluation of its prognostic impact in a larger population.

INTRODUCTION

Since previous pivotal trials have shown that transcatheter aortic valve implantation (TAVI) has a similar or better short- and long-term prognosis compared with surgical aortic valve replacement for aortic stenosis (AS),[1,2] the indications for TAVI have expanded, with the number of cases increasing in recent years. On the other hand, many studies investigating clinical outcomes after TAVI have reported that the most common cause of rehospitalization is heart failure, with incidence ranging from 12.8% to 24.1%.[3-6] In some cases, functional problems with the TAVI valve, such as severe patient-prosthesis mismatch and paravalvular leak, are known to cause heart failure after TAVI.[5,7] However, most of these patients develop heart failure despite no obvious problem with TAVI valve function and preserved left ventricular ejection fraction (LVEF) on echocardiography, known as "heart failure with preserved ejection fraction (HFpEF)", mainly due to left ventricular diastolic dysfunction. Even if AS is successfully treated by TAVI, HFpEF can possibly be caused by various factors, such as advanced age, residual left ventricular hypertrophy, concomitant chronic kidney disease, arrhythmia as represented by atrial fibrillation, increased afterload by hypertension and peripheral vascular resistance.[3-5] Since there is no established method to prevent HFpEF after TAVI, it is considered necessary to explore effective medications for HFpEF to improve long-term prognosis after TAVI.

Based on the results of previous large-scale randomized controlled trials,[8] administration of angiotensin receptor-neprilysin inhibitor (ARNI), Sacubitril/Valsartan, is recommended as one of the important options for treatment of heart failure with reduced ejection fraction (HFrEF) in the guidelines for treatment of heart failure.[9,10] On the other hand, in the PARAGON-HF trial comparing ARNI and valsartan in patients with HFpEF, although there was no statistically significant difference in the composite primary endpoint (heart failure and cardiovascular death), ARNI was associated with a significantly lower rate of the primary

endpoint in women or patients with LVEF ≤57% in prespecified subgroup analyses.[11] Therefore, ARNI is listed as a medication that may be considered for patients with HFpEF in the guidelines (class of recommendation is IIb).[9,10] However, there are no data on the efficacy of ARNI for prevention of heart failure after TAVI. Thus, the purpose of this randomized controlled trial is to clarify whether the addition of ARNI is superior to conventional medications in lowering N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, as a diagnostic biomarker for heart failure, in patients undergoing TAVI for severe AS.

METHODS

Study design

In this phase IV, prospective, single-center, open-label, randomized, parallel-group, two-arm study, participants will be randomized 1:1 to receive either conventional medications plus ARNI or conventional medications only.

Eligibility criteria

Eligible patients are those who meet all inclusion criteria mentioned below and none of the listed exclusion criteria. Inclusion criteria are: 1) patients with AS and symptoms of heart failure requiring TAVI based on the guidelines for management of valvular heart disease;[12,13] 2) patients scheduled for TAVI at Chiba University Hospital; 3) patients aged 70 years or older at the time of enrollment; and 4) patients who have provided written informed consent to participate in this study (if the patient cannot provide a signature, a family member / designate may sign on their behalf). Exclusion criteria include any of the following: 1) acute heart failure (New York Heart Association [NYHA] class IV); 2) systolic blood pressure <110 mmHg; 3) severe hepatic dysfunction (Child-Pugh class C); 4) severe renal dysfunction (serum creatinine

> 3.0mg/dL); 5) hemodialysis; 6) hyperkalemia (serum K >5.5 mEq/L); 7) bilateral renal artery stenosis; 8) history of angioedema; 9) patient with diabetes on aliskiren fumarate; 10) a patient without written informed consent; and 11) a patient whom the investigator considers to be ineligible as a subject.

Recruitment

Recruitment of this study started in September 2022 and will end in January 2025, or until a total of 84 participants have been recruited. This study is being conducted at Chiba University Hospital.

Patient and public involvement

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

Sample size calculation

The target sample size for this randomized trial is 84. This number is based on feasibility and following validity. Primary analysis of this study is to test the superiority of the ARNI group (conventional medications plus ARNI) over the control group (conventional medications only) in lowering NT-proBNP levels in patients with AS undergoing TAVI. The NT-proBNP level is determined as a surrogate marker in this study, because previous studies have reported that lower NT-proBNP levels and greater reduction of NT-proBNP levels are associated with better prognosis in HFpEF patients.[14,15] In the PARAGON-HF study, comparing ARNI and valsartan in patients with HFpEF, the NT-proBNP levels after 48 weeks were approximately 600 pg/ml in the ARNI group and 700 pg/ml in the control group (valsartan group).[16] Since it is unlikely that the NT-proBNP level in the control group (conventional medications) in this study would

be lower than that with valsartan, the NT-proBNP level after 6 months in this study was estimated to be 600 pg/ml in the ARNI group and 700 pg/ml in the control group. Assuming a standard deviation of 150 pg/ml, an overall significance level of 5% ($\alpha = 0.05$), and a target power of 80% ($1-\beta = 0.8$), the minimum number of patients required is calculated to be 37 in each group (74 in total). Considering approximately 10% of discontinuation or dropout, the total sample size of 84 patients is required for this study.

Registration and assignment methods

1) In principle, registration should be conducted within 7 days of obtaining consent. 2) The principal investigator or subinvestigators will obtain written consent and confirm that participants meet the selection criteria and do not violate the exclusion criteria as a result of the screening test. Participants deemed eligible by the principal investigator or subinvestigators will be enrolled prior to the start of study drug administration. Participants will be enrolled in the study by faxing or bringing the case registration form (CRF) with them. 3) The principal investigator and subinvestigators will complete the CRF and bring it to the data management center at Chiba Clinical Research Center. The data center will enter the necessary information for case registration on the data system and confirm the results of eligibility determination and assignment on the system. If the patient is found to be eligible, the investigator or subinvestigators will start the protocol treatment according to the results of the assignment. 4) Once a patient is registered, the registration will not be cancelled (deleted from the database). In case of duplicate registration, the initial registration information (registration number) will be used in all cases. In case of registration errors or duplicate registrations, the data center shall be notified immediately.

Assignment adjustment factors

Participants will be randomly assigned 1:1 to the study to receive conventional medications plus ARNI or conventional medications only. Eligible patients will be randomized to either the ARNI group or the control group at a ratio of 1:1, by employing a minimization method balancing for sex (male or female), age (<85 or ≥85 years), and LVEF (<50% or ≥50%).

Study procedures

The study outline is shown in Figure 1. A patient who meets inclusion criteria, and has provided written informed consent to participate in this study at least 2 days prior to TAVI procedure, will be randomly assigned into the ARNI group or the control group. In the ARNI group, ARNI will be initiated as follows, because ARNI must be administered by switching from angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) for adult heart failure based on the labeling information for prescription medicines by Pharmaceuticals and Medical Devices Agency in Japan. If a patient is on ACE-I preoperatively, ACE-I will be stopped one day prior to TAVI, and ARNI 100 mg daily (50 mg twice daily) will be started on the first postoperative day. If a patient is taking an ARB preoperatively, ARB will be switched to ARNI 100 mg daily (50 mg twice daily) on the first postoperative day. If a patient is not taking ACE-I or ARB preoperatively, candesartan 4 mg/day will be started 1-2 days before TAVI, and candesartan will be switched to ARNI 100 mg daily (50 mg twice daily) on the first postoperative day. Due to the institutional restrictions on drug use, candesartan was chosen as the starter for switch to ARNI. In a patient with tolerability to ARNI, dosage will be increased stepwise to 400 mg/day (200 mg twice daily) 2-4 weeks apart. Tolerability is evaluated by a systolic blood pressure of 100 mmHg or higher and a serum potassium level of < 5.5 mEq/L. ARNI will be continued at least until 6 months follow-up. In the control group, patients will receive conventional medications without ARNI.

Blinds

Blinds are not performed.

Endpoint

The primary endpoint of the study is the serum NT-proBNP value at 6 months follow-up after TAVI. The secondary efficacy endpoints include: 1) change in NT-proBNP value at 6 months follow-up; 2) systolic pulmonary artery pressure at 6 months follow-up; 3) edema scale at 6 months follow-up; 4) NYHA class at 6 months follow-up; 5) increase or decrease in the dose of diuretics at 6 months follow-up; 6) change in body weight at 6 months follow-up; and 7) cardiovascular events (death, admission for heart failure, myocardial infarction). The secondary safety endpoints include: 1) incidence of adverse events; 2) prevalence of patients with serum K >5.5 mEq/L; and 3) prevalence of patients with symptomatic hypotension.

Statistical analysis

The total analysis population (FAS), protocol unit population (PPS), and safety population will be analyzed; the FAS will be the primary analysis population and all 3 target populations will be analyzed. The distribution of subject background data and summary statistics for each analysis population will be calculated for each group. For nominal variables, category frequencies and proportions will be presented for each group. For continuous variables, summary statistics (number of cases, mean, standard deviation, minimum, median, maximum) will be calculated for each group. For comparisons between groups, Pearson's chi-square test is used for nominal variables, with the exception of Fisher's direct probability calculation method for cells with an expected frequency of < 5 and > 20%, Wilcoxon's rank sum test for ordinal variables, and the t-test with no correspondence for continuous variables. The significance level is set at 5% two-tailed.

For the primary endpoint, the main analysis will be performed for FAS, taking the mean value in each group for NT-proBNP levels at 6 months and testing for statistical significance by means of an unpaired t-test. For this analysis, a similar analysis will be performed for PPS as a supplementary analysis. The significance level for the hypothesis test will be 5% two-sided. For the secondary efficacy endpoints, the analyses will be performed to provide additional insight to the primary analyses. No adjustment for multiplicity will be made in the analysis of the secondary efficacy endpoints. The significance level for hypothesis testing is 5% two-sided, and confidence intervals are calculated as two-sided 95% confidence intervals. For the secondary safety endpoints, which are the frequency of adverse events, tables will be prepared for the endpoints, and exact two-sided 95% confidence intervals of the binomial distribution will be calculated for each group to estimate proportions. If necessary, Fisher's direct probability calculation method will be used to compare between groups.

Quality control

The monitoring manager is responsible for ensuring that the human rights of the subjects are protected, the study is conducted in accordance with the protocol, and the data are accurately collected. Central monitoring will be conducted on a regular basis based on data from case report forms obtained at the data center. The monitoring manager shall prepare a report that includes a summary of important findings such as diseases, nonconformities, or other facts, and shall report the results of such monitoring to the principal investigator. The independent data monitoring committee, which consists of at least 3 expert members independent of the study, will conduct safety monitoring, including comparison of the incidence of adverse events between the study treatment and control group, and detailed examination of serious adverse events, as necessary, for the purpose of ensuring patient safety. The principal investigator will make a decision to discontinue the study as a whole if it is considered difficult to continue the

study due to unforeseen adverse events, illness, or other factors.

Ethics committee

This study will be conducted in accordance with the Declaration of Helsinki (revised 2013). Ethical approval for this study has been obtained from the Chiba University Hospital Certified Clinical Research Review Board (CRB3180015) and the study is registered in the Japan Clinical Trials Registry (jRCT1031220344). The investigators will explain the concept of this study to patients and obtain written informed consent from all participating patients. The initial version of the protocol was approved on 08/23/2022 and patient recruitment began in 09/22/2022. The latest version 1.5 was approved 09/17/2024.

Informed consent

All participants will receive adequate information about the nature, purpose, possible risks and benefits of the trial, and on alternative therapeutic choices using informed consent approved by the IRB (Supplemental File 1). A participant must be given ample time and opportunity to ask questions and to consider participation in the trial. A completed informed consent is required for enrollment in the trial. The investigators must maintain the original signed consent form and a copy of the signed consent form. To assure patient confidentiality, trial participants will be allocated a unique trial identification number for reference throughout the trial.

Dissemination

The findings of this trial will be disseminated through peer-reviewed publications and conference presentations and will also be disseminated to participants

Discussion

Although TAVI is a quite effective treatment for AS, a substantial number of patients develop heart failure after TAVI, and furthermore, heart failure after TAVI has been associated with poor prognosis.[3-6] Since patients who require TAVI are often elderly and have a variety of comorbidities, they are considered to be a population at high risk of developing HFpEF even after AS is treated. To reduce the risk of heart failure after TAVI, comprehensive treatment that includes not only relieving AS but also managing comorbidities and administrating appropriate medications may be necessary. In addition, previous studies have indicated that cardiac fibrosis and hypertrophy persist after relief of AS, leading to poor prognosis in patients with severe AS.[17] Therefore, medications with an effect to inhibit cardiac fibrosis may improve prognosis after TAVI. Recently, the usefulness of sodium-glucose cotransporter 2 inhibitors (SGLT2-I) for heart failure, including HFpEF, has been reported, and thus, its use is strongly recommended in the guidelines.[10,18] Although SGLT2-I may be effective in preventing heart failure after TAVI, some patients possibly have difficulty to initiate SGLT2-I because of the elderly population with high frailty and risk for infections, such as urinary tract infections.[19]

While ARNI is widely used for treatment of heart failure, mainly HFrEF, it is also effective to some extent for heart failure with mildly-reduced ejection fraction and HFpEF.[11] Previous animal studies have shown that ARNI is effective in ameliorating cardiac maladaptive remodeling, as indicated by improvements in cardiac function and decreases in cardiac fibrosis, hypertrophy, and inflammation, suggesting that ARNI may also be beneficial after TAVI.[20,21] However, it has been unclear whether ARNI can actually reduce the risk of heart failure after TAVI. Therefore, this randomized study has been designed to investigate this issue. This study is designed to determine the impact of adding ARNI to conventional medications, such as antihypertensive agents and diuretics. Although most of the past studies showing the efficacy of ARNI in heart failure have compared it with ACE-I or ARB,[8,11] this study was designed to compare conventional medications plus ARNI with conventional medications only, because

the efficacy of ACE-I or ARB in heart failure after TAVI has not been demonstrated. Since NT-proBNP has been used as an important parameter for evaluation of heart failure in many previous studies examining the efficacy of ARNI,[16] NT-proBNP level at follow-up is set as the primary endpoint in this study. If this study shows the usefulness of ARNI for prevention of heart failure, the next step may be to investigate whether it can reduce heart failure events in a larger-scale study. In such a future study, functional outcome measures, e.g. a six-minute walk test, which is not planned to investigate in this study, should also be examined.

Acknowledgments

We thank the Translational Research and Development Center, Chiba University Hospital for their cooperation in protocol development. We thank Heidi N. Bonneau, RN, MS, CCA for her editorial review of the manuscript.

Contributors

HK designed the original concept. All co-authors contributed significantly to the conception and design of the study, with specific additional contributions from each co-author within their area of expertise. The protocol was written by HK, SO and KM, and it was critically reviewed by TS, HY, HG, HY, TK, YI, HH, GM, and YK. All authors gave approval for the publication. YK is the guarantor.

Funding

This study is funded by a CREATION-Fund (of Chiba University Hospital); Clinical Research Initiation-Fund (of Chiba University Hospital).

Competing interests

HK, SO, HY, HG, HY, TK, KM, GM, and YK are affiliated with Chiba University Graduate School of Medicine, to which Chiba University Hospital belongs, and ST, IY, and HH are affiliated with Chiba University Hospital, which provided financial support for this study. However, the institutions were not involved in the design, execution, data analysis, or interpretation of the results in this study. YK received lecture fees from Novartis Pharma. The authors declare no other competing interests.

Provenance and peer review

Not commissioned; internally peer reviewed.

Open Access

Ethical Statement:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has received an ethical approval by Chiba University Hospital Certified Clinical Research Review Board (CRB3180015) and has been registered on the Japan Registry of Clinical Trials (jRCT1031220344). Investigators will explain the concept of the trial to the patients and obtain written informed consent from all participating patients.

References

1. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019;380:1695-705.
2. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med* 2019;380:1706-15.
3. Durand E, Doutriaux M, Bettinger N, et al. Incidence, Prognostic Impact, and Predictive Factors of Readmission for Heart Failure After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2017;10:2426-36.
4. Nazzari H, Hawkins NM, Ezekowitz J, et al. The Relationship Between Heart-Failure Hospitalization and Mortality in Patients Receiving Transcatheter Aortic Valve Replacement. *Can J Cardiol* 2019;35:413-21.
5. Auffret V, Bakhti A, Leurent G, et al. Determinants and Impact of Heart Failure Readmission Following Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv* 2020;13:e008959.
6. Heger J, Trimaille A, Kibler M, et al. Electrocardiographic Strain Pattern Is a Major Determinant of Rehospitalization for Heart Failure After Transcatheter Aortic Valve Replacement. *J Am Heart Assoc* 2021;10:e014481.
7. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. *J Am Coll Cardiol* 2018;72:2701-11.
8. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
9. Tsutsui H, Ide T, Ito H, et al. JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure. *Circ J* 2021;85:2252-91.
10. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the

Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e895-e1032.

11. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019;381:1609-20.
12. Izumi C, Eishi K, Ashihara K, et al. JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease. *Circ J* 2020;84:2037-119.
13. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143:e72-e227.
14. Savarese G, Hage C, Orsini N, et al. Reductions in N-Terminal Pro-Brain Natriuretic Peptide Levels Are Associated With Lower Mortality and Heart Failure Hospitalization Rates in Patients With Heart Failure With Mid-Range and Preserved Ejection Fraction. *Circ Heart Fail* 2016;9:e003105.
15. Salah K, Stienen S, Pinto YM, et al. Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction. *Heart* 2019;105:1182-9.
16. Cunningham JW, Vaduganathan M, Claggett BL, et al. Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 2020;8:372-81.
17. Musa TA, Treibel TA, Vassiliou VS, et al. Myocardial Scar and Mortality in Severe Aortic Stenosis. *Circulation* 2018;138:1935-47.
18. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;44:3627-39.

19. Committee ADAPP. 13. Older Adults: Standards of Care in Diabetes-2024. *Diabetes Care* 2024;47:S244-S257.
20. Burke RM, Lighthouse JK, Mickelsen DM, Small EM. Sacubitril/Valsartan Decreases Cardiac Fibrosis in Left Ventricle Pressure Overload by Restoring PKG Signaling in Cardiac Fibroblasts. *Circ Heart Fail* 2019;12:e005565.
21. Li X, Zhu Q, Wang Q, et al. Protection of Sacubitril/Valsartan against Pathological Cardiac Remodeling by Inhibiting the NLRP3 Inflammasome after Relief of Pressure Overload in Mice. *Cardiovasc Drugs Ther* 2020;34:629-40.

Figure legend

Figure 1. Graphic outline of study design

Patients are randomly assigned to either the ARNI group with conventional medications plus ARNI or the control group with conventional medications only.

*ARNI will be initiated as follows, because ARNI must be administered by switching from ACE-I or ARB based on the labeling information for prescription medicines by PMDA in Japan. 1) If a patient is on ACE-I preoperatively, ACE-I will be stopped one day prior to TAVI, and ARNI 100 mg daily will be started on the first postoperative day. 2) If a patient is taking an ARB preoperatively, ARB will be switched to ARNI 100 mg daily on the first postoperative day. 3) If a patient is not taking ACE-I or ARB preoperatively, candesartan 4 mg/day will be started 1-2 days before TAVI, and candesartan will be switched to ARNI 100 mg daily on the first postoperative day.

ACE-I, Angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; PMDA, Pharmaceuticals and Medical Devices Agency; TAVI, transcatheter aortic valve implantation.

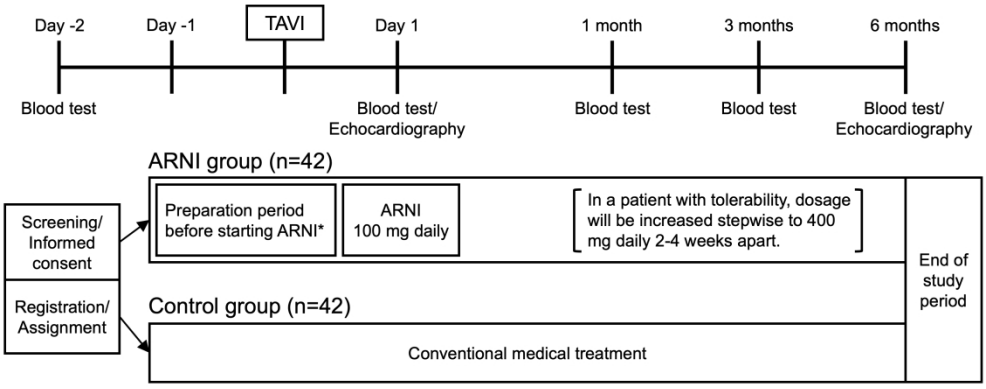


Figure 1

290x115mm (300 x 300 DPI)

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

For Patients

Clinical study: "Randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

table of contents

1. What is clinical research?

It is the role of medical institutions to establish new treatments through clinical research, and it can be achieved with the cooperation of patients. The clinical research described in this article is planned and planned by physicians involved in actual medical care in light of medical necessity and importance. It is not a clinical trial conducted by pharmaceutical companies to investigate the safety and usefulness of a new drug and obtain approval from the Ministry of Health, Labor and Welfare. This study is based on the deliberations of the Clinical Research Review Committee, Chiba University, and has obtained permission from the heads of each medical institution. In addition, in accordance with Article 5, Paragraph 1 of the Clinical Trials Act, we have submitted a prescribed implementation plan to the Minister of Health, Labour and Welfare. It is up to you to decide whether or not to participate in the exam. If you don't participate, you will not be disadvantaged.

2. Why do we conduct this clinical study?

2-1. Purpose of this clinical study

The purpose of this clinical study is to evaluate the efficacy of angiotensin receptor neprilysin inhibitors (Enrest tablets) in patients who undergo transcatheter aortic valve implantation for aortic stenosis.The aim is to find out whether the addition of the drug is more effective in reducing the recurrence of heart failure than conventional drug treatment. Currently, there is no drug treatment that is effective in preventing recurrence of heart failure after transcatheter aortic valve placement. Therefore, if Enrest is effective in improving heart failure, it is expected to be a treatment option in the future.

2-2. Conventional treatment and trial treatment

Aortic stenosis is a serious disease in which the aortic valve at the exit of the heart becomes stiff and narrowed due to arteriosclerosis, causing heart failure with shortness of breath and swelling, fainting, and sudden death.

Transcatheter aortic valve implantation is a very effective treatment, but it alone does not completely cure the disease, and there is a certain percentage of patients whose heart failure worsens or recurs after surgery, so treatment to prevent heart failure is also considered important. However, since there are no drugs that have been shown to be effective in preventing the onset of postoperative heart failure, the standard treatment so far has been to use diuretics for swelling and antihypertensive drugs for high blood pressure as appropriate. Enrest is a relatively new drug, but it is used in regular practice as a treatment for heart failure, and is listed as a drug recommended for active use for heart failure in the guidelines (treatment guidelines) of the Japan Circulation Society. Therefore, it is considered to be effective for preventing recurrence of heart failure even after transcatheter aortic valve implantation, but since there have been no studies that have examined its effect in the past, we have planned a study to clarify the effect of enrest.

3. Method and duration of clinical research

3-1. Why are you eligible?

Eligible patients are those aged 70 years or older who undergo transcatheter aortic valve placement for aortic stenosis. Those who have already developed severe heart failure, those with low blood pressure (systolic blood pressure less than 100 mmHg), and those with severe liver or kidney dysfunction are not eligible.

3-2. Methods of this clinical study

They will be divided into two groups: one that adds an enrest and the other that continues with conventional treatment. Which group you will be in is decided by the computer, and neither the patient nor the doctor can choose.

○ Entrestion group

At the start of Enrest, it is necessary to switch from angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARBs), which

are antihypertensive drugs and heart failure drugs.

1) If you have been taking an ACE inhibitor for a long time

The drug will be discontinued from 1 day before surgery, and the start will be started on the first day after surgery.

2) If you have been taking ARB internally for a long time

Switch to Entrest on the first postoperative day.

3) If neither of them was taken internally

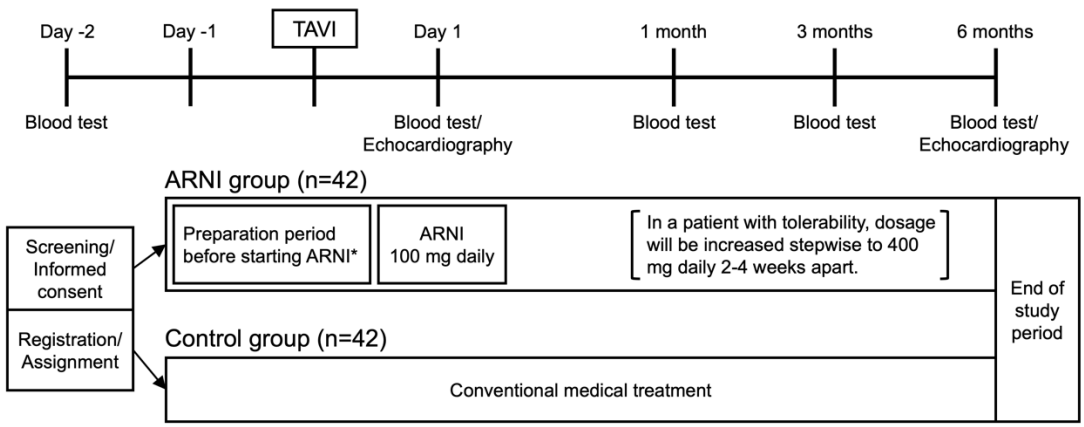
Start preoperatively (1-2 days before surgery) Bropres Tablets 4 mg (4 mg orally once a day), which is an ARB, and switch to Enrest on postoperative day 1.

Enrest starts with 100 mg per day (50 mg orally twice daily). After that, if there are no side effects or other problems, the dose is gradually increased to 400 mg per day (200 mg at a time) at intervals of 2 to 4 weeks. The criteria for determining dose increase are systolic blood pressure of 100 mmHg or more and serum potassium level of less than 5.5 mEq/L. Entress will continue until the time of examination at least 6 months later.

○ Control group

Those who are assigned to the control group will receive the usual drug treatment (antihypertensives, diuretics, etc.) that has been used in the past.

After discharge from the hospital, medical examinations and examinations will be conducted 1 month, 3 months, and 6 months after the transcatheter aortic valve implantation procedure to determine the effect of adding Enrest.



Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

Schedule

season / item	Screening Testing/Enrollment/Randomization	Duration of treatment				At the time of cancellation
		Postoperatively～ At the time of discharge from the hospital	1 month	Three months	6 months	
schedule (Acceptable)	2 days before surgery (-28 days)	On the day of surgery to when you are discharged from the hospital	(± 14)	(± 28)	(± 28)	
Obtaining Consent	●					
Patient's Basic Info A	●					
Confirmation of surgical information		●				
Observation of adverse events b		●	●	●	●	●
Checking for Symptoms	●	●	●	●	●	●
Physical examination	●	●	●	●	●	●
Weighing yourself	●	●	●	●	●	●
Blood test [C,D]	●	●	●	●	●	●
Investigation of oral medications	●	●	●	●	●	●
Echocardiography	●	●			●	

A: Age, gender, illnesses you have had, illnesses in your family, etc.

b : Adverse events are all undesirable events, such as side effects, regardless of the causal relationship with the drug.

c: NT-proBNP will be measured as a hematologic test. This is done to confirm the effect of the drug.

d: Measure WBC, Hb, Plt, GOT, GPT, T-BIL, TP, ALB, BUN, Cr, eGFR, Na and K as hematologic tests. These are done to ensure the safety of the test.

e : Data for echocardiography up to 3 months before surgery are available.

3-3. Duration of this clinical study and the number of participants

If you participate in this study, the maximum length of participation will be approximately 8 months, including the screening period.

We plan to invite 84 participants (42 in the entrestion group and 42 in the usual care group) to participate in this study.

4. Anticipated benefits and disadvantages of conducting this clinical study

< expected profits>

This study may be able to prevent the onset of heart failure, improve subjective symptoms, and reduce the dose of other heart failure medications (e.g., diuretics) in patients after transcatheter aortic valve placement for aortic stenosis. In addition, fewer patients will be admitted to the hospital for postoperative heart failure, which may lead to social benefits such as reduced medical costs.

< disadvantages that may occur>

In the Enrest group, side effects (hypotension, hyperKemia, etc.) may be more likely to occur due to oral Enrest. Therefore, carefully follow up while taking Entrest, and if side effects occur, reduce or discontinue as appropriate.

5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study

Carry out the usual drug treatment (for example, antihypertensive drugs and diuretics). However, these drugs lower blood pressure for complicated hypertension (antihypertensive drugs) and excrete water accumulated in the body due to heart failure as urine (diuretics), and cannot be said to be a fundamental treatment.

6. In the event of damage to your health

This clinical trial is scientifically planned and carefully conducted based on

previous reports. If you experience any side effects or other health problems during or after the clinical trial, your doctor will provide you with appropriate medical examination and treatment.

Since this study will be conducted using drugs that are already on the market within their indication, the treatment of health damage caused by the drugs will be carried out using the patient's health insurance in the same way as regular medical care.

7. Participation in this clinical study is of the patient's own volition

You can decide whether or not to participate in this study at your own discretion. You can decline to participate in the study, or you can withdraw at any time once you have agreed to participate. If you do not participate or withdraw your consent, you will be treated in the most appropriate way for your patient and will not be treated unfavorably or lose any benefits that you should have received prior to participating in the study.

8. Information about this clinical study will be communicated from time to time

We will notify you immediately of any new information that may affect your intention to continue participating in the trial during your time in this clinical trial. In addition, if important information is obtained regarding this treatment, we will confirm your intention to continue to participate in the trial.

9. This clinical study may be discontinued

Even after obtaining consent to participate, participation may be refused or treatment may be discontinued in the following cases. Even after discontinuing treatment, you may be asked to undergo an examination if your doctor deems it necessary.

1） If you request to withdraw from the study

2） If it is found that you do not meet the conditions for participation in the study

3） If transcatheter aortic valve implantation is unsuccessful

4） If your doctor determines that you need other treatments due to worsening of your illness

5） If you have difficulty taking medication due to any adverse events

6） If this entire study is discontinued

7） In addition, if the attending physician deems it necessary to discontinue the study

10. If you agree to participate in this study, please observe the following

○ If you are currently visiting another hospital, please let us know the hospital, the name of the disease, and the medication you are using.

○ Please let us know if you have any medications that you purchase and use at pharmacies.

○ If you are visiting another hospital, we may inform you that you are participating in this study and ask you to provide information about your medical treatment at another hospital. Please note that these are important for the safety of the exam. In that case, we will contact you again.

11. Handling of your personal information

By signing a consent form, you consent to the collection, viewing, use and sharing of your information. In this case, personal information such as your name will still be kept confidential. Details are explained in the following sections.

11-1. It will not be identified as yours

Your research data will be collected for the purpose of this study (see 2-1 Purpose of this clinical study) and will be used or shared with the people involved in this study (e.g., staff of this hospital). When you collect research

data, it is coded, so no personal information, such as your name or address, is directly collected, and the data cannot be identified as yours from the report. Monitoring and auditing are conducted to confirm that research is being conducted appropriately in accordance with laws and regulations, and that there are no problems with the quality of the data. People from companies that have been entrusted with monitoring and audits, members of the Ministry of Health, Labour and Welfare and committees that review clinical research may view your medical records such as medical records. However, these people have a duty of confidentiality, so the confidentiality of information about you will be preserved.

11-2. Even if the results of this test are made public, your identity will not be revealed

The results obtained in this test may be published in medical journals, but your privacy will be protected because we will not reveal any personal information such as your name.

12. Method of Disclosure of Information on Specific Clinical Research

Information on this clinical research is registered in the Japan Registry of Clinical Trials (jRCT), a database maintained by the Ministry of Health, Labour and Welfare.

13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research

If you would like to find out in what form your data is provided and how it will be used, please consult your doctor. It is possible to view the research proposal. However, please note that we will not be able to comply with all the information disclosure requests if the information is related to confidential research.

14. Methods of storage and disposal of samples and information, etc., and secondary use of data

The data collected for the study will be properly stored. Medical records and other information are stored at medical institutions, but information that has been deleted from descriptions that can identify individuals and important documents related to research are kept by the principal investigator. The retention period is until 5 years after the end of the research, but in some cases it may be stored for a longer period of time to maintain the integrity of the research. After the retention period ends, the data stored in paper media will be disposed of after being shredded into a state where it cannot be reproduced.

Even if the patient withdraws their consent, the data collected so far will still be used for the study. If you wish to withdraw your data, including the use of your data, please consult your doctor. Please note that if the information has already been analyzed or the results have been announced at the time of the withdrawal, we will not be able to remove your data.

There are currently no plans to use the data obtained in this study for any purpose other than this research, but it may be necessary for new research planned in the future. If you wish to use the stored data for any other purpose, you will apply to the Ethics Committee again in accordance with laws and regulations, obtain approval, and confirm your consent again.

15. Intellectual Property Rights and Conflicts of Interest

○ Intellectual Property Rights

There is a possibility that the results of this study will give rise to intellectual property such as patent rights, but in such cases, the intellectual property rights belong to the researcher or the research institution to which he or she belongs.

O Conflicts of interest

A conflict of interest (COI) is a situation in which a third party may be concerned that a company's involvement in research or the existence of an economic interest relationship between a company involved in research and a researcher may impair fair and appropriate judgment. This can undermine the credibility of the study and neglect patient protection. On the other hand, in order to properly conduct clinical research, it is necessary to secure a certain amount of research funds and receive goods, and there is no problem for researchers to receive such support from companies. For this reason, it is necessary to gain trust in clinical research by appropriately managing possible conflicts of interest and providing sufficient explanations.

This research is being carried out with the support of Chiba University Hospital's Advanced Medical Development Promotion Fund System. The research co-investigators at Chiba University Hospital receive personal benefits (lecture fees) from Novartis Pharma K.K., and the content of such conflicts of interest is appropriately managed by the Clinical Research Conflict of Interest Management Committee of our hospital. In addition, it has been reviewed by the Chiba University Clinical Research Jury.

16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?

This trial is conducted within the scope of general health insurance. In addition, there is no remuneration, including money, for cooperation in research such as examinations and medical treatments.

17. Review of Specific Clinical Research (About the Clinical Research

Review Board)

At Chiba University, the president of Chiba University has established a Clinical Research Review Committee within the University Hospital, and experts and non-specialists in medical fields such as medicine, pharmacy, nursing, and people who have no interest in Chiba University are invited to serve as committee members to examine whether there are any problems with the conduct of clinical research from the standpoint of medical professionals and patients.

Name of Clinical Research Review Committee: Chiba University Clinical Research Review Board

Established by the Clinical Research Review Committee: President, Chiba University

Location: 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba

URL : https://jcrb.niph.go.jp/applications/detail/55

18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

If you have any questions or concerns about this study, please do not hesitate to contact your physician or clinical trials.

Chiba University Hospital (Tel: 043-222-7171)

Investigator Department of Cardiovascular Medicine and Coronary Artery Disease: Hideki Kitahara (ext. 6390)

Clinical Trials: Mon-Fri 8:30 a.m. to 5:00 p.m. (ext. 6460)

Patient Talk: 9:00 a.m. to 5:00 p.m (ext. 6090)

Emergency Nighttime and Holiday Consultation Desk (Main phone: 043-222-7171)

Tell us that you are participating in a clinical trial in cardiology.

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

for clinical research methods

For Doctors

Letter of Intent

Title: A randomized, open-label, comparative study to investigate the efficacy of angiotensin receptor neprilysin inhibitors in patients with aortic stenosis after transcatheter aortic valve placement

<Instructions>

1. What is clinical research?
2. Why do we conduct this clinical study?
3. Method and duration of clinical research
4. Anticipated benefits and disadvantages of conducting this clinical study
5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study
6. In the event of damage to your health
7. Participation in this clinical study is voluntary of the patient.
8. Information about this clinical study will be communicated from time to time
9. This clinical study may be discontinued
10. If you agree to participate in this study, please observe the following
11. Handling of your personal information
12. Method of Disclosure of Information on Specific Clinical Research
13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research
14. Methods of storage and disposal of samples and information, etc., and secondary use of data
15. Intellectual Property Rights and Conflicts of Interest
16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?
17. Review of Specific Clinical Research (About the Clinical Research Review Board)
18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

[Patient's signature line]
In participating in this exam, I have received a sufficient explanation of the above matters, received an explanation of consent, and fully understood the contents, etc., and I agree to participate in this examination.

Consent date:

Patient Name: _____

[Signature line of the substitute] (only if necessary)

Author's Name: _____

Relationship with the person:

[Doctor's signature line]
I have fully explained this study to the above patients.

Explanation date:
Affiliation:
Name: _____

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

for clinical research methods

For secretariat

Letter of Intent

Title: A randomized, open-label, comparative study to investigate the efficacy of angiotensin receptor neprilysin inhibitors in patients with aortic stenosis after transcatheter aortic valve placement

<Instructions>

1. What is clinical research?
2. Why do we conduct this clinical study?
3. Method and duration of clinical research
4. Anticipated benefits and disadvantages of conducting this clinical study
5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study
6. In the event of damage to your health
7. Participation in this clinical study is voluntary of the patient.
8. Information about this clinical study will be communicated from time to time
9. This clinical study may be discontinued
10. If you agree to participate in this study, please observe the following
11. Handling of your personal information
12. Method of Disclosure of Information on Specific Clinical Research
13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research
14. Methods of storage and disposal of samples and information, etc., and secondary use of data
15. Intellectual Property Rights and Conflicts of Interest
16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?
17. Review of Specific Clinical Research (About the Clinical Research Review Board)
18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

[Patient's signature line]

In participating in this exam, I have received a sufficient explanation of the above matters, received an explanation of consent, and fully understood the contents, etc., and I agree to participate in this examination.

Consent date:

Patient Name: _____

[Signature line of the substitute] (only if necessary)

Author's Name: _____

Relationship with the person:

[Doctor's signature line]

I have fully explained this study to the above patients.

Explanation date:

Affiliation:

Name: _____

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

for clinical research methods

for patients

Letter of Intent

Title: A randomized, open-label, comparative study to investigate the efficacy of angiotensin receptor neprilysin inhibitors in patients with aortic stenosis after transcatheter aortic valve placement

<Instructions>

1. What is clinical research?
2. Why do we conduct this clinical study?
3. Method and duration of clinical research
4. Anticipated benefits and disadvantages of conducting this clinical study
5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study
6. In the event of damage to your health
7. Participation in this clinical study is voluntary of the patient.
8. Information about this clinical study will be communicated from time to time
9. This clinical study may be discontinued
10. If you agree to participate in this study, please observe the following
11. Handling of your personal information
12. Method of Disclosure of Information on Specific Clinical Research
13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research
14. Methods of storage and disposal of samples and information, etc., and secondary use of data
15. Intellectual Property Rights and Conflicts of Interest
16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?
17. Review of Specific Clinical Research (About the Clinical Research Review Board)
18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

[Patient's signature line]

In participating in this exam, I have received a sufficient explanation of the above matters, received an explanation of consent, and fully understood the contents, etc., and I agree to participate in this examination.

Consent date:

Patient Name: _____

[Signature line of the substitute] (only if necessary)

Author's Name: _____

Relationship with the person:

[Doctor's signature line]

I have fully explained this study to the above patients.

Explanation date:

Affiliation:

Name: _____

BMJ Open

Protocol of the randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor-neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-095105.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Apr-2025
Complete List of Authors:	Kitahara, Hideki; Chiba University Graduate School of Medicine School of Medicine, Cardiovascular Medicine Okita, Shogo; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine Sugawara, Takeshi; Chiba University Hospital, Ophthalmology Yaginuma, Hiroaki; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine Goto, Hiroki; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine Yamamoto, Hiroaki; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Kanda, Tomoyoshi; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Matsuura, Kaoru; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Inaba, Yosuke; Chiba University Hospital, Clinical Research Center Hanaoka, Hideki; Chiba University Hospital, Clinical Research Center Matsumiya, Goro; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Surgery Kobayashi, Yoshio; Chiba University Graduate School of Medicine School of Medicine, Department of Cardiovascular Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical management
Keywords:	Adult cardiology < CARDIOLOGY, Valvular heart disease < CARDIOLOGY, Heart failure < CARDIOLOGY

Protocol of the randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor-neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Hideki Kitahara[1)], Shogo Okita[1)], Takeshi Sugawara[2)], Hiroaki Yaginuma[1)], Hiroki Goto[1)], Hiroaki Yamamoto[3)], Tomoyoshi Kanda[3)], Kaoru Matsuura[3)], Yosuke Inaba[2)], Hideki Hanaoka[2)], Goro Matsumiya[3)], Yoshio Kobayashi[1)]

Author affiliations:

1) Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan.

2) Clinical Research Center, Chiba University Hospital, Chiba, Japan.

3) Department of Cardiovascular Surgery, Chiba University Graduate School of Medicine, Chiba, Japan.

Running title: *Kitahara et al.; Efficacy of ARNI in patients undergoing TAVI*

Address for correspondence:

Hideki Kitahara, MD, PhD

Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine

1-8-1 Inohana, Chuo-ku, Chiba, Chiba 260-8677, Japan

Phone: +81-43-226-2340

Fax: +81-43-226-2340

E-mail: hidekitahara0306@gmail.com

Word count: 4,253 words

ABSTRACT

Introduction: There are a substantial number of patients developing heart failure after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS), even though AS has been successfully treated. The purpose of this randomized controlled trial was to determine whether the addition of an angiotensin receptor neprilysin inhibitor (ARNI), Sacubitril/Valsartan, is superior to conventional medications in lowering N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients undergoing TAVI for AS.

Methods and analysis: The study design is a prospective, single-center, open-label, randomized, parallel-group, two-arm study, in which participants will be randomized 1:1 to receive either conventional medications plus ARNI or conventional medications only. In the ARNI group, if a patient was on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker before TAVI, it will be switched to ARNI 100 mg/day (50 mg twice daily) on the first postoperative day. If not, candesartan 4 mg/day will be started 1-2 days before TAVI, and switched to ARNI 100 mg/day on the first postoperative day. As the patient has tolerability to ARNI, dosage will be increased stepwise to 400 mg/day 2-4 weeks apart. ARNI will be continued until at least 6 months follow-up. In the control group, the patient will receive conventional medications. The primary endpoint is the serum NT-proBNP value at 6 months follow-up after TAVI. Each group includes 42 patients (84 total patients).

Ethics and dissemination: Ethical approval for this study has been obtained from the Chiba University Hospital Certified Clinical Research Review Board. The study is ongoing. Findings from this study will be disseminated through peer-reviewed publications and conference presentations.

Trial registration: This trial has been registered on the Japan Registry of Clinical Trials jRCT1031220344 (https://jrct.niph.go.jp/latest-detail/ jRCT1031220344).

Strengths and limitations of this study

- This is a randomized controlled trial to investigate the efficacy of angiotensin receptor neprilysin inhibitor (ARNI) in patients undergoing transcatheter aortic valve implantation for severe aortic stenosis.
- The primary endpoint is the N-terminal pro-B-type natriuretic peptide value at 6 months follow-up, which is a well-established surrogate biomarker for heart failure.
- This study incorporates a comprehensive set of secondary endpoints, including hemodynamic parameters, functional status, and diuretic use, to support interpretation of the primary endpoint.
- Potential limitations of the trial are that the primary endpoint is a surrogate marker for heart failure, and clinical outcomes or functional outcome measures cannot be assessed.
- If this study shows the potential of ARNI for prevention of heart failure development, it can serve as a platform for further evaluation of its prognostic impact in a larger population.

INTRODUCTION

Since previous pivotal trials have shown that transcatheter aortic valve implantation (TAVI) has a similar or better short- and long-term prognosis compared with surgical aortic valve replacement for aortic stenosis (AS),[1,2] the indications for TAVI have expanded, with the number of cases increasing in recent years. On the other hand, many studies investigating clinical outcomes after TAVI have reported that the most common cause of rehospitalization is heart failure, with incidence ranging from 12.8% to 24.1%.[3-6] In some cases, functional problems with the TAVI valve, such as severe patient-prosthesis mismatch and paravalvular leak, are known to cause heart failure after TAVI.[5,7] However, most of these patients develop heart failure despite no obvious problem with TAVI valve function and preserved left ventricular ejection fraction (LVEF) on echocardiography, known as "heart failure with preserved ejection fraction (HFpEF)", mainly due to left ventricular diastolic dysfunction. Even if AS is successfully treated by TAVI, HFpEF can possibly be caused by various factors, such as advanced age, residual left ventricular hypertrophy, concomitant chronic kidney disease, arrhythmia as represented by atrial fibrillation, increased afterload by hypertension and peripheral vascular resistance.[3-5] Since there is no established method to prevent HFpEF after TAVI, it is considered necessary to explore effective medications for HFpEF to improve long-term prognosis after TAVI.

Based on the results of previous large-scale randomized controlled trials,[8] administration of angiotensin receptor-neprilysin inhibitor (ARNI), Sacubitril/Valsartan, is recommended as one of the important options for treatment of heart failure with reduced ejection fraction (HFrEF) in the guidelines for treatment of heart failure.[9,10] On the other hand, in the PARAGON-HF trial comparing ARNI and valsartan in patients with HFpEF, although there was no statistically significant difference in the composite primary endpoint (heart failure and cardiovascular death), ARNI was associated with a significantly lower rate of the primary

endpoint in women or patients with LVEF ≤57% in prespecified subgroup analyses.[11] Therefore, ARNI is listed as a medication that may be considered for patients with HFpEF in the guidelines (class of recommendation is IIb).[9,10] However, there are no data on the efficacy of ARNI for prevention of heart failure after TAVI. Thus, the purpose of this randomized controlled trial is to clarify whether the addition of ARNI is superior to conventional medications in lowering N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, as a diagnostic biomarker for heart failure, in patients undergoing TAVI for severe AS.

METHODS

Study design

In this phase IV, prospective, single-center, open-label, randomized, parallel-group, two-arm study, participants will be randomized 1:1 to receive either conventional medications plus ARNI or conventional medications only.

Eligibility criteria

Eligible patients are those who meet all inclusion criteria mentioned below and none of the listed exclusion criteria. Inclusion criteria are: 1) patients with AS and symptoms of heart failure requiring TAVI based on the guidelines for management of valvular heart disease;[12,13] 2) patients scheduled for TAVI at Chiba University Hospital; 3) patients aged 70 years or older at the time of enrollment; and 4) patients who have provided written informed consent to participate in this study (if the patient cannot provide a signature, a family member / designate may sign on their behalf). Exclusion criteria include any of the following: 1) acute heart failure (New York Heart Association [NYHA] class IV); 2) systolic blood pressure <110 mmHg; 3) severe hepatic dysfunction (Child-Pugh class C); 4) severe renal dysfunction (serum creatinine

> 3.0mg/dL); 5) hemodialysis; 6) hyperkalemia (serum K >5.5 mEq/L); 7) bilateral renal artery stenosis; 8) history of angioedema; 9) patient with diabetes on aliskiren fumarate; 10) a patient without written informed consent; and 11) a patient whom the investigator considers to be ineligible as a subject.

Recruitment

Recruitment of this study started in September 2022 and will end in January 2025, or until a total of 84 participants have been recruited. This study is being conducted at Chiba University Hospital.

Patient and public involvement

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

Sample size calculation

The target sample size for this randomized trial is 84. This number is based on feasibility and following validity. Primary analysis of this study is to test the superiority of the ARNI group (conventional medications plus ARNI) over the control group (conventional medications only) in lowering NT-proBNP levels in patients with AS undergoing TAVI. The NT-proBNP level is determined as a surrogate marker in this study, because previous studies have reported that lower NT-proBNP levels and greater reduction of NT-proBNP levels are associated with better prognosis in HFpEF patients.[14,15] In the PARAGON-HF study, comparing ARNI and valsartan in patients with HFpEF, the NT-proBNP levels after 48 weeks were approximately 600 pg/ml in the ARNI group and 700 pg/ml in the control group (valsartan group).[16] Since it is unlikely that the NT-proBNP level in the control group (conventional medications) in this study would

be lower than that with valsartan, the NT-proBNP level after 6 months in this study was estimated to be 600 pg/ml in the ARNI group and 700 pg/ml in the control group. Assuming a standard deviation of 150 pg/ml, an overall significance level of 5% ($\alpha = 0.05$), and a target power of 80% ($1-\beta = 0.8$), the minimum number of patients required is calculated to be 37 in each group (74 in total). Considering approximately 10% of discontinuation or dropout, the total sample size of 84 patients is required for this study.

Registration and assignment methods

1) In principle, registration should be conducted within 7 days of obtaining consent. 2) The principal investigator or subinvestigators will obtain written consent and confirm that participants meet the selection criteria and do not violate the exclusion criteria as a result of the screening test. Participants deemed eligible by the principal investigator or subinvestigators will be enrolled prior to the start of study drug administration. Participants will be enrolled in the study by faxing or bringing the case registration form (CRF) with them. 3) The principal investigator and subinvestigators will complete the CRF and bring it to the data management center at Chiba Clinical Research Center. The data center will enter the necessary information for case registration on the data system and confirm the results of eligibility determination and assignment on the system. If the patient is found to be eligible, the investigator or subinvestigators will start the protocol treatment according to the results of the assignment. 4) Once a patient is registered, the registration will not be cancelled (deleted from the database). In case of duplicate registration, the initial registration information (registration number) will be used in all cases. In case of registration errors or duplicate registrations, the data center shall be notified immediately.

Assignment adjustment factors

Participants will be randomly assigned 1:1 to the study to receive conventional medications plus ARNI or conventional medications only. Eligible patients will be randomized to either the ARNI group or the control group at a ratio of 1:1, by employing a minimization method balancing for sex (male or female), age (<85 or ≥85 years), and LVEF (<50% or ≥50%).

Study procedures

The study outline is shown in Figure 1. A patient who meets inclusion criteria, and has provided written informed consent to participate in this study at least 2 days prior to TAVI procedure, will be randomly assigned into the ARNI group or the control group. In the ARNI group, ARNI will be initiated as follows, because ARNI must be administered by switching from angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) for adult heart failure based on the labeling information for prescription medicines by Pharmaceuticals and Medical Devices Agency in Japan. If a patient is on ACE-I preoperatively, ACE-I will be stopped one day prior to TAVI, and ARNI 100 mg daily (50 mg twice daily) will be started on the first postoperative day. If a patient is taking an ARB preoperatively, ARB will be switched to ARNI 100 mg daily (50 mg twice daily) on the first postoperative day. If a patient is not taking ACE-I or ARB preoperatively, candesartan 4 mg/day will be started 1-2 days before TAVI, and candesartan will be switched to ARNI 100 mg daily (50 mg twice daily) on the first postoperative day. Due to the institutional restrictions on drug use, candesartan was chosen as the starter for switch to ARNI. In a patient with tolerability to ARNI, dosage will be increased stepwise to 400 mg/day (200 mg twice daily) 2-4 weeks apart. Tolerability is evaluated by a systolic blood pressure of 100 mmHg or higher and a serum potassium level of < 5.5 mEq/L. ARNI will be continued at least until 6 months follow-up. In the control group, patients will receive conventional medications without ARNI.

Blinds

Blinds are not performed.

Endpoint

The primary endpoint of the study is the serum NT-proBNP value at 6 months follow-up after TAVI. The secondary efficacy endpoints include: 1) change in NT-proBNP value at 6 months follow-up; 2) systolic pulmonary artery pressure at 6 months follow-up; 3) edema scale at 6 months follow-up; 4) NYHA class at 6 months follow-up; 5) increase or decrease in the dose of diuretics at 6 months follow-up; 6) change in body weight at 6 months follow-up; and 7) cardiovascular events (death, admission for heart failure, myocardial infarction). The secondary safety endpoints include: 1) incidence of adverse events; 2) prevalence of patients with serum K >5.5 mEq/L; and 3) prevalence of patients with symptomatic hypotension.

Statistical analysis

The total analysis population (FAS), protocol unit population (PPS), and safety population will be analyzed; the FAS will be the primary analysis population and all 3 target populations will be analyzed. The distribution of subject background data and summary statistics for each analysis population will be calculated for each group. For nominal variables, category frequencies and proportions will be presented for each group. For continuous variables, summary statistics (number of cases, mean, standard deviation, minimum, median, maximum) will be calculated for each group. For comparisons between groups, Pearson's chi-square test is used for nominal variables, with the exception of Fisher's direct probability calculation method for cells with an expected frequency of < 5 and > 20%, Wilcoxon's rank sum test for ordinal variables, and the t-test with no correspondence for continuous variables. The significance level is set at 5% two-tailed.

For the primary endpoint, the main analysis will be performed for FAS, taking the mean value in each group for NT-proBNP levels at 6 months and testing for statistical significance by means of an unpaired t-test. For this analysis, a similar analysis will be performed for PPS as a supplementary analysis. The significance level for the hypothesis test will be 5% two-sided. For the secondary efficacy endpoints, the analyses will be performed to provide additional insight to the primary analyses. No adjustment for multiplicity will be made in the analysis of the secondary efficacy endpoints. The significance level for hypothesis testing is 5% two-sided, and confidence intervals are calculated as two-sided 95% confidence intervals. For the secondary safety endpoints, which are the frequency of adverse events, tables will be prepared for the endpoints, and exact two-sided 95% confidence intervals of the binomial distribution will be calculated for each group to estimate proportions. If necessary, Fisher's direct probability calculation method will be used to compare between groups.

Quality control

The monitoring manager is responsible for ensuring that the human rights of the subjects are protected, the study is conducted in accordance with the protocol, and the data are accurately collected. Central monitoring will be conducted on a regular basis based on data from case report forms obtained at the data center. The monitoring manager shall prepare a report that includes a summary of important findings such as diseases, nonconformities, or other facts, and shall report the results of such monitoring to the principal investigator. The independent data monitoring committee, which consists of at least 3 expert members independent of the study, will conduct safety monitoring, including comparison of the incidence of adverse events between the study treatment and control group, and detailed examination of serious adverse events, as necessary, for the purpose of ensuring patient safety. The principal investigator will make a decision to discontinue the study as a whole if it is considered difficult to continue the

study due to unforeseen adverse events, illness, or other factors.

Informed consent

All participants will receive adequate information about the nature, purpose, possible risks and benefits of the trial, and on alternative therapeutic choices using informed consent approved by the IRB (Supplemental File 1). A participant must be given ample time and opportunity to ask questions and to consider participation in the trial. A completed informed consent is required for enrollment in the trial. The investigators must maintain the original signed consent form and a copy of the signed consent form. To assure patient confidentiality, trial participants will be allocated a unique trial identification number for reference throughout the trial.

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki (revised 2013). Ethical approval for this study has been obtained from the Chiba University Hospital Certified Clinical Research Review Board (CRB3180015) and the study is registered in the Japan Clinical Trials Registry (jRCT1031220344). The investigators will explain the concept of this study to patients and obtain written informed consent from all participating patients. The initial version of the protocol was approved on 08/23/2022 and patient recruitment began in 09/22/2022. The latest version 1.5 was approved 09/17/2024.

A manuscript summarizing the results of the primary endpoint will be published in a peer-reviewed journal. Separate manuscripts for the secondary objectives will also be written and submitted for publication in peer-reviewed journals. The findings of this study will be disseminated through presentations at academic conferences.

Discussion

Although TAVI is a quite effective treatment for AS, a substantial number of patients develop heart failure after TAVI, and furthermore, heart failure after TAVI has been associated with poor prognosis.[3-6] Since patients who require TAVI are often elderly and have a variety of comorbidities, they are considered to be a population at high risk of developing HFpEF even after AS is treated.[17] To reduce the risk of heart failure after TAVI, comprehensive treatment that includes not only relieving AS but also managing comorbidities and administrating appropriate medications may be necessary.[18,19] In addition, previous studies have indicated that cardiac fibrosis and hypertrophy persist after relief of AS, leading to poor prognosis in patients with severe AS.[20] Therefore, medications with an effect to inhibit cardiac fibrosis may improve prognosis after TAVI. Recently, the usefulness of sodium-glucose cotransporter 2 inhibitors (SGLT2-I) for heart failure, including HFpEF, has been reported, and thus, its use is strongly recommended in the guidelines.[10,21] Although SGLT2-I may be effective in preventing heart failure after TAVI, some patients possibly have difficulty to initiate SGLT2-I because of the elderly population with high frailty and risk for infections, such as urinary tract infections.[22]

While ARNI is widely used for treatment of heart failure, mainly HFrEF, it is also effective to some extent for heart failure with mildly-reduced ejection fraction and HFpEF.[11] Previous animal studies have shown that ARNI is effective in ameliorating cardiac maladaptive remodeling, as indicated by improvements in cardiac function and decreases in cardiac fibrosis, hypertrophy, and inflammation, suggesting that ARNI may also be beneficial after TAVI.[23,24] However, it has been unclear whether ARNI can actually reduce the risk of heart failure after TAVI. Therefore, this randomized study has been designed to investigate this issue. This study is designed to determine the impact of adding ARNI to conventional medications, such as antihypertensive agents and diuretics. Although most of the past studies showing the efficacy of ARNI in heart failure have compared it with ACE-I or ARB,[8,11] this study was designed to compare conventional medications plus ARNI with conventional medications only, because

the efficacy of ACE-I or ARB in heart failure after TAVI has not been demonstrated. Since NT-proBNP has been used as an important parameter for evaluation of heart failure in many previous studies examining the efficacy of ARNI,[16] NT-proBNP level at follow-up is set as the primary endpoint in this study. If this study shows the usefulness of ARNI for prevention of heart failure, the next step may be to investigate whether it can reduce heart failure events in a larger-scale study. In such a future study, functional outcome measures, e.g. a six-minute walk test, which is not planned to investigate in this study, should also be examined.

Acknowledgments

We thank the Translational Research and Development Center, Chiba University Hospital for their cooperation in protocol development. We thank Heidi N. Bonneau, RN, MS, CCA for her editorial review of the manuscript.

Contributors

HK designed the original concept. All co-authors contributed significantly to the conception and design of the study, with specific additional contributions from each co-author within their area of expertise. The protocol was written by HK, SO and KM, and it was critically reviewed by TS, HY, HG, HY, TK, YI, HH, GM, and YK. All authors gave approval for the publication. YK is the guarantor.

Funding

This study is funded by a CREATION-Fund (of Chiba University Hospital); Clinical Research Initiation-Fund (of Chiba University Hospital).

Competing interests

HK, SO, HY, HG, HY, TK, KM, GM, and YK are affiliated with Chiba University Graduate School of Medicine, to which Chiba University Hospital belongs, and ST, IY, and HH are affiliated with Chiba University Hospital, which provided financial support for this study. However, the institutions were not involved in the design, execution, data analysis, or interpretation of the results in this study. YK received lecture fees from Novartis Pharma. The authors declare no other competing interests.

Provenance and peer review

Not commissioned; internally peer reviewed.

Open Access

Ethical Statement:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has received an ethical approval by Chiba University Hospital Certified Clinical Research Review Board (CRB3180015) and has been registered on the Japan Registry of Clinical Trials (jRCT1031220344). Investigators will explain the concept of the trial to the patients and obtain written informed consent from all participating patients.

References

1. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019;380:1695-705.
2. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med* 2019;380:1706-15.
3. Durand E, Doutriaux M, Bettinger N, et al. Incidence, Prognostic Impact, and Predictive Factors of Readmission for Heart Failure After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2017;10:2426-36.
4. Nazzari H, Hawkins NM, Ezekowitz J, et al. The Relationship Between Heart-Failure Hospitalization and Mortality in Patients Receiving Transcatheter Aortic Valve Replacement. *Can J Cardiol* 2019;35:413-21.
5. Auffret V, Bakhti A, Leurent G, et al. Determinants and Impact of Heart Failure Readmission Following Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv* 2020;13:e008959.
6. Heger J, Trimaille A, Kibler M, et al. Electrocardiographic Strain Pattern Is a Major Determinant of Rehospitalization for Heart Failure After Transcatheter Aortic Valve Replacement. *J Am Heart Assoc* 2021;10:e014481.
7. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. *J Am Coll Cardiol* 2018;72:2701-11.
8. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
9. Tsutsui H, Ide T, Ito H, et al. JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure. *Circ J* 2021;85:2252-91.
10. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the

Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e895-e1032.

11. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019;381:1609-20.
12. Izumi C, Eishi K, Ashihara K, et al. JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease. *Circ J* 2020;84:2037-119.
13. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143:e72-e227.
14. Savarese G, Hage C, Orsini N, et al. Reductions in N-Terminal Pro-Brain Natriuretic Peptide Levels Are Associated With Lower Mortality and Heart Failure Hospitalization Rates in Patients With Heart Failure With Mid-Range and Preserved Ejection Fraction. *Circ Heart Fail* 2016;9:e003105.
15. Salah K, Stienen S, Pinto YM, et al. Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction. *Heart* 2019;105:1182-9.
16. Cunningham JW, Vaduganathan M, Claggett BL, et al. Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 2020;8:372-81.
17. Takahashi M, Takaoka H, Yashima S, et al. Extracellular Volume Fraction by Computed Tomography Predicts Prognosis After Transcatheter Aortic Valve Replacement. *Circ J* 2024;88:492-500.
18. Matsushita K, Morel O, Ohlmann P. Contemporary issues and lifetime management in patients underwent transcatheter aortic valve replacement. *Cardiovasc Interv Ther*

2023;38:275-86.

19. Miyahara D, Izumo M, Sato Y, et al. Calcium channel blocker use and outcomes following transcatheter aortic valve intervention for aortic stenosis. *Cardiovasc Interv Ther* 2025;40:352-61.
20. Musa TA, Treibel TA, Vassiliou VS, et al. Myocardial Scar and Mortality in Severe Aortic Stenosis. *Circulation* 2018;138:1935-47.
21. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;44:3627-39.
22. Committee ADAPP. 13. Older Adults: Standards of Care in Diabetes-2024. *Diabetes Care* 2024;47:S244-S257.
23. Burke RM, Lighthouse JK, Mickelsen DM, Small EM. Sacubitril/Valsartan Decreases Cardiac Fibrosis in Left Ventricle Pressure Overload by Restoring PKG Signaling in Cardiac Fibroblasts. *Circ Heart Fail* 2019;12:e005565.
24. Li X, Zhu Q, Wang Q, et al. Protection of Sacubitril/Valsartan against Pathological Cardiac Remodeling by Inhibiting the NLRP3 Inflammasome after Relief of Pressure Overload in Mice. *Cardiovasc Drugs Ther* 2020;34:629-40.

Figure legend

Figure 1. Graphic outline of study design

Patients are randomly assigned to either the ARNI group with conventional medications plus ARNI or the control group with conventional medications only.

*ARNI will be initiated as follows, because ARNI must be administered by switching from ACE-I or ARB based on the labeling information for prescription medicines by PMDA in Japan. 1) If a patient is on ACE-I preoperatively, ACE-I will be stopped one day prior to TAVI, and ARNI 100 mg daily will be started on the first postoperative day. 2) If a patient is taking an ARB preoperatively, ARB will be switched to ARNI 100 mg daily on the first postoperative day. 3) If a patient is not taking ACE-I or ARB preoperatively, candesartan 4 mg/day will be started 1-2 days before TAVI, and candesartan will be switched to ARNI 100 mg daily on the first postoperative day.

ACE-I, Angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; PMDA, Pharmaceuticals and Medical Devices Agency; TAVI, transcatheter aortic valve implantation.

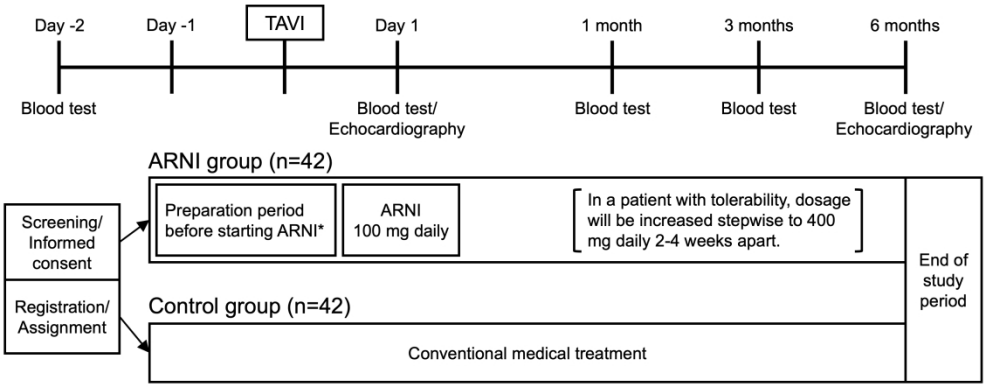


Figure 1

290x115mm (300 x 300 DPI)

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

For Patients

Clinical study: "Randomized, open-label, controlled study to evaluate the efficacy of angiotensin receptor neprilysin inhibitor in patients with aortic stenosis undergoing transcatheter aortic valve implantation

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

table of contents

1. What is clinical research?

It is the role of medical institutions to establish new treatments through clinical research, and it can be achieved with the cooperation of patients. The clinical research described in this article is planned and planned by physicians involved in actual medical care in light of medical necessity and importance. It is not a clinical trial conducted by pharmaceutical companies to investigate the safety and usefulness of a new drug and obtain approval from the Ministry of Health, Labor and Welfare. This study is based on the deliberations of the Clinical Research Review Committee, Chiba University, and has obtained permission from the heads of each medical institution. In addition, in accordance with Article 5, Paragraph 1 of the Clinical Trials Act, we have submitted a prescribed implementation plan to the Minister of Health, Labour and Welfare. It is up to you to decide whether or not to participate in the exam. If you don't participate, you will not be disadvantaged.

2. Why do we conduct this clinical study?

2-1. Purpose of this clinical study

The purpose of this clinical study is to evaluate the efficacy of angiotensin receptor neprilysin inhibitors (Enrest tablets) in patients who undergo transcatheter aortic valve implantation for aortic stenosis.The aim is to find out whether the addition of the drug is more effective in reducing the recurrence of heart failure than conventional drug treatment. Currently, there is no drug treatment that is effective in preventing recurrence of heart failure after transcatheter aortic valve placement. Therefore, if Enrest is effective in improving heart failure, it is expected to be a treatment option in the future.

2-2. Conventional treatment and trial treatment

Aortic stenosis is a serious disease in which the aortic valve at the exit of the heart becomes stiff and narrowed due to arteriosclerosis, causing heart failure with shortness of breath and swelling, fainting, and sudden death.

Transcatheter aortic valve implantation is a very effective treatment, but it alone does not completely cure the disease, and there is a certain percentage of patients whose heart failure worsens or recurs after surgery, so treatment to prevent heart failure is also considered important. However, since there are no drugs that have been shown to be effective in preventing the onset of postoperative heart failure, the standard treatment so far has been to use diuretics for swelling and antihypertensive drugs for high blood pressure as appropriate. Enrest is a relatively new drug, but it is used in regular practice as a treatment for heart failure, and is listed as a drug recommended for active use for heart failure in the guidelines (treatment guidelines) of the Japan Circulation Society. Therefore, it is considered to be effective for preventing recurrence of heart failure even after transcatheter aortic valve implantation, but since there have been no studies that have examined its effect in the past, we have planned a study to clarify the effect of enrest.

3. Method and duration of clinical research

3-1. Why are you eligible?

Eligible patients are those aged 70 years or older who undergo transcatheter aortic valve placement for aortic stenosis. Those who have already developed severe heart failure, those with low blood pressure (systolic blood pressure less than 100 mmHg), and those with severe liver or kidney dysfunction are not eligible.

3-2. Methods of this clinical study

They will be divided into two groups: one that adds an enrest and the other that continues with conventional treatment. Which group you will be in is decided by the computer, and neither the patient nor the doctor can choose.

○ Entrestion group

At the start of Enrest, it is necessary to switch from angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARBs), which

are antihypertensive drugs and heart failure drugs.

1) If you have been taking an ACE inhibitor for a long time

The drug will be discontinued from 1 day before surgery, and the start will be started on the first day after surgery.

2) If you have been taking ARB internally for a long time

Switch to Entrest on the first postoperative day.

3) If neither of them was taken internally

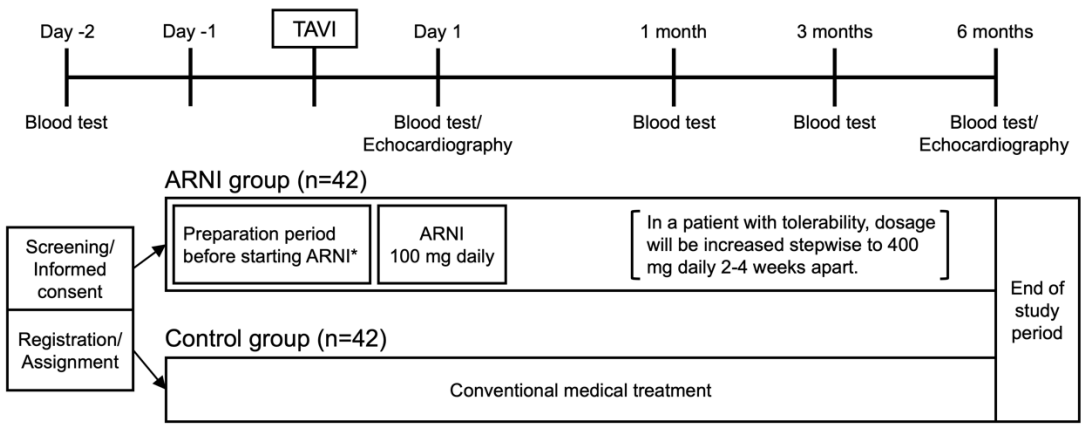
Start preoperatively (1-2 days before surgery) Bropres Tablets 4 mg (4 mg orally once a day), which is an ARB, and switch to Enrest on postoperative day 1.

Enrest starts with 100 mg per day (50 mg orally twice daily). After that, if there are no side effects or other problems, the dose is gradually increased to 400 mg per day (200 mg at a time) at intervals of 2 to 4 weeks. The criteria for determining dose increase are systolic blood pressure of 100 mmHg or more and serum potassium level of less than 5.5 mEq/L. Entress will continue until the time of examination at least 6 months later.

○ Control group

Those who are assigned to the control group will receive the usual drug treatment (antihypertensives, diuretics, etc.) that has been used in the past.

After discharge from the hospital, medical examinations and examinations will be conducted 1 month, 3 months, and 6 months after the transcatheter aortic valve implantation procedure to determine the effect of adding Enrest.



Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

Schedule

season / item	Screening Testing/Enrollment/Randomization	Duration of treatment				At the time of cancellation
		Postoperatively～ At the time of discharge from the hospital	1 month	Three months	6 months	
schedule (Acceptable)	2 days before surgery (-28 days)	On the day of surgery to when you are discharged from the hospital	(± 14)	(± 28)	(± 28)	
Obtaining Consent	●					
Patient's Basic Info A	●					
Confirmation of surgical information		●				
Observation of adverse events b		●	●	●	●	●
Checking for Symptoms	●	●	●	●	●	●
Physical examination	●	●	●	●	●	●
Weighing yourself	●	●	●	●	●	●
Blood test [C,D]	●	●	●	●	●	●
Investigation of oral medications	●	●	●	●	●	●
Echocardiography	●	●			●	

A: Age, gender, illnesses you have had, illnesses in your family, etc.

b : Adverse events are all undesirable events, such as side effects, regardless of the causal relationship with the drug.

c: NT-proBNP will be measured as a hematologic test. This is done to confirm the effect of the drug.

d: Measure WBC, Hb, Plt, GOT, GPT, T-BIL, TP, ALB, BUN, Cr, eGFR, Na and K as hematologic tests. These are done to ensure the safety of the test.

e : Data for echocardiography up to 3 months before surgery are available.

3-3. Duration of this clinical study and the number of participants

If you participate in this study, the maximum length of participation will be approximately 8 months, including the screening period.

We plan to invite 84 participants (42 in the entrestion group and 42 in the usual care group) to participate in this study.

4. Anticipated benefits and disadvantages of conducting this clinical study

< expected profits>

This study may be able to prevent the onset of heart failure, improve subjective symptoms, and reduce the dose of other heart failure medications (e.g., diuretics) in patients after transcatheter aortic valve placement for aortic stenosis. In addition, fewer patients will be admitted to the hospital for postoperative heart failure, which may lead to social benefits such as reduced medical costs.

< disadvantages that may occur>

In the Enrest group, side effects (hypotension, hyperKemia, etc.) may be more likely to occur due to oral Enrest. Therefore, carefully follow up while taking Entrest, and if side effects occur, reduce or discontinue as appropriate.

5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study

Carry out the usual drug treatment (for example, antihypertensive drugs and diuretics). However, these drugs lower blood pressure for complicated hypertension (antihypertensive drugs) and excrete water accumulated in the body due to heart failure as urine (diuretics), and cannot be said to be a fundamental treatment.

6. In the event of damage to your health

This clinical trial is scientifically planned and carefully conducted based on

previous reports. If you experience any side effects or other health problems during or after the clinical trial, your doctor will provide you with appropriate medical examination and treatment.

Since this study will be conducted using drugs that are already on the market within their indication, the treatment of health damage caused by the drugs will be carried out using the patient's health insurance in the same way as regular medical care.

7. Participation in this clinical study is of the patient's own volition

You can decide whether or not to participate in this study at your own discretion. You can decline to participate in the study, or you can withdraw at any time once you have agreed to participate. If you do not participate or withdraw your consent, you will be treated in the most appropriate way for your patient and will not be treated unfavorably or lose any benefits that you should have received prior to participating in the study.

8. Information about this clinical study will be communicated from time to time

We will notify you immediately of any new information that may affect your intention to continue participating in the trial during your time in this clinical trial. In addition, if important information is obtained regarding this treatment, we will confirm your intention to continue to participate in the trial.

9. This clinical study may be discontinued

Even after obtaining consent to participate, participation may be refused or treatment may be discontinued in the following cases. Even after discontinuing treatment, you may be asked to undergo an examination if your doctor deems it necessary.

1） If you request to withdraw from the study

2） If it is found that you do not meet the conditions for participation in the study

3） If transcatheter aortic valve implantation is unsuccessful

4） If your doctor determines that you need other treatments due to worsening of your illness

5） If you have difficulty taking medication due to any adverse events

6） If this entire study is discontinued

7） In addition, if the attending physician deems it necessary to discontinue the study

10. If you agree to participate in this study, please observe the following

○ If you are currently visiting another hospital, please let us know the hospital, the name of the disease, and the medication you are using.

○ Please let us know if you have any medications that you purchase and use at pharmacies.

○ If you are visiting another hospital, we may inform you that you are participating in this study and ask you to provide information about your medical treatment at another hospital. Please note that these are important for the safety of the exam. In that case, we will contact you again.

11. Handling of your personal information

By signing a consent form, you consent to the collection, viewing, use and sharing of your information. In this case, personal information such as your name will still be kept confidential. Details are explained in the following sections.

11-1. It will not be identified as yours

Your research data will be collected for the purpose of this study (see 2-1 Purpose of this clinical study) and will be used or shared with the people involved in this study (e.g., staff of this hospital). When you collect research

data, it is coded, so no personal information, such as your name or address, is directly collected, and the data cannot be identified as yours from the report. Monitoring and auditing are conducted to confirm that research is being conducted appropriately in accordance with laws and regulations, and that there are no problems with the quality of the data. People from companies that have been entrusted with monitoring and audits, members of the Ministry of Health, Labour and Welfare and committees that review clinical research may view your medical records such as medical records. However, these people have a duty of confidentiality, so the confidentiality of information about you will be preserved.

11-2. Even if the results of this test are made public, your identity will not be revealed

The results obtained in this test may be published in medical journals, but your privacy will be protected because we will not reveal any personal information such as your name.

12. Method of Disclosure of Information on Specific Clinical Research

Information on this clinical research is registered in the Japan Registry of Clinical Trials (jRCT), a database maintained by the Ministry of Health, Labour and Welfare.

13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research

If you would like to find out in what form your data is provided and how it will be used, please consult your doctor. It is possible to view the research proposal. However, please note that we will not be able to comply with all the information disclosure requests if the information is related to confidential research.

14. Methods of storage and disposal of samples and information, etc., and secondary use of data

The data collected for the study will be properly stored. Medical records and other information are stored at medical institutions, but information that has been deleted from descriptions that can identify individuals and important documents related to research are kept by the principal investigator. The retention period is until 5 years after the end of the research, but in some cases it may be stored for a longer period of time to maintain the integrity of the research. After the retention period ends, the data stored in paper media will be disposed of after being shredded into a state where it cannot be reproduced.

Even if the patient withdraws their consent, the data collected so far will still be used for the study. If you wish to withdraw your data, including the use of your data, please consult your doctor. Please note that if the information has already been analyzed or the results have been announced at the time of the withdrawal, we will not be able to remove your data.

There are currently no plans to use the data obtained in this study for any purpose other than this research, but it may be necessary for new research planned in the future. If you wish to use the stored data for any other purpose, you will apply to the Ethics Committee again in accordance with laws and regulations, obtain approval, and confirm your consent again.

15. Intellectual Property Rights and Conflicts of Interest

○ Intellectual Property Rights

There is a possibility that the results of this study will give rise to intellectual property such as patent rights, but in such cases, the intellectual property rights belong to the researcher or the research institution to which he or she belongs.

O Conflicts of interest

A conflict of interest (COI) is a situation in which a third party may be concerned that a company's involvement in research or the existence of an economic interest relationship between a company involved in research and a researcher may impair fair and appropriate judgment. This can undermine the credibility of the study and neglect patient protection. On the other hand, in order to properly conduct clinical research, it is necessary to secure a certain amount of research funds and receive goods, and there is no problem for researchers to receive such support from companies. For this reason, it is necessary to gain trust in clinical research by appropriately managing possible conflicts of interest and providing sufficient explanations.

This research is being carried out with the support of Chiba University Hospital's Advanced Medical Development Promotion Fund System. The research co-investigators at Chiba University Hospital receive personal benefits (lecture fees) from Novartis Pharma K.K., and the content of such conflicts of interest is appropriately managed by the Clinical Research Conflict of Interest Management Committee of our hospital. In addition, it has been reviewed by the Chiba University Clinical Research Jury.

16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?

This trial is conducted within the scope of general health insurance. In addition, there is no remuneration, including money, for cooperation in research such as examinations and medical treatments.

17. Review of Specific Clinical Research (About the Clinical Research

Review Board)

At Chiba University, the president of Chiba University has established a Clinical Research Review Committee within the University Hospital, and experts and non-specialists in medical fields such as medicine, pharmacy, nursing, and people who have no interest in Chiba University are invited to serve as committee members to examine whether there are any problems with the conduct of clinical research from the standpoint of medical professionals and patients.

Name of Clinical Research Review Committee: Chiba University Clinical Research Review Board

Established by the Clinical Research Review Committee: President, Chiba University

Location: 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba

URL : https://jcrb.niph.go.jp/applications/detail/55

18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

If you have any questions or concerns about this study, please do not hesitate to contact your physician or clinical trials.

Chiba University Hospital (Tel: 043-222-7171)

Investigator Department of Cardiovascular Medicine and Coronary Artery Disease: Hideki Kitahara (ext. 6390)

Clinical Trials: Mon-Fri 8:30 a.m. to 5:00 p.m. (ext. 6460)

Patient Talk: 9:00 a.m. to 5:00 p.m (ext. 6090)

Emergency Nighttime and Holiday Consultation Desk (Main phone: 043-222-7171)

Tell us that you are participating in a clinical trial in cardiology.

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

for clinical research methods

For Doctors

Letter of Intent

Title: A randomized, open-label, comparative study to investigate the efficacy of angiotensin receptor neprilysin inhibitors in patients with aortic stenosis after transcatheter aortic valve placement

<Instructions>

1. What is clinical research?
2. Why do we conduct this clinical study?
3. Method and duration of clinical research
4. Anticipated benefits and disadvantages of conducting this clinical study
5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study
6. In the event of damage to your health
7. Participation in this clinical study is voluntary of the patient.
8. Information about this clinical study will be communicated from time to time
9. This clinical study may be discontinued
10. If you agree to participate in this study, please observe the following
11. Handling of your personal information
12. Method of Disclosure of Information on Specific Clinical Research
13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research
14. Methods of storage and disposal of samples and information, etc., and secondary use of data
15. Intellectual Property Rights and Conflicts of Interest
16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?
17. Review of Specific Clinical Research (About the Clinical Research Review Board)
18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

[Patient's signature line]
In participating in this exam, I have received a sufficient explanation of the above matters, received an explanation of consent, and fully understood the contents, etc., and I agree to participate in this examination.

Consent date:

Patient Name: _____

[Signature line of the substitute] (only if necessary)

Author's Name: _____

Relationship with the person:

[Doctor's signature line]
I have fully explained this study to the above patients.

Explanation date:
Affiliation:
Name: _____

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

for clinical research methods

For secretariat

Letter of Intent

Title: A randomized, open-label, comparative study to investigate the efficacy of angiotensin receptor neprilysin inhibitors in patients with aortic stenosis after transcatheter aortic valve placement

<Instructions>

1. What is clinical research?
2. Why do we conduct this clinical study?
3. Method and duration of clinical research
4. Anticipated benefits and disadvantages of conducting this clinical study
5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study
6. In the event of damage to your health
7. Participation in this clinical study is voluntary of the patient.
8. Information about this clinical study will be communicated from time to time
9. This clinical study may be discontinued
10. If you agree to participate in this study, please observe the following
11. Handling of your personal information
12. Method of Disclosure of Information on Specific Clinical Research
13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research
14. Methods of storage and disposal of samples and information, etc., and secondary use of data
15. Intellectual Property Rights and Conflicts of Interest
16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?
17. Review of Specific Clinical Research (About the Clinical Research Review Board)
18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

[Patient's signature line]

In participating in this exam, I have received a sufficient explanation of the above matters, received an explanation of consent, and fully understood the contents, etc., and I agree to participate in this examination.

Consent date:

Patient Name: _____

[Signature line of the substitute] (only if necessary)

Author's Name: _____

Relationship with the person:

[Doctor's signature line]

I have fully explained this study to the above patients.

Explanation date:

Affiliation:

Name: _____

Reference No. : CRB0062-22
Ver. No. 1.5 (July/26/2024)

for clinical research methods

for patients

Letter of Intent

Title: A randomized, open-label, comparative study to investigate the efficacy of angiotensin receptor neprilysin inhibitors in patients with aortic stenosis after transcatheter aortic valve placement

<Instructions>

1. What is clinical research?
2. Why do we conduct this clinical study?
3. Method and duration of clinical research
4. Anticipated benefits and disadvantages of conducting this clinical study
5. Other treatment methods and anticipated benefits and disadvantages if not participating in this study
6. In the event of damage to your health
7. Participation in this clinical study is voluntary of the patient.
8. Information about this clinical study will be communicated from time to time
9. This clinical study may be discontinued
10. If you agree to participate in this study, please observe the following
11. Handling of your personal information
12. Method of Disclosure of Information on Specific Clinical Research
13. Disclosure and Viewing of Materials Related to the Conduct of Specific Clinical Research
14. Methods of storage and disposal of samples and information, etc., and secondary use of data
15. Intellectual Property Rights and Conflicts of Interest
16. What are the costs of your expenses, and how do you intend to reduce the burden of your participation in this exam?
17. Review of Specific Clinical Research (About the Clinical Research Review Board)
18. Contact information and consultation desk for the doctor in charge of the study (complaints and inquiries)

[Patient's signature line]

In participating in this exam, I have received a sufficient explanation of the above matters, received an explanation of consent, and fully understood the contents, etc., and I agree to participate in this examination.

Consent date:

Patient Name: _____

[Signature line of the substitute] (only if necessary)

Author's Name: _____

Relationship with the person:

[Doctor's signature line]

I have fully explained this study to the above patients.

Explanation date:

Affiliation:

Name: _____