

BMJ Open Protocol, rationale and design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS): a randomised, open-label study

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ABSTRACT

Introduction Current international guidelines recommend non-vitamin K oral anticoagulants (NOACs) for stroke prevention among patients with non-valvular atrial fibrillation (AF) at significant ischaemic stroke risk given the superior safety and comparable efficacy of NOACs over warfarin. Nonetheless, the safety and effectiveness of NOACs have not been evaluated in patients with AF with underlying moderate or severe mitral stenosis (MS), hence the recommended stroke prevention strategy remains warfarin therapy.

Method and analysis MS remains disproportionately prevalent in Asian countries compared with the developed countries. This prospective, randomised, open-label trial with blinded endpoint adjudication aims to evaluate the safety and efficacy of dabigatran for stroke prevention in AF patients with moderate or severe MS. Patients with AF aged ≥ 18 years with moderate or severe MS not planned for valvular intervention in the coming 12 months will be randomised in a 1:1 ratio to receive dabigatran 110 mg or 150 mg two times per day or warfarin with international normalised ratio 2–3 in an open-label design. Patients with estimated creatinine clearance < 30 mL/min, or with a concomitant indication for antiplatelet therapy will be excluded. The primary outcome is a composite of stroke and systemic embolism. Secondary outcomes are ischaemic stroke, systemic embolism, haemorrhagic stroke, intracranial haemorrhage, major bleeding and death. The estimated required sample size is approximately 686 participants.

Ethics and dissemination The study protocol has been approved by the Institutional Review Board of the University of Hong Kong and Hong Kong West Cluster, Hospital Authority, Hong Kong for Fung Yiu King Hospital, Grantham Hospital, Queen Mary Hospital and Tung Wah Hospital in Hong Kong. Results will be published in peer-reviewed journals.

Trial registration number ClinicalTrials.gov Registry (NCT04045093); pre-results.

Strengths and limitations of this study

- This is the first investigator-initiated, open-label, randomised clinical trial to compare the effectiveness and safety of dabigatran and warfarin therapy for stroke prevention in patients with atrial fibrillation (AF) and moderate or severe mitral stenosis (MS).
- The study is designed to provide clinicians with robust, much-needed information regarding stroke prevention strategy for patients with AF and moderate or severe MS.
- The results of study will have immediate and long-term impacts on the management of these very high-risk patients with AF.
- This study will provide the necessary evidence for establishing international clinical practice guidelines for stroke prevention in patients with AF and MS.
- Since the clinical trial will be conducted mainly in Hong Kong and Mainland China, it is expected that most recruited subjects will be of Chinese ethnicity, which may limit generalisability of the trial results.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice.¹ Patients with AF are at increased risk of ischaemic stroke and systemic thromboembolism due to the formation and embolism of left atrial thrombi,^{1–3} hence long-term oral anticoagulant for thromboprophylaxis is the cornerstone in AF management. In previous randomised clinical trials in the last century, warfarin has been shown to be highly effective in reducing stroke risk compared with placebo by as much as 64% in patients with AF.⁴ More recently, non-vitamin

Oral anticoagulants (NOACs) have consistently demonstrated to be safer and more effective for stroke prevention in patients with non-valvular AF compared with warfarin and have become the recommended standard of care for the management of stroke prevention in non-valvular AF.

While the stroke risk among patients with AF appears heterogeneous,^{5,6} patients with underlying valvular heart disease, particularly mitral stenosis (MS) are at very high risk for stroke with an annual stroke risk ranging from 4% to 17% if left un-anticoagulated⁷ and the highest recurrences.⁸ However, patients with AF and underlying MS are typically excluded in randomised control trials.⁹ As a result, current international guidelines for management of AF do not recommend NOACs for stroke prevention in patients with AF and underlying moderate or severe MS.³ Nonetheless, off-label use of NOAC in patients with AF and MS is not uncommon in the real-world practice. In a recently published retrospective, observational analysis from the Republic of Korea,¹⁰ in a cohort of 7357 patients with MS receiving anticoagulation therapy, 35% of these patients were in fact treated with NOAC with the remaining 65% with warfarin. More importantly, after propensity matching, it was shown that patients treated with NOAC had a substantially lower risk of ischaemic stroke/systemic embolism with an annualised risk of 2.22%/year, compared with that of 4.19%/year for patients treated with warfarin, (adjusted HR: 0.28; 95% CI: 0.18–0.45), suggesting a potential role of NOAC among patients with AF and underlying MS.^{8,10,11}

This is of particular importance for Asian patients with AF, in whom MS remains relatively prevalent despite a declining trend.⁷ More importantly, the much higher baseline risk of intracranial haemorrhage and apparently higher ischaemic stroke risk in Asian populations potentially undermine the benefits of warfarin therapy.^{12–14} Notably, compared with warfarin, the effectiveness and safety of NOACs appear to be even more superior in Asian populations than Caucasian populations as shown in subanalyses of pivotal randomised control trials^{15–17} as well as in studies using real-world data.^{18–23} To our knowledge, this is the first multicentre randomised control trial aims to comparing NOAC with warfarin to address the knowledge in stroke prevention strategy in patients with AF and moderate or severe MS. This will have immediate and long-term impacts on the management of these very high-risk patients with AF.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials.^{24,25} The underlying protocol follows the Consolidated Standards of Reporting Trials.^{26,27}

Study design

This is an investigator-initiated, open-label randomised clinical trial to compare the effectiveness and safety of

Box 1 Inclusion and exclusion criteria

Inclusion criteria

- ▶ Patients with AF documented with standard 12-lead ECG documented AF on the day of screening or randomisation.
- ▶ Patients with age >18 years.
- ▶ Patients with moderate or severe MS that is, MVA <1.5 cm².
- ▶ Patients should be able to provide a written, informed consent.
- ▶ Patients should have all four inclusion criteria fulfilled to be qualified for the study.

Exclusion criteria

- ▶ Patients with prosthetic valve or with active endocarditis.
- ▶ Patients with heart failure symptom.
- ▶ Patients with planned valvular intervention within 1 year.
- ▶ Patients with left atrial appendage occlusive device.
- ▶ Patients with planned AF ablation.
- ▶ Patients with a history of intracranial, intraocular, spinal or retroperitoneal bleeding.
- ▶ Unexplained anaemia (haemoglobin level <100 g/L) or thrombocytopenia (platelet count <100×10⁹/L).
- ▶ Need for anticoagulant therapy of disorders other than AF.
- ▶ Patients receiving antiplatelet therapy for disorders other than AF.
- ▶ Patients receiving concomitant P-gp inhibitors and/or medications known to interact with dabigatran.
- ▶ Uncontrolled hypertension (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >100 mm Hg).
- ▶ Estimated creatinine clearance ≤30 mL/min.
- ▶ Liver dysfunction of Child-Pugh stage B or C.
- ▶ Women who are pregnant or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study.
- ▶ Patients considered unreliable by the investigator or have a life expectancy less than 1 year because of concomitant disease, or has any condition, which in the opinion of the investigator, would not allow safe participation in the study (eg, drug addiction, alcohol abuse).

AF, atrial fibrillation; MS, mitral stenosis; MVA, mitral valvular area; P-gp, P-glycoprotein.

dabigatran 150 mg or 110 mg two times per day according to kidney function with warfarin therapy with target international normalised ratio (INR) 2–3 for stroke prevention in patients with AF and moderate or severe MS.

Study participants

Patients will be recruited from participating specialist cardiology centres in Hong Kong Special Administrative Region (SAR) of China and Mainland China. Written informed consent will be obtained from all study participants. **Box 1** summarises the inclusion and exclusion criteria for the study. In brief, patients with no symptoms, aged 18 years or above will be eligible if they have AF documented on standard 12-lead ECG performed at screening or randomisation and moderate or severe MS as defined as the mitral valvular area of 1.0–1.5 cm² and <1.0 cm², respectively. Reasons for exclusion include the presence of symptoms, prosthetic valve, left atrial appendage occlusive device and/or active endocarditis; planned valvular intervention and/or planned AF ablation; history of major bleeding including intracranial, intraocular, spinal

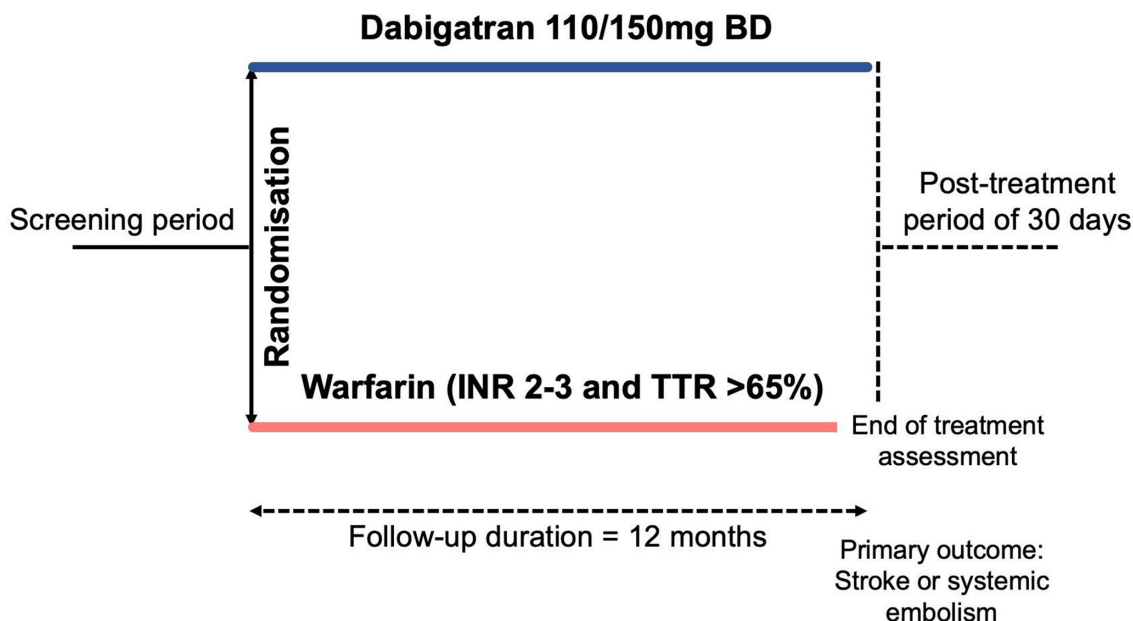


Figure 1 Design of the DAVID-MS Study. BD, two times per day; DAVID-MS, DABigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis; INR, international normalised ratio; TTR, time in therapeutic range.

or retroperitoneal haemorrhage; unexplained anaemia with haemoglobin level $<100\text{g/L}$ or thrombocytopenia with platelet count $<100 \times 10^9/\text{L}$; need for anticoagulant or antiplatelet therapy of conditions other than AF; concomitant use of potent P-glycoprotein inhibitor(s) or drugs with a known interaction with dabigatran; uncontrolled hypertension; significant kidney impairment with estimated creatinine clearance (CrCl) $\leq 30\text{mL/min}$ by the Cockcroft-Gault Formula²⁸; liver dysfunction of Child-Pugh stage B or C²⁹; pregnancy or if there is childbearing potential during the full duration of the study. In addition, patients considered unsuitable by the investigator including short life expectancy <1 year due to concomitant disease, substance and/or alcohol abuse or other medical conditions.

Study procedures

After providing written informed consent, all study participants will be randomly assigned to receive dabigatran or to receive warfarin. The procedure of the trial is summarised in figure 1, the trial will primarily be conducted in Hong Kong and Mainland China. In Hong Kong, there is no local guideline on dabigatran dosage in relation to renal function. In Mainland China, dosage reduction to 110 mg two times per day was recommended in patients with CrCl in the range 30–49 mL/min. For patients randomised to receive dabigatran, the dosage regimen will be determined according to the respective estimated CrCl or if concomitantly taking interacting drugs requiring dosage adjustment. Patients with estimated CrCl above 50 mL/min will receive dabigatran 150 mg two times per day, whereas those with CrCl between 30 and 50 mL/min will receive dabigatran 110 mg two times per day. For patients previously on warfarin randomised to receive dabigatran, dabigatran will initiate after discontinuation of warfarin

with an INR less than or equal to 2. At the end of study, patients randomised to dabigatran will be switched back to warfarin. Warfarin will be initiated 3 days prior to the termination of dabigatran. INR will be checked 5 days after initiation of warfarin, that is, 2 days after termination of dabigatran to minimise the potential impact of remaining dabigatran levels in elevating the INR. On the other hand, for those randomised to receive warfarin, INR will be measured at least every 8 weeks with a target INR of 2.0–3.0. The time in therapeutic range (TTR) will be calculated for each study participant using Rosendaal method,³⁰ in which INR will be assumed to change in a linear manner between measurements, and INR values on the days without measurement are interpolated. The percentage of time during which a study participant has an INR within 2.0–3.0 is taken as TTR. The first follow-up visit will be scheduled 14 days after randomisation and then every 4 months during the study period of 1 year (table 1). Criteria for discontinuation or change of allocated treatment include patient request, drug allergy, intolerable adverse drug reaction and development of other contraindication. Patients who are randomised to receive dabigatran would be switched to warfarin if CrCl is below 30 mL/min and/or develop liver dysfunction of Child-Pugh stage B or C.

Outcomes

The primary outcome is a composite of stroke or systemic embolism at 1 year. Secondary outcomes are ischaemic stroke, systemic embolism, haemorrhagic stroke, intracranial haemorrhage, major bleeding and death at 1 year. Stroke is defined as a neurological deficit of sudden onset that persisted for more than 24 hours and corresponded to a vascular territory that cannot be explained by other causes (such as trauma, infection or vasculitis). Stroke

Table 1 Study visits

Visits	-1	0	1	2	3	4	5	6	7	UNS†	EOS‡
Weeks	-2 to 0	0	8	16	24	32	40	48	56	--	56–60
Informed consent		X									
Inclusion and exclusion criteria		X									
Randomisation		X									
Medical history		X									
Physical examination		X	X	X	X	X	X	X	X	X	X
Echocardiography		X									
INR		X	X*	X*	X*	X*	X*	X*	X*	X*	X
Renal function		X		X		X		X		X	X
Drug dispensing		X	X	X	X	X	X	X	X		
Drug collection			X	X	X	X	X	X	X		X
Outcome events			X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X

*Only for patients randomised to receive warfarin.

†UNS (unplanned visit): (X) the marked item is optimal and performed according to the judgement of researchers.

‡EOS (final visit): make arrangement according to the study end time (if there is a visit within 1 month before the end of study, it is regarded as a final visit, but needs to be supplemented with the items required completely).

INR, international normalised ratio.

will be further classified as ischaemic stroke and haemorrhagic stroke according to computerised axial tomography or MRI of the brain. Intracranial haemorrhage (ICH) consists of haemorrhagic stroke (intracerebral haemorrhage and cerebellar haemorrhage), subdural haemorrhage and subarachnoid haemorrhage, and will be confirmed with computerised axial tomography or MRI of the brain. Systemic embolism is defined as an acute vascular occlusion of an extremity or organ other than the brain, documented by imaging, surgery and/or autopsy.

Major bleeding is defined as a drop in the haemoglobin level of at least 20 g/L, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ. Life-threatening bleeding includes fatal bleeding, symptomatic intracranial bleeding, bleeding with a haemoglobin drop of at least 50 g/L or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or requiring surgery. All outcomes will be adjudicated by two independent investigators in a blinded fashion.

Sample size calculation

The primary analysis is to test whether dabigatran is non-inferior to warfarin for ischaemic stroke prevention in patients with AF and moderate or severe MS. The potential for dabigatran to preserve at least 50% of the effectiveness of warfarin is considered clinically meaningful, as non-inferior in patients with AF and moderate or severe MS. The non-inferiority margin is 1.49, which is derived from the only observation study comparing vitamin K antagonist with NOAC in patients with AF and MS.¹⁰ In the study, the annual ischaemic stroke risk of patients with AF and MS receiving vitamin K antagonist and NOAC are 4.19%/

year and 2.22%/year, respectively. Accordingly, based on the margin of error (4.66%) and the current population of Hong Kong (7 500 700), a sample size of 686 patients (343 patients in the vitamin K antagonist group and 343 in the dabigatran group) including 10% attrition would be needed to satisfy the non-inferiority hypothesis with the upper boundary of the one-sided 95% CI (or equivalent with a 90% two-sided CI) and the HR of the primary outcome below the non-inferiority margin of 1.49. Hierarchical analysis for superiority will be performed if non-inferiority is established.

Statistical analysis

Baseline data will be reported as means and SD for continuous data and as numbers and percentages for categorical data. All endpoints will be analysed according to the intention-to-treat principle, with all patients who undergo randomisation included in the analysis. Clinical events that occur after randomisation and until the end of the study (at 1 year or mortality) will be included in the primary analysis of clinical outcomes. A p value < 0.05 considered as significant. Calculations will be performed using SPSS software (V.12.0).

Randomisation

Randomisation will be stratified to each study site to account for variations in patient demographics and diagnoses. At each site, patients will be randomised to 'permuted blocks of four' (two of each study arm) to assist in equality of numbers in each arm. An independent research officer who is blinded to this study will generate the random-number table. Study staff responsible for enrolment will be informed of randomisation

assignment by phone. Subjects and clinicians will not be blinded to the randomisation assignment. Data staff responsible for data entry will be blinded from randomisation assignment.

Data collection and management

After enrolment, each subject will be assigned a unique identifier to be used in database. Data will be entered by study staff and data accuracy will be verified by study principal investigator. Data quality control measures include queries to identify missing data, outliers and discrepancies. The database will be password protected and encrypted. Only study staff will have access to the database. All paper records will be deidentified and stored securely in a locked cabinet for 5 years. Subjects who withdraw from the study will have continuous monitoring stopped, usual care continued and final outcome collected for analysis.

Data monitoring and safety

An independent Safety Committee will be established comprising of an emergency clinician, clinical pharmacologist and toxicologist. They will receive regular reports during patient enrolment and be notified of any adverse drug reaction and study protocol violation. The Safety Committee is led by Professor Bernard Cheung from the Clinical Pharmacology, Faculty of Medicine, the University of Hong Kong, Hong Kong SAR, China. For patient safety, discontinuation of the study is at the discretion of the cardiology clinician to enable informed decisions to be made regarding subsequent management and alternative medication use. Any medication or therapy, intervention or procedure thought to be necessary for the safe management of the patient may be administered at the discretion of the managing clinician.

Patient and public involvement

We received input from clinicians and patients which guided the design of the current study and choice of research questions. No patients were directly involved in the design of the study and choice of outcome measures. No patients will be involved in recruitment or conduct of the study. Results of the study will be disseminated to subjects, the public and the scientific community.

ETHICS AND DISSEMINATION

This research protocol complies with the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practice. The study protocol has been approved by the Institutional Review Board of the University of Hong Kong and Hong Kong West Cluster, Hospital Authority, Hong Kong for Fung Yiu King Hospital, Grantham Hospital, Queen Mary Hospital and Tung Wah Hospital in Hong Kong. Written informed consents will be obtained from all study participants by study staff responsible for recruitment (online supplemental file 1). Important protocol modifications will be

<p style="text-align: center;">High CHA₂DS₂-VASc</p> <p style="text-align: center;">Stroke risk: 2.2-11.4%/year</p> <p style="text-align: center;">NOAC & VKA</p>	<p style="text-align: center;">Hypertrophic Cardiomyopathy</p> <p style="text-align: center;">Stroke risk: ~3.75%/year</p> <p style="text-align: center;">NOAC & VKA</p>
<p style="text-align: center;">Mitral Stenosis</p> <p style="text-align: center;">Stroke risk: 4-17%/year</p> <p style="text-align: center;">NOAC: mild MS VKA: moderate or severe MS</p>	<p style="text-align: center;">Mechanical heart valve</p> <p style="text-align: center;">Stroke risk: Extremely high</p> <p style="text-align: center;">VKA only</p>

Figure 2 Four main groups of patients with AF requiring long-term anticoagulation therapy. AF, atrial fibrillation; MS, mitral stenosis; NOAC, non-vitamin K oral anticoagulant; VKA, vitamin K antagonist.

conveyed to investigators, Institutional Review Board, trial registries, regulators, journals and trial participants. After enrolment, each subject will be assigned a unique identifier to be used in database. Personal identity of subjects will not be used for any public purpose, publication or transmitted outside of the study team.

Dataset used during the study will be available from the corresponding author on reasonable request. Collaboration with other investigators will be welcomed. The results of the trial will be published in peer-reviewed journals and presented in conferences.

DISCUSSION

To our knowledge, this is the first study to evaluate dabigatran as an alternative to warfarin for stroke prevention in patients with AF and moderate or severe MS. The results could fill the gap in stroke prevention strategy for this specific group of patients with AF with immediate and long-term impacts on clinical practice.

AF is the most commonly encountered sustained cardiac arrhythmia in clinical practice.^{1 31} While patients with AF have in general increased risk of stroke, four subgroups are at particularly high risk necessitating long-term anticoagulation therapy. These include (1) patients with non-valvular AF and high CHA₂DS₂-VASc score, (2) patients with AF and hypertrophic cardiomyopathy, (3) patients with AF and MS, and (4) patients with AF and mechanical heart valves (figure 2). In the past decade, NOAC has emerged as the preferred agent over warfarin for stroke prevention in patients with non-valvular AF and high CHA₂DS₂-VASc score. In the four pivotal studies

comparing NOACs and warfarin in patients with non-valvular AF, NOACs are at least as effective as warfarin to reduce stroke and at the same time are much safer alternatives in terms of life-threatening bleeding complications. Nonetheless, direct extrapolation of these results to other subgroups of AF patients may not be appropriate, given the different mechanisms of thrombus formation in different diseases. For instance, in the RE-ALIGN trial randomising 252 patients with recent mechanical valvular replacement in a 2:1 ratio to receive either dabigatran or warfarin, there was an excess of thromboembolic as well as bleeding events among patients randomised to dabigatran, rendering the study prematurely terminated.³²

On the other hand, international guidelines do not recommend NOACs for patients with AF and moderate or severe MS due to the lack of reliable data from clinical trials. Nonetheless, it remains undetermined whether NOACs can be used as an alternative to warfarin for patients with AF and moderate or severe MS due to the lack of clinical trial. The current study has several important implications, particularly in Asian countries. First, while MS is now a rare condition in developed countries, it remains relatively prevalent in many Asian countries. In addition, the risk of stroke among patients with AF and MS is only second to those with mechanical valvular replacement ranging from 4% to 17%. Second, previous epidemiological studies^{12–14 21 33 34} and subanalyses of the pivotal NOAC trials^{15–17} have consistently reported a much higher nominal risk of ICH among Asians than non-Asians, favouring NOACs over warfarin therapy. More importantly, the notoriously poor TTR for warfarin in Asian populations observed in real-world data^{18 34–38} and pivotal NOAC trials^{15–17} substantially undermines the overall clinical benefits of warfarin therapy. In fact, the annual incidence of ICH among patients with AF and MS treated with warfarin has been reported to be as high as 0.93% per year,¹⁰ urging a much safer alternative.

In the present study, the NOAC of choice is dabigatran, the first NOAC with an approved indication for stroke prevention in patients with non-valvular AF from the United States Food and Drug Administration in 2009. In the pivotal study, the RE-LY Study,³⁹ patients with non-valvular AF with CHADS₂ >1 were randomly assigned to two doses of dabigatran: 110 mg or 150 mg two times per day; or adjusted-dose warfarin. After a median follow-up of 2.0 years, the low-dose regime was found to be as effective as warfarin in preventing the primary endpoint (a composite of stroke and systemic embolism) (1.52%/year vs 1.69%/year), but with a substantially lower risk of major bleeding and ICH.³⁹ On the other hand, the standard dose dabigatran (150 mg two times per day) is superior to warfarin in reducing the primary composite endpoint and ICH, with a comparable risk of major bleeding.³⁹ In an analysis comparing the effectiveness and safety of dabigatran according to the ethnicity of study participants, dabigatran appears to be more effective in stroke prevention as well as safer in terms of ICH compared with warfarin. This is in concordance to subsequent real-world cohorts

of patients with AF from territory-wide registries from Asia Pacific region. Plausible explanations include suboptimal quality of warfarin therapy with low TTR and a higher risk of ICH in Asian populations.^{18 23 35 40 41} An additional reason for the choice of dabigatran in the present study is the wide availability of its antidote, idarucizumab in Asian countries, which provides extra-protection of patients in the clinical trial.

The study is designed to provide clinicians with robust, much-needed information regarding stroke prevention strategy for patients with AF and moderate or severe MS. The results will have immediate and long-term impacts on the management of these very high-risk patients with AF.

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