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

Kitahara H, *et al*. *BMJ Open* 2025; 15:e095105. doi: 10.1136/bmjopen-2024-095105

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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

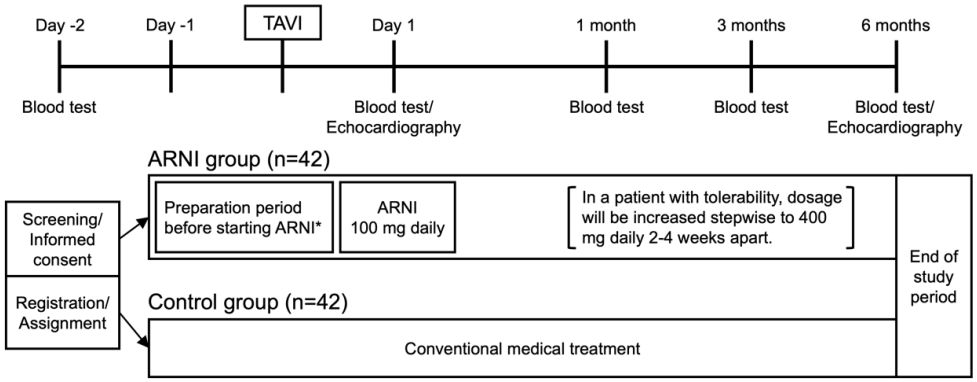
Start preoperatively (1-2 days before surgery) Bropres Tablets 4 mg (4 mg orally once a day), which is an ARB, and switch to Enrest on postoperative day 1.

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.



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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

O 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.

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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
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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: _____

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for clinical research methods

For secretariat

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Consent date:

Patient Name: _____

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

Author's Name: _____

Relationship with the person:

[Doctor's signature line]
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Explanation date:
Affiliation:
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for clinical research methods

for patients

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Consent date:

Patient Name: _____

[Signature line of the substitute] (only if necessary)
Author's Name: _____
Relationship with the person:

[Doctor's signature line]
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Explanation date:
Affiliation:
Name: _____