A multicenter, parallel-group, prospective study to evaluate the safety and efficacy of dabigatran compared with warfarin as a control in perioperative period of atrial fibrillation ablation in patients with non-valvular atrial fibrillation scheduled to undergo atrial fibrillation ablation.

Study protocol

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1. Background

Atrial fibrillation is known to be a strong risk factor of cerebral infarction and embolic shower \(^1,2\); accordingly, the Japanese "Guideline for Atrial Fibrillation Treatment (Drug Therapies) (2008 Revised Ver.)" \(^3\) recommends evaluating the risks of cerebral infarction and bleeding pertinent to anticoagulation therapy for non-valvular atrial fibrillation (NVAF), and providing warfarin therapy with PT-INR 2.0 to 3.0 (1.6 to 2.6 for patients \(\geq 70\)-years old).

Catheter ablation has been actively used to electrically cauterize lesions causing arrhythmia such as sites peripheral to the opening of the pulmonary vein for treatment of atrial fibrillation accompanied by symptoms and decreased QOL and refractory to drug treatment, or otherwise intolerable to adverse reactions of drug therapies \(^4\); catheter ablation is now positioned as an established therapy for treatment of atrial fibrillation. Up to now, anticoagulation therapy with warfarin to prevent thrombus formation has been provided as the standard of care in the perioperative period of catheter ablation.

Meanwhile, a new anticoagulant drug dabigatran, which is a direct antithrombin, has been confirmed for its efficacy and safety in atrial fibrillation patients in Study RE-LY \(^5\) in which dabigatran was compared with warfarin for preventive effects against cerebral infarction. In March 2011, the ACC/AHA/HRS Guideline was revised to add and recommend dabigatran as a drug beneficial for preventing cerebral infarction and embolic stroke in patients with non-valvular atrial fibrillation \(^6\). In Japan, dabigatran was made available in March 2011 for clinical use under the brand name of Prazaxa, which expanded the choice of anticoagulation therapies for treatment of atrial fibrillation. The benefit of dabigatran as an anticoagulation therapy in the perioperative period of catheter ablation has also been reported primarily in retrospective studies \(^7\).

However, there has been no reporting of an independent, large-scale, prospective, randomized study to evaluate the efficacy and safety of dabigatran in comparison with warfarin in the perioperative period of atrial fibrillation catheter ablation; thus, there is a need for analysis on risk factors of hemorrhagic complications as a concern of anticoagulation therapies in addition to the prevention of cerebral infarction and embolism. Also, there is a need for anticoagulation therapies to prevent or reduce such events.

Accordingly, this study is designed as a prospective intervention study in patients indicated to undergo catheter ablation for treatment of non-valvular atrial fibrillation, and it is intended to evaluate the safety and efficacy of dabigatran in comparison with warfarin as an anticoagulation therapy in the perioperative period of ablation.

2. Study objective

This study is intended to evaluate the safety and efficacy of dabigatran in comparison with warfarin as an anticoagulation therapy in the perioperative period of ablation (\(\geq 4\) weeks before and \(\geq 3\) months after ablation).
3. Overview of study drug
   Nonproprietary name: Dabigatran Etexilate Methanesulfonate
   Chemical name: Ethyl 3-\{2-\{4-(amino\}[[hexyloxy]carbonyl]imino\}methyl\}phenyl\}amino\}
methyl\}-1-methyl-1H-benzoimidazol-5-yl\}carbonyl\}\{pyridin\}-2-yl\}amino\}propanoate
   monomethanesulfonate

   Structural formula:
   ![Structural formula image]

   Molecular formula : C_{34}H_{41}N_{7}O_{5} \cdot CH_{4}O_{3}S

   [Brand name]
   Prazaxa Capsules 75 mg/Prazaxa Capsules 110 mg

   Refer to the latest package insert and Interview Form for details.

4. Indication and inclusion/exclusion criteria

   4.1 Indication
   Patients with non-valvular atrial fibrillation scheduled to undergo catheter ablation

   4.2 Inclusion criteria
   Patients meeting all of the following criteria [1] to [4] at the time of eligibility assessment:
   [1] Patients with non-valvular atrial fibrillation scheduled to undergo catheter ablation for the first
time for treatment of atrial fibrillation
   [2] Patients currently receiving or scheduled to receive dabigatran or warfarin as an anticoagulation
   therapy to prevent ischemic stroke and embolic shower attributable to atrial fibrillation
   [3] Patients aged 20 to 85 years at the time of informed consent
   [4] Patients willing and able to consent in writing

   4.3 Exclusion criteria
   Patients meeting any of the following criteria [1] to [14] at the time of eligibility assessment will be
excluded from this study (patients already receiving dabigatran or warfarin should also be checked for
the exclusion criteria).
   [1] Patients with a history of hypersensitivity to an ingredient of dabigatran or warfarin drug;
[2] Patients with severe renal disorder (creatinine clearance <30 mL/min) including dialyzed patients;

[3] Patients with a hemorrhagic symptom (thrombocytopenic purpura, bleeding tendency attributable to a vascular disorder, hemophilia and other blood coagulation disorders, patients in menstruation period, patients during surgery, gastrointestinal ulcer, urinary tract bleeding, haemoptysis, women with genital bleeding immediately following miscarriage, premature birth, or childbirth, and patients with suspected intracranial hemorrhage, etc.), patients with hemorrhagic diathesis, and patients with hemostatic disorder;

[4] Patients with organic lesion with a clinically important bleeding risk (including hemorrhagic cerebral stroke within the past 6 months);

[5] Patients in whom spine/peridural catheter is placed;

[6] Patients currently receiving itraconazole (oral agent);

[7] Women who are or may be pregnant, or currently lactating, or women who intend to conceive during enrollment in this study;

[8] Patients with a risk of bleeding (visceral tumor, diverticulitis of digestive tract, colonitis, subacute bacterial endocarditis, severe hypertension, severe diabetes mellitus, etc.);

[9] Patients with serious liver disorder;

[10] Patients who have recently undergone a central nervous system surgery or trauma;


[12] Patients currently receiving iguratimod;

[13] Patients scheduled to undergo a surgery other than ablation, or invasive procedures inappropriate for the study as determined by the investigator; or

[14] Patients otherwise inappropriate for the study as determined by the investigator.

*1: Evaluated based on the result of Cockcroft-Gault formula as follows.

- Men: \(= \frac{(140 - \text{Age}) \times \text{Body weight}}{72 \times \text{Serum creatinine level}}\)
- Women: \(= 0.85 \times \frac{(140 - \text{Age}) \times \text{Body weight}}{72 \times \text{Serum creatinine level}}\)

5. Consent of subjects

5.1 Preparation of patient information and consent form

Principal investigator shall prepare a patient information and consent form containing the following information to obtain the consent of candidate subjects to take part in this study, and shall obtain the approval of the Ethical Review Board on the patient information and consent form.

[1] Voluntary nature of subjects' enrollment in this study;

[2] The absence of penalty in any form or shape for subjects to not consent to take part in this study;

[3] Rights of subjects to withdraw their consent at any time during this study, and the absence of penalty in any form or shape for subjects to withdraw their consent;

[4] Reasons for requesting subjects to take part in this study;

[5] The purpose, objective, method, and duration of this study;
Names and titles of investigators and other study staff;

Expected benefits and anticipated disadvantages and inconvenience for taking part in this study; contents of anticipated adverse events (AE) and treatment and other actions to be provided upon occurrence of such AEs;

The fact that the cost for treatment and possible compensation will be covered by the health-insurance system, and the contents of compensation for a health hazard that may occur during this study;

Subjects' rights to obtain or review the protocol and other study-related materials upon their request, provided that such a disclosure would not violate the protection of other subjects' personal information or interfere with the originality of this study;

Alternative methods of treatment to be provided if subjects decide not to take part in this study;

Handling of personal information;

The fact that the results of this study will be publicized while the identity of individual subjects will be made untraceable;

Secondary use of data:

A possibility that the study data may be transferred to other research institutions under the condition that the Ethical Review Board approves the objective for use; provided that transfer of such information is allowable only if all of the personal information is omitted;

The absence of subjects' rights to patents and other intellectual properties generated from the results of this study;

Source of funding for this study, and the fact that subjects will not lose any of their rights or interest by taking part in this study; and

Contact information for any question or complaints.

Method of obtaining informed consent

Before the start of this study in each candidate subject, the investigator will use the patient information form to explain to the subject the descriptions specified in the preceding section, and obtain the subject's voluntary consent in writing to take part in this study. A carbon copy of the patient information and consent form will be provided to the subject, and the original copy of the consent form will be retained by the medical institution.

Remarks concerning informed consent:

The following remarks should be paid attention to when obtaining informed consent.

Investigator will use the patient information form to provide adequate briefing on this study to each candidate subject, and specify the date of patient briefing on, and name/seal or sign the form. Investigator will provide each candidate subject with adequate time and opportunity to ask questions, and then, obtain his/her voluntary consent. If a study coordinator provides a supplementary briefing, such a study coordinator will also specify the date of patient briefing on, and name/seal or sign the form.

Investigator will provide to each subject the patient information form and a copy of the consent
form with the name/seal or signature provided pertinent to above procedures [1].

[3] In no event may an investigator force subjects to take part or remain in the study, or inappropriately influence their decisions.

[4] In no event may an investigator, pertinent to patient briefing, use any term that forces or implies forcing subjects to give up their rights, or any term that pardons or implies pardoning the legal responsibilities of the Investigator or the medical institution.

[5] Pertinent to patient briefing, the investigator must use non-technical and easy-to-understand expressions as much as possible.

[6] Before obtaining a subject's consent, the investigator must provide the subject with adequate time and opportunity to ask questions about the content of the patient information form and other matters concerning the study, and adequately respond to such questions.

[7] Upon obtaining information during the study that may influence subjects' willingness to stay in the study, the investigator must explain such information to subjects, verify their intention to stay in the study, and document the record of such a briefing.

[8] If the patient information form is revised pursuant to above [7], each subject's consent to stay in the study must be obtained in writing at each such occasion.
6. Study method

6.1 Study design

This study is intended to evaluate the efficacy and safety of dabigatran as an anticoagulation therapy in the perioperative period of catheter ablation in comparison with warfarin, which is a standard therapy, in patients with non-valvular atrial fibrillation scheduled to undergo catheter ablation and currently receiving or scheduled to receive dabigatran or warfarin.

*1: Patients already receiving dabigatran and warfarin are also applicable.
*2: Timing to discontinue dabigatran (the evening of the previous day, or the morning of the day) will be determined based on the scheduled time of ablation, and patient characteristics, etc.
*3: Use heparin i.v. if the duration from discontinuation of dabigatran to ablation is expected to be prolonged (i.e., ≥18 hours).
*4: Upon confirmation of hemostasis, resume dabigatran within 18 hours of ablation.
*5: Use heparin i.v. if the duration from discontinuation of dabigatran to ablation is expected to be prolonged (i.e., ≥12 hours).
*6: Use the study drug for 3 months following ablation regardless of the CHA2DS2-VASc score. Continuation of treatment thereafter should be determined based on the CHA2DS2-VASc score. The study treatment should remain unchanged as much as possible if a decision is made to continue the treatment.
*7: During the assessment period, assessments and tests should be performed up to Month 12 visit.
6.2 Procedures for subjects’ consent, enrollment, and the start of treatment:

Procedures for subjects’ consent, enrollment, and the start of treatment are as follows.

- Investigator will use the patient information form to explain the study objective, method, and other information to each candidate subject indicated to undergo catheter ablation for treatment of atrial fibrillation and meeting the inclusion criteria and currently receiving or scheduled to receive dabigatran or warfarin as an anticoagulation therapy, and obtain written consent of the subject to take part in the study.

- Subjects should be selected seamlessly in a sequential manner as much as possible.

- Investigator will enter, in the subjects registration system, the information concerning each subject's eligibility, register the subject, and confirm the registration on screen.

- Randomization should be performed dynamically and to ensure the number of subjects on the following factors would roughly be the same between the treatment groups.
  (1) Risk factors of cerebral infarction included in the CHA2DS2-VASc score;
  (2) Disease pattern of atrial fibrillation;
  (3) Number of antiplatelet agents

Efforts should be made to randomize subjects so that the number of subjects in the warfarin group and dabigatran group would be the same in each medical institution.

- Investigator will follow up subjects and perform relevant tests during a period between 4 weeks before and 12 months after ablation.

* A subject not recovered or recovering from an adverse event at the completion or discontinuation of assessment shall be followed up for the outcome until it is confirmed to be "recovered" or "recovering," or the follow-up is no longer required as determined by the investigator.

6.3 Procedure for study treatment:

The latest package inserts and other relevant materials should be reviewed before the use of study drugs.

1) Administration of dabigatran

(1) Use of dabigatran for the first time

Dabigatran should be started no later than 4 weeks before the scheduled date of ablation.

[1] Dosage regimen of dabigatran

The dosage of dabigatran shall be 150 mg/dose BID (75 mg capsules x 2 capsules/dose x 2 doses/day); provided that, for the following subjects, 110 mg/dose BID (110 mg capsule x 1 capsule/dose x 2 doses/day) should be considered, and the drug should be carefully administered [Refer to Prazaxa package insert <Precautions for dosage and administration>].
Subjects with moderate renal impairment (creatinine clearance 30 to 50 mL/min)\(^1\)
- Subjects concomitantly receiving a P-glycoprotein inhibitor (oral agent)\(^2\)
- Subjects with a high risk of bleeding such as,
  - Subjects aged \(\geq\) 70 years
  - Subjects with a history of gastrointestinal bleeding

\(^1\): Creatinine clearance shall be calculated based on the Cockcroft-Gault formula.

**Cockcroft-Gault formula:**

\[
\text{Men: } = \frac{(140 - \text{Age}) \times \text{Body weight}}{72 \times \text{Serum creatinine level}} \\
\text{Women: } = 0.85 \times \frac{(140 - \text{Age}) \times \text{Body weight}}{72 \times \text{Serum creatinine level}}
\]

\(^2\): Refer to "[5] Contraindications and precautions for coadministration with dabigatran" in this section.

<**Prazaxa package insert, Precautions for dosage and administration**>

(1) The blood concentration of dabigatran may increase in the following patients; thus, for such patients, 110 mg/dose BID should be considered, and the drug should be carefully administered.
- Subjects with moderate renal impairment (creatinine clearance 30 to 50 mL/min)
- Subjects concomitantly receiving a P-glycoprotein inhibitor (oral agent)

(2) A hundred and ten milligram/dose BID of the drug should be considered, and the drug should be carefully administered for subjects with a high risk of bleeding such as,
- Patients aged \(\geq\) 70 years
- Patients with a history of gastrointestinal bleeding

[2] Switching from warfarin
- When switching from warfarin to dabigatran, discontinue warfarin, and then, confirm that PT-INR becomes \(<\) 2.0 before starting dabigatran.

[3] Switching from other NOAC (rivaroxaban and apixaban)
- When switching from rivaroxaban to dabigatran, do not start dabigatran within 24 hours from the discontinuation of rivaroxaban.
- When switching from apixaban to dabigatran, do not start dabigatran within 12 hours from the discontinuation of apixaban.

[4] When a dose of dabigatran is missed:
- If a dose of dabigatran is missed, the subject should take a dose as early as possible during the day, and leave at least 6 hours until the next dose. Do not take 2 doses at the same time even if a dose is missed.

[5] Contraindication and precautions for coadministration with dabigatran:
- Concomitant use of drugs specified in the drug interaction section of the Prazaxa package insert is prohibited or requires caution for coadministration [See Attachment 2].
(2) Subjects already receiving dabigatran

Verify that the current dosage of dabigatran is within the approval and in compliance with [1] Dosage regimen of dabigatran in the preceding section "(1) Use of dabigatran for the first time."

The duration of treatment with dabigatran before ablation should be ≥4 weeks at an approved dosage.

Refer to the preceding sections [4] and [5] for actions to be taken when a dose of dabigatran is missed, and contraindications and precautions for coadministration with dabigatran.

(3) Discontinuation of dabigatran before ablation, and inpatient management

Ablation shall not be performed in subjects in whom left atrial thrombus is confirmed on transesophageal ultrasound before ablation.

The timing to discontinue dabigatran will be determined based on the scheduled time of ablation.

(4) ACT management

The target ACT during ablation shall be 300 to 400 seconds. ACT will be measured at the entry of the operation room, and then routinely (in principle every 30 to 60 minutes) from the start of the operation, and then, immediately following the completion of the operation. If ACT following the completion of the operation is ≥300 seconds, protamine may be used to reverse it. Upon completion of ablation, confirm the hemostasis on the site of puncture, and resume oral dabigatran within 18 hours.

2) Administration of warfarin

(1) Use of warfarin for the first time

Subjects should receive warfarin for at least 4 weeks after PT-INR becomes ≥2.0 (≥1.6 for subjects aged ≥70 years) and before ablation.

[1] Dosage regimen of warfarin

Following the initial oral dose once daily, the dosage should be adjusted within a few days so that PT-INR meets the target level (2.0 to 3.0 in subjects aged <70 years, and 1.6 to 2.6 in subjects aged ≥70 years), and based on which, the maintenance dosage should be determined.

[2] When switching from dabigatran or other NOAC (rivaroxaban and apixaban)

When switching from dabigatran or other NOAC to warfarin, such a medication should be concomitantly used until the PT-INR following the start of warfarin therapy becomes ≥2.0 (1.6 for subjects aged ≥70 years), and dabigatran or other NOAC should be discontinued when PT-INR
exceeds 2.0 (1.6 for subjects ≥70 years).

[3] When a dose of warfarin is missed:

Subjects should be instructed to take a dose of warfarin immediately upon discovery of missed dose. When missing warfarin dose is discovered on the following day, the subject should receive the routine dose on that day (the subject should not receive 2 doses at the same time).

[4] Contraindication and precautions for coadministration with warfarin:

Concomitant use of drugs specified in the drug interaction section of the warfarin package insert is prohibited or requires caution for coadministration [See Attachment 3].

(2) Subjects already receiving warfarin

Subjects should receive warfarin for at least 4 weeks after PT-INR becomes ≥2.0 (≥1.6 for subjects aged ≥70 years) and before ablation.

(3) Administration of warfarin before ablation, and inpatient management

Ablation shall not be performed in subjects in whom left atrial thrombus is confirmed on transesophageal ultrasound before ablation.

Warfarin should be continuously given without interruption.

(4) ACT management

The target ACT during ablation shall be 300 to 400 seconds. ACT will be measured at the entry of the operation room, and then routinely (in principle every 30 to 60 minutes) from the start of the operation, and then, immediately following the completion of the operation. If ACT following the completion of the operation is ≥300 seconds, protamine may be used to reverse it.

3) Management after hospital discharge

The study drug should be orally administered for 3 months after ablation regardless of the CHA2DS2-VASc score. The administration thereafter shall be determined based on CHA2DS2-VASc scores. If the study treatment is to be continued, the study drug should remain unchanged as much as possible. Assessment and tests should be performed until Month 12 of ablation (or until the subsequent visit if the final visit is beyond Month 12).
6.4 Endpoints

1) Primary endpoint
   • Development of embolism in the perioperative period
   • Presence/absence of intracardiac blood clot on transesophageal ultrasound or intracardiac ultrasound performed immediately before ablation

2) Secondary endpoints
   • Development of major bleeding and embolism in the perioperative period
   • Development of major bleeding in the perioperative period
   • Development of all bleedings in the perioperative period
   • Development of life-threatening bleeding in the perioperative period
   • Development of major bleeding and embolism in the perioperative period, and 6-month postoperative period
   • Number of days in the hospital
   • Individual event of ischemic stroke (fatal or nonfatal), embolic shower, pulmonary embolism, acute myocardial infarction, transient ischemic attack, cardiac death (including that from bleeding), all-cause mortality, and hospitalization, and the composite endpoint comprising these events
   • NCB (net clinical benefit) determined based on a composite endpoint comprising cerebral stroke, embolic shower, pulmonary embolism, acute myocardial infarction, all-cause mortality, and major bleeding
   • All adverse events

7. Assessment and laboratory parameters

   The investigation will be in line with the following schedule. The assessment period shall last until Month 12 of ablation (or until the subsequent visit if the final visit is beyond Month 12).

   If a subject discontinues receiving a study drug due to a medical or other reason, the subject should immediately visit the hospital to receive measurements of blood pressure and pulse rate, electrocardiography, and blood tests. Adverse events confirmed at the discontinuation of study treatment should be followed up continuously.

   Also, even if the study drug is discontinued within 3 months after ablation, the subject should be continuously followed up until Month 12 of ablation to verify the clinical course of atrial fibrillation, hemorrhagic complications, embolism, and other complications of ablation.

* Cautions concerning administration of study drug

   Subjects in the dabigatran group should be monitored for dose compliance.
   Warfarin should be switched to an appropriate anticoagulant promptly in a subject in the warfarin group whose PT-INR becomes remarkably unstable as determined by the investigator.
## [Assessment and laboratory parameters]

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- **○**: To be measured after informed consent in writing and before the start of study treatment, if the subject newly receives the study drug.
- **O**: Required items
- **Δ**: Non-required items
*1 Optional time points from the day following ablation and until hospital discharge
*2 The assessments should be performed even if the visit is not on schedule (±2 weeks) due to the subject's personal reasons; provided that Month 12 assessments should be performed even if the visit is outside the window of ±2 weeks.
*3 These assessments should be performed in line with the schedule of treatment.
*4 Verify the presence/absence of left atrial appendage thrombus and spontaneous echo contrast, and measure the left atrial appendage flow velocity.
*5 Measure the left atrial dimension, left ventricular ejection fraction, interatrial septum wall thickness, left atrial volume, and left ventricular end-diastolic dimension (Data within the past 3 months is acceptable). Interatrial septum wall thickness may be measured on transesophageal echocardiogram, and will be a non-required item.
*6 Hematological tests: WBC, RBC, hemoglobin, hematocrit, and platelet count
Chemistry tests: AST, ALT, ALP, T-Bil, Cr, BUN, Na, K, Cl, albumin, total protein, total cholesterol, HDL-cholesterol, LDL-cholesterol, TG (neutral fat), and uric acid
*7 Data within 1 month before informed consent is acceptable.
*8 When switching from warfarin to dabigatran, discontinue warfarin, and then, confirm that PT-INR becomes <2.0 before starting dabigatran.
*9 Data within 3 months before informed consent are acceptable.
*10 Evaluated based on the result of Cockcroft-Gault formula as follows.

Cockcroft-Gault formula
Men: = (140 - Age) × Body weight/(72 × Serum creatinine level)
Women: = 0.85× (140 - Age) × Body weight/(72 × Serum creatinine level)

Details of the investigation and assessment variables shall be as follows.

[1] Subjects background
The following parameters will be investigated at the time of the informed consent.
Age, gender, height, body weight, BMI, abdominal circumference, timing at which the diagnosis of atrial fibrillation is given, category of atrial fibrillation (paroxysmal, prolonged, or permanent), past history/pre-existing condition [Cerebral vascular disease, coronary artery disease, heart failure (NYHA classification), myocarditis, diabetes mellitus, hypertension, gastrointestinal bleeding, intracranial hemorrhage, other hemorrhagic disease, gastrointestinal ulcer, respiratory disease], CHADS2 score, CHA2DS2-VASc score, HAS-BLED score, treatment history of atrial fibrillation (drug treatment, electrical defibrillation, surgical treatment), history of warfarin use, and concomitant medications (antiarrhythmic drug, antiplatelet agent, antidiabetic, antihypertensive agent, hypolipidemic drug, peptic ulcer drug, and non-steroidal anti-inflammatory drug)

Table: CHADS2 score; risks and point allocation 8)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S A history of cerebral stroke or transient cerebral ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>
Table: CHA2DS2-VASc score; risks and point allocation 9)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure/Left ventricular dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S A history of cerebral stroke, transient cerebral ischemic attack, and embolism</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular disease (a history of myocardial infarction, peripheral artery disease, and aortae plaque)</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65 to 74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sc Gender: Women</td>
<td>1</td>
</tr>
</tbody>
</table>

Maximum score: 9 points

Table: HAS-BLED score; risks and point allocation 10)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>H Hypertension *1</td>
<td>1</td>
</tr>
<tr>
<td>A Renal<em>2 or hepatic function abnormal</em>3 (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S A history of cerebral stroke</td>
<td>1</td>
</tr>
<tr>
<td>B Bleeding history/tendency</td>
<td>1</td>
</tr>
<tr>
<td>L Unstable INR *4</td>
<td>1</td>
</tr>
<tr>
<td>E Age &gt;65 years</td>
<td>1</td>
</tr>
<tr>
<td>D Drug addict*5 or alcoholic dependence (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

*1: Systolic blood pressure: ≥160 mm Hg  
*2: Dialysis or kidney transplantation; Serum creatinine ≥2.26 mg/dL  
*3: Chronic liver disease (liver cirrhosis, etc.), bilirubin >2 times the upper limit of normal, or AST/ALT/ALP >3 times the upper limit of normal  
*4: Unstable or high INR, or INR not reaching the therapeutic range (<60%)  
*5: Use of antiplatelet agent or non-steroidal anti-inflammatory drug

[2] Clinical course of atrial fibrillation  
Investigate the surgical technique used for ablation (pv isolation, superior vena cava isolation, linear ablation, etc.).

[3] Concomitant medications  
Investigate the regimens of antithrombotic therapy, medications for atrial fibrillation, and other concomitant medications.

[4] Investigation on hemorrhagic complications, embolism, complications of ablation, and other AEs  
Investigate AEs that occur during the study period. The details of investigation should be in compliance with section "9. Definition and handling of, and investigation on adverse events." Among all AEs, identify hemorrhagic complications, embolism, and complications of ablation, and evaluate
the cause of such events (study drug, concomitant medications, surgical procedures, etc.).

Hemorrhagic complications and embolism should include the following events.

<table>
<thead>
<tr>
<th>Category</th>
<th>Name of event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic complications</td>
<td>• Intracranial hemorrhage: Cerebral haemorrhage (except for haemorrhagic cerebral infarction), subarachnoidal hemorrhage, and subdural haemorrhage</td>
</tr>
<tr>
<td></td>
<td>• Gastrointestinal bleeding</td>
</tr>
<tr>
<td></td>
<td>• Major bleeding: Bleeding events applicable to any of the following:</td>
</tr>
<tr>
<td></td>
<td>Bleeding with $\geq 2$ g/dL decrease in hemoglobin, bleeding requiring blood transfusion of $\geq 4.5$ units, intraocular, intracranial, intraspinal, and intramuscular compartment syndrome, retroperitoneal hemorrhage, non-traumatic intraarticular hemorrhage, and hemopericardium</td>
</tr>
<tr>
<td></td>
<td>Life-threatening bleeding: Bleeding events applicable to any of the following:</td>
</tr>
<tr>
<td></td>
<td>Fatal bleeding, symptomatic intracranial hemorrhage, bleeding with $\geq 5$ g/dL decrease in hemoglobin, bleeding requiring blood transfusion of $\geq 9$ units, use of cardiotonic for bleeding, and bleeding requiring surgery</td>
</tr>
<tr>
<td></td>
<td>• Minor bleeding: Bleeding events not applicable to major bleeding</td>
</tr>
<tr>
<td></td>
<td>• Hemorrhagic death</td>
</tr>
<tr>
<td>Embolism</td>
<td>Cerebral infarction and embolic shower: Acute vessel occlusion in a limb or organ (kidney, mesenteric artery, spleen, retinae, etc.), transient cerebral ischemic attack, pulmonary embolism, and myocardial infarction</td>
</tr>
</tbody>
</table>

8. Discontinuation of study treatment and dropout
   (1) Discontinuation of study treatment
   Investigator shall change or discontinue the study treatment (anticoagulation therapy) and take other appropriate actions if a subject is applicable to any of the below. If the study treatment is discontinued, assessment and tests should be performed in accordance with section "7. Assessment and laboratory parameters" at the time of discontinuation. Also, if the study treatment is discontinued after ablation, the subject should be continuously followed up until Month 12 of ablation to verify the clinical course of atrial fibrillation, bleeding complications, embolism, and other complications of ablation.
   [1] Continuation of study treatment is not appropriate due to an adverse reaction as determined by the investigator.
   [2] Continuation of study treatment is not appropriate due to a complication during or after ablation as determined by the investigator.
   [3] Continuation of study treatment is not appropriate due to exacerbation or treatment of the underlying disease as determined by the investigator.
   [4] Continuation of study treatment is not appropriate due to exacerbation or development of
complication or occurrence of AE other than [1] to [3] as determined by the investigator.

[5] Study treatment is discontinued due to pregnancy of the subject.

[6] Study treatment is difficult to continue as determined by the investigator due to a reason other than the above.

[7] PT-INR becomes remarkably unstable in subject in the warfarin group as determined by the investigator.

[8] Change in or discontinuation of study drug is required within 3 months of ablation.

(2) Dropout

Subjects applicable to any of the following shall be considered as "dropout."

[1] Left atrial thrombus is confirmed on transesophageal ultrasound or other examinations performed before ablation, and due to which, ablation is discontinued, and thus, study treatment cannot be continued.


[3] The subject stops visiting the study site.

9. Definition and handling of, and investigation on adverse events

9.1 Definition concerning adverse events

(1) Definition of adverse events

Adverse events shall be all events applicable to the following definition:

"An adverse event is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product, and does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product."

If an abnormal change is observed in clinical laboratory value, vital sign, or other relevant test value along with a symptom, sign, or disease, such a symptom, sign, or disease shall be reported as an adverse event. A test value not specified in the study protocol shall be reported as additional information on the adverse event.

(2) Definition of serious adverse event:

A serious adverse event is any untoward medical occurrence that:

[1] Results in death
[2] Is life-threatening
[3] Requires inpatient hospitalization or prolongation of existing hospitalization
[4] Results in persistent or significant disability/incapacity
[5] Is a congenital anomaly/birth defect
[6] Is a medically important event or reaction

Medically important event or reaction specified in [6] means any medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or
may require intervention to prevent one of the other outcomes listed in [1] to [5] above.

(3) Definition of adverse reaction

AEs for which a causal relation with the study drug is determined to be at a level other than "unrelated" as defined in section "9.3 Investigation on adverse events" shall be handled as an adverse reaction attributable to the study drug.

9.2 Handling of adverse events upon occurrence of an adverse event

(1) Handling of subjects

Upon occurrence of an adverse event associated with a subjective symptom, objective sign, or test value (vital sign, clinical laboratory), the investigator shall promptly provide appropriate intervention to the subject, and monitor and confirm the clinical course and outcome.

(2) Reporting to the head of the medical institution, and to the Ministry of Health, Labour and Welfare and the pharmaceutical company:

Principal investigator shall notify the head of the medical institution promptly upon occurrence of an event that may be applicable to the definition specified in section "9.1.(2) Definition of serious adverse event." Adverse events should be reported in accordance with the procedures set out by each study site.

Also, the investigator should report to the Minister of Health, Labour and Welfare (spontaneous reporting) in accordance with the Drug and Medical Device Safety Information Reporting System pursuant to the Pharmaceutical Affairs Law, and also cooperate with the pharmaceutical company's reporting of adverse reactions (corporate reporting).

9.3 Investigation on adverse events

On each adverse event, the investigator should investigate the name, date of occurrence, severity, seriousness (in accordance with section "9.1.(2) Definition of serious adverse event"), intervention provided, outcome, and the date of confirmed outcome, and evaluate and determine the causal relation between the event and the study drug, concomitant medication, and surgical operation.

[Criteria for severity assessment]

Each adverse event should be evaluated for the following 3 levels of severity based on the most severe level during the period in which the adverse event is confirmed.

<table>
<thead>
<tr>
<th>Category</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Confirmed sign or symptom, which does not interfere with normal daily living, nor require intervention</td>
</tr>
<tr>
<td>Moderate</td>
<td>Confirmed discomfort that interferes with normal daily living, or affects a clinical state, requiring intervention</td>
</tr>
<tr>
<td>Severe</td>
<td>Disables normal daily living, or otherwise poses a serious clinical impact.</td>
</tr>
</tbody>
</table>

[Criteria for assessment of outcome]

Outcomes should be evaluated for the following 5 grades. If the outcome is recovered, recovering,
or death, the date on which the outcome is confirmed shall be the date of confirmed outcome. If the follow up is cut off while the outcome is either unrecovered or unknown, the date on which the investigator last confirmed the outcome shall be the date of confirmed outcome, and the reason for cutting off the follow up or the reason for unknown outcome should be specified in the comment section.


[Assessment criteria for intervention to study treatment]

[Assessment criteria for causal relation of AE]
Causal relation between the event and the study drug, concomitant medication, and surgical operation shall be determined based on the following 4 categories and in reference to the definitions thereof. Also, the reason for the judgment should be specified in the comment section.

<table>
<thead>
<tr>
<th>Category</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td>An event for which a reasonable temporal relationship with the drug (procedures) exists, and there is no other factor that can be described as a cause of the event</td>
</tr>
<tr>
<td>Probably related</td>
<td>An event which is unlikely attributable to a cause other than the drug (procedures)</td>
</tr>
<tr>
<td>Possibly related</td>
<td>An event which is likely attributable to a cause other than the drug (procedures), but a causal relation with the drug (procedures) cannot be ruled out</td>
</tr>
<tr>
<td>Unrelated</td>
<td>An event for which there is a factor other than the drug (procedures) that can be described as a cause of the event, or there is no reasonable temporal relationship with the drug (procedures)</td>
</tr>
</tbody>
</table>

9.4 Follow-up of adverse events
A subject not recovered or recovering from an adverse event at study discontinuation shall be followed up for the outcome until it is confirmed to be "recovered" or "recovering," or the follow-up is no longer required as determined by the investigator.

9.5 Anticipated adverse reactions
Refer to the latest package inserts or other materials of the study drug.
Bleeding [gastrointestinal bleeding (1.6%) intracranial hemorrhage (incidence unknown), etc.] and interstitial pneumonia (incidence unknown) have been reported as important adverse reactions of the study drug. Other adverse reactions that have been reported to date include dyspepsia, gastroesophagitis, nausea, abdominal discomfort, upper abdominal pain, epigastric discomfort, vomiting, gastrointestinal ulcer, nasal bleeding, subcutaneous hemorrhage, hematuria, chest pain, and edema.
10. Protocol deviation and amendment

10.1 Protocol deviation

In no event may an investigator deviate from or change the study protocol before the approval of the head of the medical institution given based on the recommendation of the Ethical Review Board unless otherwise such a deviation is medically inevitable and required as an urgent action to prevent a potential hazard in a subject.

10.2 Protocol amendment

Study Owner shall amend the study protocol upon discussion with a study group or other relevant organization if such an amendment is determined to be essential. The contents of the amendment shall be notified to each study site. Principal investigator of each study site shall submit the amended protocol to the Ethical Review Board of the medical institution for its review. The informed consent form should be promptly amended if determined to be necessary upon the protocol amendment, and with which, consent to remain in the study should be obtained from subjects who have consented to take part in the study based on the informed consent form before amendment.

If a site-specific protocol amendment is required, the principal investigator of the study site shall report the contents of such an amendment to the Study Owner, and upon approval of the Study Owner, obtain the approval of the site's Ethical Review Board.

11. Study termination/discontinuation/interruption

11.1 Study discontinuation or interruption

Study Owner may discontinue this study upon discovery of important safety or efficacy information related to this study. Upon decision to discontinue or interrupt this study, the Study Owner shall promptly report to the heads of all study sites in writing along with the reason for such a decision.

11.2 Study termination, discontinuation or interruption at an individual study site

Principal investigator shall promptly notify the Study Owner upon study termination, discontinuation or interruption at the study site. Also, if the study is discontinued or interrupted at the site based on its own decision or reason, the principal investigator shall report to the Study Owner in writing along with the reason for such a decision.

12. Study period

March 2014 to February 2017 (End of enrollment: October 2015)

13. Method of data tabulation and statistical analysis

A detailed statistical analysis plan shall be specified separately in the "Statistical analysis plan," and based on which, the analysis shall be performed.
The proportion of subjects with each background factor will be calculated, and elementary statistics will be calculated for continuous data. The frequency and incidence of bleeding complications, embolism, and other adverse events shall be computed.

Subjects shall be sorted based on the presence/absence of each event, and their background characteristics will be compared. Events will be explored for their relations with baseline patient characteristics and test values after the start of treatment (marker).

14. Target sample size, and the rationale therefor

Target sample size: 450 subjects (225 in each group)

Rationale:

The study was started under an assumption that the study sites are capable of enrolling 1,000 subjects; however, due to expanded choice of anticoagulants and change in medical environment, subjects' consent became very difficult to obtain because of warfarin as a control used in the study, and such a trend is ongoing in an accelerated fashion.

According to a clinical study "J-ROCKET AF" conducted in Japanese patients, the annual incidence of the primary endpoint in the safety analysis set among subjects receiving the study drug was 18.04%/year in the rivaroxaban group and 16.42%/year in the warfarin group, and the incidence of important bleeding was 3.00%/year and 3.59%/year, respectively, and that of non-important but clinically relevant bleeding was 15.42%/year and 12.99%/year. In regard to the primary efficacy endpoint, the annual incidence in the per-protocol set among subjects receiving the study drug was 1.26%/year and 2.61%/year, respectively, while that of all cerebral stroke (ischaemic or hemorrhagic) was 1.20%/year and 2.50%/year, and that of ischemic stroke was 0.80%/year and 2.00%/year 11).

Thus, the enrollment of ≥400 subjects (200 in each group) in this study should enable generation of at least 1 subject with each event in each group during the 1-year assessment period, and thus, enable safety and efficacy comparison between the treatment groups; therefore, the target sample size will be changed from 1,000 to 450 subjects considering dropouts and the current state of enrollment.

15. Consideration of human rights and safety of and disadvantages to subjects

15.1 Consideration of subjects' human rights

The records and documents on subjects associated with this study shall be handled with care under the responsibility of each investigator and in consideration of subjects' confidentiality. For data reporting, subjects’ identification codes will be used to anonymize subjects. The protection of subjects' privacy will be fully considered for samples to be analyzed by external laboratories. In no event shall the data of subjects obtained in this study be used for any purpose other than for this study. In no event will study results to be publicized include contents by which a subject's identity is traceable.
15.2 Consideration of subjects' safety
Investigators shall adequately consider subjects' safety during this study. Appropriate actions will be taken promptly upon occurrence of a health hazard in a subject.

15.3 Benefits and disadvantages to subjects
This study will be conducted under the same contents and schedule as ordinary clinical practice. Adequate cautions will be taken in anticoagulation therapy for prevention of cerebral stroke and embolism in subjects with atrial fibrillation and the occurrence of bleeding complications pertinent to this study. While there won't be any additional physical burden on subjects taking part in this study, treatment, diagnosis, and tests need to be performed in line with a strict visit schedule. There won't be any additional cost for subjects to take part in this study.

16. Cost to subjects
Drug therapies and tests/examinations in this study will be provided within the scope of ordinary health insurance treatment, and covered by each subject's national health insurance.

17. Treatment of and compensation for health hazard
Treatment cost for a health hazard associated with this study shall be covered by the national health insurance.
A health hazard attributable to an adverse reaction of drugs used in this study despite proper usage shall be subject to the Fund to Support Patients with Adverse Drug Reaction.
Meanwhile, clinical study insurance will be purchased as a measure to compensate for the health hazard associated with this study.

18. Compliance to Declaration of Helsinki and ethical guidelines
This study will be conducted in compliance with Declaration of Helsinki (Fortaleza General Conference dated October 16, 2013), Ethical Guidelines for Clinical Studies (Fully-amended Ver. dated July 31, 2008), and this study protocol.

19. Storage of records
Medical institutions taking part in this study shall assign a relevant storage manager for this study, and appropriately retain study-related records and materials for 5 years from the termination or discontinuation of this study; provided that the duration of storage may be extended upon agreement with the Study Owner.
20. Monitoring

Medical institutions taking part in this study and investigators shall cooperate with monitoring by study support secretariat (including monitoring staff's source document verification at the medical institution) to maintain and guarantee the reliability of the study and its records. The contents and procedures of monitoring conducted by the study support secretariat shall be specified in the operating procedures to be separately prepared.

21. Study fund, and conflict of interest

This study is funded by Boehringer Ingelheim. There is no "potential conflict of interest" that could affect the results and interpretation of this study pertinent to planning, execution, and reporting. It is hereby represented and warranted that in no event will the conduct of this study cause the loss of the rights or benefits to which subjects taking part in the study are entitled.

22. Release of study results

The results of this study shall be released at an academic conference, medical journal, or other venues or means selected upon discussion at Research Group of Anticoagulation Therapy for NVAF Ablation.

23. Study organization

23.1 Study owner

In charge of overall study management

Kazutaka Kiyonuma, Department of Cardiovascular Medicine, Tsukuba University Hospital

See Attachment for details of the study organization.

24. Reference material and literature

[Reference material]

1) Ethical Guidelines for Clinical Studies (MHLW Notification dated July 30, 2003, and amended as of July 31, 2008)

[Reference literature]


2) Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke...


A multicenter, parallel-group, prospective study to evaluate the safety and efficacy of dabigatran compared with warfarin as a control in perioperative period of atrial fibrillation ablation in patients with non-valvular atrial fibrillation scheduled to undergo atrial fibrillation ablation.

Statistical analysis plan

Version 1.0 (2016/12/2)
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1 Study objective
This study is intended to evaluate the safety and efficacy of dabigatran in comparison with warfarin as an anticoagulation therapy in the perioperative period of ablation.

2 Overview of study plan
Subjects: Patients with non-valvular atrial fibrillation scheduled to undergo catheter ablation.

Intervention: Dabigatran (Dabigatran regimen will be started at ≥4 weeks before ablation, and continued for at least 3 months following ablation.)

Control: Warfarin (Warfarin regimen will be started at ≥4 weeks before ablation, and continued for at least 3 months following ablation.)

Outcome: Development of embolism in the perioperative period*
Presence/absence of intracardiac blood clot on transesophageal ultrasound or intracardiac ultrasound performed immediately before ablation

*The perioperative period is herein defined as a period between 4 weeks before and 3 months after ablation.

Study design: Randomized, open-label, parallel-group, active-control study

After screening (for eligibility assessment), subjects will be randomized, and patient background characteristic data at the time (described as "upon enrollment" in the case report forms) will be obtained. Thereafter, subjects will receive the same study drug (dabigatran or warfarin) until ablation (≥4 weeks), and for at least 3 months after ablation, and will be followed up for 12 months after ablation.

Assessment timepoints will be 8 to 6 weeks before ablation (optional), 4 weeks before ablation, on hospital admission, before ablation on the day of ablation, on hospital discharge, and 4 weeks, and 3, 6, and 12 months after ablation. Assessment and measurement variables at each timepoint shall be as specified in the following chart.
<table>
<thead>
<tr>
<th></th>
<th>Outpatient (-8 to -6 weeks)</th>
<th>-4 On admission</th>
<th>Before ablation on the day of ablation</th>
<th>Before discharge</th>
<th>Week 4</th>
<th>Mont h 3</th>
<th>Mont h 6</th>
<th>Mont h 12</th>
<th>Early termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examination</td>
<td>○</td>
<td>○</td>
<td>Perform as necessary</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Subjects background</td>
<td>○</td>
<td>○</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration of study drug</td>
<td>●</td>
<td>△</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, pulse rate, and heart rate</td>
<td>●*7</td>
<td>△</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Transesophageal echocardiography</td>
<td>△*4</td>
<td>○</td>
<td>△</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Transthoracic echocardiography</td>
<td>○*5</td>
<td>△</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>ECG</td>
<td>●*7</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Holter ECG</td>
<td>Δ*7</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>Head MRI</td>
<td>Δ</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>General hematological test</td>
<td>●*7</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Blood chemistry test*6</td>
<td>●*7</td>
<td>○</td>
<td>○</td>
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<tr>
<td>D-dimer</td>
<td>●*7</td>
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<tr>
<td>APTT and PT-INR</td>
<td>●*7</td>
<td>△*8</td>
<td>○*8</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>BNP</td>
<td>●*7</td>
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<tr>
<td>TSH, FT3, FT4</td>
<td>●*7</td>
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<td>○</td>
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<td>○</td>
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<tr>
<td>CLC*10</td>
<td>●*7</td>
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<tr>
<td>Dose compliance</td>
<td>Δ</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<td>○</td>
<td>○</td>
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<tr>
<td>Clinical course of atrial fibrillation</td>
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<td>○</td>
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<td>○</td>
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<tr>
<td>Concomitant medications</td>
<td>○</td>
<td>Δ</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Hemorrhagic complications, embolism, and complications of ablation</td>
<td>○</td>
<td>Δ</td>
<td>○</td>
<td>○</td>
<td>○</td>
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</tbody>
</table>
3 Statistical analysis set

3.1 Efficacy analysis set

ITT (intention-to-treat) group, that is all subjects randomized, will be defined as the primary efficacy analysis set. Subjects randomized but withdrawing consent before ablation or ended up not receiving a randomized study drug at all will be excluded. Subjects not evaluated for the primary endpoints (presence/absence of embolism, and presence/absence of left atrial thrombus) will also be excluded.

PPS (Per protocol set), that is, subjects meeting the study protocol, will be defined as the secondary efficacy analysis set. Subjects found to be ineligible for the study, subjects for whom the duration between randomization and ablation is less than 4 weeks, and subjects not receiving a study drug for ≥3 months after ablation will be excluded from ITT. Efficacy analysis will be performed on these 2 analysis sets.

3.2 Safety analysis set

Subjects who are randomized and receive at least 1 dose of dabigatran or warfarin will be included in the safety analysis set; provided that subjects withdrawing consent before ablation will be excluded.

3.3 Analysis set for marker evaluation

All subjects randomized and evaluated for "presence/absence of embolism,” a primary endpoint, and whose marker is measured will be defined as the analysis set for marker evaluation. Subjects randomized but withdrawing consent before ablation or ended up not receiving a randomized study drug at all will be excluded.

4 Tabulation of subject composition

According to the declaration of CONSORT 2010, the number of subjects discontinuing the study during a period between the screening (for eligibility assessment) and randomization
(upon enrollment) will be calculated. The number of subjects discontinuing or dropping out of the study after randomization and before ablation will be determined for each randomized group and each subgroup stratified by the reason for discontinuation/dropout. The number of subjects discontinuing or dropping out of the study no later than 3 months following ablation will be determined for each randomized group and each subgroup stratified by the reason for discontinuation/dropout. The number of subjects discontinuing or dropping out of the study in 3 months of ablation or later but before 6/12 months following ablation will be determined for each randomized group and each subgroup stratified by the reason for discontinuation/dropout.

The reason for study discontinuation shall be tabulated based on the "Reason for discontinuation of study treatment" specified in Case Report Form: Discontinuation.

The reason for dropout shall be tabulated based on the "Reason for dropout" specified in Case Report Form: Discontinuation.

5. Analysis on data at randomization

Summary statistics to be presented for numerical data shall be the number of subjects, arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, and maximum. Summary statistics to be presented for character data shall be the number and proportion of subjects.

Intergroup comparison of numerical data will be presented for p value based on unpaired t-test and Wilcoxon rank-sum test. Intergroup comparison of character data will be presented for p value based on chi-square test and Fisher's exact test.

5.1 Demographic characteristics

[Case report form: Enrollment (for randomization)]

Age
Gender
Height
Body weight
BMI (body-mass index) = Body weight kg / (height m)²
Abdominal circumference

5.2 Underlying disease

[Case report form: Enrollment (for randomization)]

Duration of atrial fibrillation (defined as the number of days between the month in which
atrial fibrillation was diagnosed and the date of randomization)

Category of atrial fibrillation (paroxysmal, prolonged, or permanent)

Treatment history of atrial fibrillation (drug treatment, electrical defibrillation, surgical treatment [other than ablation], none)

Note: In the categorization, "/" means exclusive event, and [ , ] means compounding events.

5.3 Past history

[Case report form: Enrollment (for randomization)]

Cerebral vascular disease

Breakdown (cerebral infarction, transient ischemic attack, cerebral hemorrhage, subarachnoidal hemorrhage, and others)

Coronary artery disease

Breakdown (myocardial infarction, angina pectori, others)

Embolic shower

Gastrointestinal bleeding

Gastrointestinal ulcer

Other hemorrhagic diseases

Note: In the categorization, "/" means exclusive event, and [ , ] means compounding events.

5.4 Pre-existing conditions

[Case report form: Enrollment (for randomization)]

Heart failure

Breakdown (congestive heart failure, and others)

NYHA classification (I/ II/ III/ IV)

Vascular disease

Breakdown (peripheral artery disease, aortae plaque, and others)

Renal function abnormal

Hepatic function abnormal

Breakdown (chronic liver disease, and others)

Alcoholic dependence

Diabetes mellitus

Hypertension

Myocarditis

Respiratory disease

Other complications

Note: In the categorization, "/" means exclusive event, and [ , ] means compounding events.
5.5  Previous use of anticoagulation therapy
[Case report form: Enrollment (for randomization)]
- Presence/absence of previous warfarin use
- Presence/absence of previous anticoagulant use before randomization
- Type of anticoagulants (dabigatran/warfarin/rivaroxaban/apixaban/others)
- Presence/absence of unstable INR
- Breakdown [unstable/high INR, INR not reaching the therapeutic range (<60%)]
Note: In the categorization, "/" means exclusive event, and [, ] means compounding events.

5.6  Concomitant medications
[Case report form: Enrollment (for randomization)]
- Presence/absence of antiplatelet use
- Breakdown (aspirin, clopidogrel, ticlopidine, cilostazol, eicosapentaenoic acid, and others)
- Presence/absence of NSAIDs use
Note: In the categorization, "/" means exclusive event, and [, ] means compounding events.

5.7  Cardiac function
[Case report form: Enrollment (for randomization)]
- LVEF
- Inspection method (echocardiogram/others)
Note: In the categorization, "/" means exclusive event, and [, ] means compounding events.

5.8  Renal function
[Case report form: Enrollment (for randomization)]
- Serum creatinine
  - Creatinine clearance (Calculate as follows).
    - Men: (140 - Age) × Body weight/(72 × Serum creatinine level)
    - Women: 0.85× (140 - Age) × Body weight/(72 × Serum creatinine level)
  - e-GFR [mL/min/1.73m²] (Calculate as follows).
    - Men: 194 × (Serum creatinine) - 1.094 × Age - 0.287
    - Women: e-GFR (for Men) × 0.739

5.9  Risk score of embolism and bleeding
[Case report form: Enrollment (for randomization)]
- CHADS2 score
Defined as Congestive heart failure (1 point) + Hypertension (1 point) + Age ≥75 years (1 point) + Diabetes mellitus (1 point) + History of cerebral stroke or transient ischemic attack (2 points)
[Minimum: 0 point, Maximum: 6 points]

CHA2DS2-VASc score
Defined as Congestive heart failure or left ventricular dysfunction (1 point) + Hypertension (1 point) + Aged ≥75 years (2 points) + Diabetes mellitus (1 point) + History of cerebral stroke or transient ischemic attack or embolism (2 points) + Vascular disease: History of myocardial infarction, or pre-existing peripheral artery disease or aortae plaque (1 point) + Aged 65 to 74 years (1 point) + Gender: Women (1 point).
[Minimum: 0 point, Maximum: 9 points]

HAS-BLED score
Defined as Hypertension*1 (1 point) + Renal function abnormal*2 (1 point) + Hepatic function abnormal*3 (1 point) + History of cerebral stroke (1 point) + Bleeding history and tendency (1 point) + Unstable INR*4 (1 point) + Age >65 years (1 point) + Drug dependence*5 (1 point) + Alcoholic dependence (1 point)
*1: Systolic blood pressure ≥160 mmHg
*2: Dialysis or kidney transplantation, and serum creatinine ≥2.26 mg/dL
*3: Chronic liver disease (liver cirrhosis, etc.), bilirubin >2 times the upper limit of normal, or AST/ALT/ALP >3 times the upper limit of normal
*4: Unstable or high INR, or INR not reaching the therapeutic range (<60%)
*5: Use of antiplatelet agent or non-steroidal anti-inflammatory drug
[Minimum: 0 point, Maximum: 9 points]

5.10 Vital signs
[Case report form: Enrollment (for baseline data)]
Systolic and diastolic blood pressures
Pulse rate
Heart rate

5.11 Test value
[Case report form: Enrollment (for baseline data)]
Hematological test
WBC
RBC
Hemoglobin
Hematocrit
Platelet count

Chemistry tests
AST
ALT
ALP
Total bilirubin
BUN
Na
K
Cl
Albumin
Total protein
Total cholesterol
HDL-C
LDL-C  Use values based on direct method if available, or else use values based on indirect method)
Neutral fat
Uric acid

Coagulation factor
D-dimer
APTT
PT-INR

Cardiac function
BNP

Thyroid function
TSH
FT₃
FT₄

ECG
Presence/absence of abnormality
Breakdown (atrial fibrillation, atrial flutter, sick sinus syndrome, atrio-ventricular block II, atrio-ventricular block III, right bundle branch block, left bundle branch block, WPW syndrome, change in ST, change in T-wave, abnormal Q wave, supraventricular premature contraction, premature ventricular
contraction, and others)

Holter ECG
  Presence/absence of abnormality
  Breakdown (atrial fibrillation, atrial flutter, and others)
  Atrial fibrillation rate

Transesophageal echocardiography and intracardiac ultrasound
  Test method (transesophageal echocardiogram/intracardiac ultrasound)
  Presence/absence of abnormality
  Breakdown (confirmed left atrial thrombus, confirmed spontaneous echo contrast in the left atrium, and others)
  Left atrial appendage flow velocity

Transthoracic echocardiography
  Left atrial dimension
  Wall thickness of interatrial septum
  Left ventricular end-diastolic dimension
  Left atrial volume
  Left atrial capacity coefficient (automatic ticketing)

Head MRI
  Presence/absence of abnormality

Note: In the categorization, "/" means exclusive event, and [ , ] means compounding events.

6 Tabulation and analysis of data related to catheter ablation
[Case report form: Date of ablation - Ablation before the date of ablation]

6.1 Statistical variables
  Presence/absence of ablation
  Reason for discontinuation of ablation (left atrial thrombus, others)
  Ablation technique [pulmonary vein isolation (high-frequency ablation), pulmonary vein isolation (cryocautery), superior vena cava isolation (high-frequency ablation), linear ablation of the isthmus between the tricuspid valve and inferior vena cava (high-frequency ablation), linear ablation of the isthmus between the tricuspid valve and inferior vena cava (cryocautery), linear ablation of the left atrium (high-frequency ablation), linear ablation of the left atrium (cryocautery), others (high-frequency ablation), and others (cryocautery)]

6.2 Method of analysis
  The proportion of each breakdown and its 95% confidence interval will be calculated for each treatment group. Normal approximation and score method will be used for the
calculation of 95% confidence interval. Chi-square test and Fisher's exact test will be performed for the intergroup comparison of the proportion.

7 Statistical analysis on efficacy data

7.1 Primary endpoint

1) Development of embolism in the perioperative period
   Definition: [Event applicable to "embolism" as an AE category in Case Report Form, and occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation]
   Only the events assessed by event adjudication shall be considered as adverse events.

2) Presence/absence of left atrial thrombus on transesophageal or intracardiac ultrasound before ablation
   Definition: [Case report form: Presence/absence of left atrial thrombus before ablation on the scheduled date of ablation]

7.2 Method of analysis for primary endpoint

1) The incidence of embolism and its 95% confidence interval will be calculated for each treatment group. Normal approximation and score method will be used for the calculation of calculate 95% confidence interval. Chi-square test and Fisher's exact test will be performed for the intergroup comparison of the incidence of embolism. Also, time to occurrence of embolism (days) will be plotted for Kaplan-Meier estimate in each group, and compared between groups using a Log-rank test. Moreover, a univariate Cox regression (group effect only) will be used to calculate the univariate hazard ratio of dabigatran to warfarin, and its 95% confidence interval. Furthermore, a multivariate Cox regression with factors including compared groups, the category of atrial fibrillation, age, gender, and CHADS2 score, will be used to calculate the hazard ratio of dabigatran to warfarin, and its 95% confidence interval.

2) The incidence of left atrial thrombus before ablation and its 95% confidence interval will be calculated for each treatment group. Normal approximation and score method will be used for the calculation of calculate 95% confidence interval. Chi-square test and Fisher's exact test will be performed for the intergroup comparison of the incidence of left atrial thrombus.

While 2 primary endpoints are set out, no adjustment for multiplicity will be performed.
7.3 **Secondary endpoints**

Only the events assessed by event adjudication shall be considered as adverse events.

1) **Occurrence of major bleeding and embolism in the perioperative period**

Definition (major bleeding): [Events other than "Other bleeding" in "Details of bleeding events" and other than "Bleeding events other than above" in "Status of bleeding" in Case report form: Adverse event, and occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation]

Definition (embolism): [Event applicable to "embolism" as an AE category in Case Report Form, and occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation]

Occurrence of either of these events will be defined as endpoint.

2) **Occurrence of major bleeding in the perioperative period**

Definition: [Events other than "Other bleeding" in "Details of bleeding events" and other than "Bleeding events other than above" in "Status of bleeding" in Case report form: Adverse event, and occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation]

3) **Occurrence of any bleeding in the perioperative period**

Definition: [Event applicable to "bleeding event" as an AE category in Case Report Form, and occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation]

4) **Occurrence of life-threatening bleeding in the perioperative period**

Definition: [Event applicable to "bleeding event" as an AE category and "life-threatening" as a seriousness category in Case Report Form: AE, and occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation]

5) **Occurrence of major bleeding and embolism in the perioperative period, and until postoperative month 6**

Definition: [Event applicable to "bleeding event" or "embolism" as a category in Case Report Form: AE, and occurred no earlier than 4 weeks before ablation and no later than 6 months after ablation]

6) **Number of days in the hospital**
Definition: [Case report form: Number of days from "Date of hospital admission" to "Date of discharge"]

7) A composite endpoint comprising ischemic stroke (fatal or nonfatal), embolic shower, pulmonary embolism, acute myocardial infarction, transient ischemic attack, cardiovascular death (including that from bleeding), all-cause mortality, and hospitalization
   Definition: [Events applicable to "embolism" as an AE category, or "death" as an outcome category, or "Requires inpatient hospitalization or prolongation of existing hospitalization" as a seriousness category, or "hospitalization or prolongation of existing hospitalization" as an other intervention category in Case Report Forms]

8) NCB (net clinical benefit) determined based on a composite endpoint comprising cerebral stroke, embolic shower, pulmonary embolism, acute myocardial infarction, all-cause mortality, and major bleeding
   Definition: [Events other than "Other bleeding" as a category of "Details of embolism"], all-cause mortality [Death in Case Report Form: Outcome], or Major bleeding [Case Report Form: AE Details of bleeding events], or "Bleeding events other than above" in "Status of bleeding"

   Net Clinical Benefit should be calculated based on the following formula
   \[
   \{\text{Intergroup difference in the incidence of thromboembolism or all-cause mortality}\} - 1.5 \times \{\text{Intergroup difference in the incidence of major bleeding}\}
   \]
   The intergroup difference shall be dabigatran group minus warfarin group.

9) Recurrence of atrial fibrillation in the perioperative period
   Definition (1): [Atrial fibrillation detected on ECG no earlier than 4 weeks before ablation and no later than 3 months after ablation based on "Presence/absence of atrial fibrillation" in clinical course of atrial fibrillation, "Atrial fibrillation" in abnormal ECG findings, or "Atrial fibrillation" in abnormal finding of Holter ECG in Case Report Forms]
   Definition: [Event applicable to "recurrence of underlying disease" as an AE category in Case Report Form, and occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation]

7.4 Method of analysis for secondary endpoints
Above 1) to 4) are restricted to the perioperative period; for which, verify that the applicable events occurred no earlier than 4 weeks before ablation and no later than 3 months after ablation. Define the presence/absence of events for each secondary endpoint, calculate the incidence of the event for each treatment group, and perform chi-square test and Fisher's exact test to verify the difference. Furthermore, calculate a univariate risk ratio of dabigatran group to warfarin group, as well as its 95% confidence interval.

Events applicable to 5) are those that occur in the perioperative period plus within 6 months postoperative; therefore, verify that the events occurred no earlier than 4 weeks before ablation and no later than 6 months (180 days) after ablation, and calculate the incidence of each applicable event in each treatment group, and perform chi-square test and Fisher's exact test to verify the difference. Furthermore, calculate a univariate risk ratio of dabigatran group to warfarin group, as well as its 95% confidence interval.

The number of days in the hospital in 6) should be calculated for summary statistics (number of subjects, arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, and maximum), and also, 95% confidence interval on the mean number of days in the hospital should be calculated (using normal approximation and score method). The difference in the number of days in the hospital should be verified with unpaired t-test and Wilcoxon rank-sum test.

The composite endpoint specified in 7) should be calculated for the incidence in each treatment group, and the difference should be verified with chi-square test and Fisher's exact test. Furthermore, calculate a univariate risk ratio of dabigatran group to warfarin group, as well as its 95% confidence interval.

Net Clinical Benefit for thromboembolism or major bleeding associated with all-cause mortality as per 8) should be calculated based on the following formula.

\[
\text{Intergroup difference in the incidence of thromboembolism or all-cause mortality} - 1.5 \times \text{Intergroup difference in the incidence of major bleeding}
\]

The intergroup difference shall be dabigatran group minus warfarin group.

For recurrence of atrial fibrillation in the perioperative period specified in 9) above, calculate the recurrence rate in each group, and perform chi-square test and Fisher's exact test to verify the difference between the groups. Furthermore, calculate a univariate risk ratio of dabigatran group to warfarin group, as well as its 95% confidence interval.
7.5 Subgroup analysis

The same analysis as above on the following subgroups should be performed exclusively on the primary endpoints (7.1 and 7.2).

- Age (<65 years, ≥65 years)
- Age (<65 years, 65 to 74 years, ≥75 years)
- Gender
- BMI (<25, ≥25)
- Category of atrial fibrillation (paroxysmal, prolonged, or permanent)
- CHADS2 score (0-6 points)
- CHAD2DS2-VASc score (0-9 points)
- HAS-BLED score (0-9 points)

Risk score will be handled as a character variable.

8 Statistical analysis on safety data

8.1 Safety endpoints

Presence/absence of bleeding event [Events categorized as "Bleeding event" in Case report form: AE]

- Cerebral haemorrhage, subarachnoidal hemorrhage, subdural haemorrhage, upper gastrointestinal haemorrhage, lower gastrointestinal hemorrhage, intraocular haemorrhage, myelapoplexy, compartment syndrome (muscle hemorrhage), Retroperitoneal hemorrhage, non-traumatic intraarticular hemorrhage, hemopericardium, and other bleedings Based on "Details of bleeding events" in Case report form: Adverse event]

- Bleeding with ≥2 g/dL decrease in hemoglobin, bleeding with ≥5 g/dL decrease in hemoglobin, bleeding requiring blood transfusion of ≥4.5 units, bleeding requiring blood transfusion of ≥9 units [Based on "Status of bleeding" in Case report form: Adverse event]

- Fatal bleeding, symptomatic intracranial hemorrhage, use of cardiotonic for bleeding, bleeding requiring surgical operation, bleeding other than the above [Based on "Status of bleeding" in Case report form: Adverse event]

- All-cause mortality [Defined by the outcome of death in Case report form: Adverse event]

- Serious adverse event [Events for which the seriousness category is "Serious" in Case report form: Adverse event]
form: Adverse event]
All adverse events

8.2 Method of analysis for safety endpoints
All data should be handled as binary (presence/absence), and its incidence and 95% confidence interval should be calculated for each treatment group, and the difference between which should be verified with chi-square test and Fisher's exact test.

8.3 Vital signs and test value
Vital signs, hematological test values, chemistry test values, cardiac function (BNP, LVEF), renal function (serum creatinine, creatinine clearance, and eGFR), thyroid function, coagulation factors (D-dimer, APTT/PT-INR) will be analyzed.

8.4 Method of analysis for vital signs and test values
Present the summary statistics at assessment timepoints (4 weeks before ablation, on hospital admission, on hospital discharge, and 4 weeks, and 3, 6, and 12 months of ablation) in each randomized group.

Summary statistics to be presented for numerical data shall be the number of subjects, arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, and maximum. Summary statistics to be presented for character data shall be the number and proportion of subjects.

9 Exploratory analysis of biomarkers
9.1 Outcome variables
The presence/absence of embolism [Events applicable to "Embolism" as a category of adverse events in Case Report Form] shall be defined as an outcome variable. Furthermore, 1) Presence/absence of cerebral infarction or transient ischemic attack, 2) Presence/absence of embolic shower, and 3) Presence/absence of acute myocardial infarction [based on "Details of embolism" in Case Report Form: Adverse event] shall be defined as secondary outcome variables.

9.2 Biomarkers to be evaluated
The following variables and biomarkers will be analyzed as factors that may potentially affect outcome variables: Age, gender, hypertension, diabetes mellitus, cerebral stroke/transient ischemic attack, heart failure, history of vascular disease, cardiac function
(LVEF and BNP), coagulation factors (D-dimer, APTT, and PT-INR), presence/absence of left atrial thrombus, and presence/absence of recurrent atrial fibrillation. The baseline information at enrollment will be used primarily; provided that the information during the study (4 weeks before ablation, at hospital admission, before ablation on the day of ablation, and at hospital discharge) will be analyzed for LVEF, BNP, coagulation factor, and the presence/absence of left atrial thrombus, and the information at hospital discharge will be analyzed for the presence/absence of recurrent atrial fibrillation.

9.3 Method of analysis
A simple logistic regression model with 1 biomarker for each outcome variable will be used to calculate the univariate (unadjusted) odds ratio and its 95% confidence interval. In addition, p value will be calculated to detect biomarkers with \( p < 0.2 \). A multiple logistic regression model incorporating all of those biomarkers will be used to calculate the multivariate (adjusted) odds ratio, and its 95% confidence interval and p value.

10 Handling of data in the statistical analysis
10.1 Handling of missing value
Missing value will not be complemented unless specified otherwise.

10.2 Acceptable window for each assessment timepoint
All data recorded in Case Report Forms for each timepoint will be in principle accepted; provided that deviations may be considered as missing data pertinent to data management.

10.3 Digits presented for calculation
P values will be rounded off to the 6th decimal place, and presented to the 4th decimal place; provide that \( p < 0.00001 \) will be presented as \( p < 0.0001 \). Arithmetic mean, median, quantile, and standard deviation will be rounded off to the 2nd digit, and presented to the 1st digit. Minimum and maximum values will be fully presented without rounding. Proportions (rates) will be rounded off to the 2nd decimal place, and presented to the 1st decimal place.

10.4 Software to be used for statistical analysis
SAS Version 9.4 or higher will be used for the statistical analysis.