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Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study

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Rationale and Design of

DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study

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ABSTRACT

Introduction Current international guidelines recommend non-vitamin K oral anticoagulants (NOACs) for stroke prevention amongst patients with non-valvular atrial fibrillation (AF) at significant ischemic 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.

Methods and analysis MS remains disproportionately prevalent in Asian countries compared with the developed countries. This prospective, randomized, open-label trial with blinded end-point 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 mitral stenosis not planned for valvular intervention in the coming 12 months will be randomized in 1:1 ratio to receive dabigatran 110 mg or 150 mg twice daily or warfarin with INR 2-3 in an open-label design. Patients with estimated creatinine clearance <30 ml/min, or with concomitant indication for anti-platelet therapy will be excluded. The primary outcome is a composite of stroke and systemic embolism. Secondary outcomes are ischemic stroke, systemic embolism, hemorrhagic stroke, intracranial haemorrhage, major bleeding and death. The estimated required sample size is approximately 686 participants.

Ethics and dissemination The study protocol of DAVID-MS has been approved by the Institutional Review Board of The University of Hong Kong, and Hong Kong West Cluster, Hospital Authority, Hong Kong.

PROSPERO registration number

The study is registered with the www.ClinicalTrials.gov (NCT04045093).

Strengths and limitations of this study

This study is the first study to test an alternative to warfarin in patients with AF and moderate or severe MS.

The results will provide important insights to the stroke prevention strategy for patients with MS and may be immediately translatable to real clinical practice.

This study will provide the necessary evidence for establishing international clinical practice guidelines for stroke prevention in patients with AF and MS.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice.[1, 2] Patients with AF are at increased risk of ischemic stroke and systemic thromboembolism due to the formation and embolism of left atrial thrombi,[1-3] hence long-term oral anticoagulant (OAC) for thromboprophylaxis is the cornerstone in AF management. In previous randomized 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 K 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 amongst 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-anticoagulated.[7] However, patients with AF and underlying MS are typically excluded in randomized control trials.[8] 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.[9] 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 7,357

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 ischemic stroke/systemic embolism with an annualized risk of 2.22%/year, compared to that of 4.19%/year for patients treated with warfarin, (adjusted HR: 0.28; 95% confidence interval (CI): 0.18 to 0.45), suggesting a potential role of NOAC amongst patients with AF and underlying MS.[10, 11]

This is of particular importance for Asian AF patients, in whom MS remains relatively prevalent despite a declining trend.[7] More importantly, the much higher baseline risk of intracranial haemorrhage and apparently higher ischemic stroke risk in Asian populations potentially undermines the benefits of warfarin therapy.[12,13, 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 sub-analyses of pivotal randomized controls trials[15-17] as well as in studies using real world data.[18-23] To our knowledge, this is the first multicentre randomized control trial comparing NOAC to 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

Study Design

This is an investigator-initiated, open-label, randomized clinical trial to compare effectiveness and safety of dabigatran 150mg or 110 mg twice daily according to kidney function with warfarin therapy with target international normalized ratio (INR) 2-3 for stroke prevention in patients with AF and moderate or severe MS. The study is registered with the www.ClinicalTrials.gov (NCT04045093). The investigation conforms with the principles outlined in the Declaration of Helsinki. 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. Approvals at other participating sites will be subsequently obtained. This research protocol complies with the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practice.

Study Participants

Patients will be recruited from participating specialist cardiology centres in Hong Kong SAR China and Mainland China. Written informed consent will be obtained from all study participants. Table 1 summarizes the inclusion and exclusion criteria for the study. In brief, patients aged 18 years or above will be eligible if they have AF documented on standard 12-lead electrocardiography (ECG) performed at screening or randomization and moderate or severe MS as defined as the mitral valvular area (MVA) of 1.0-1.5cm^2 and <1.0 cm^2, respectively. Reasons for exclusion include the presence of 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 or retroperitoneal haemorrhage; unexplained anaemia with haemoglobin level <10 g/dL, or thrombocytopenia with platelet count $<100\times10^9$/L; need for anticoagulant or antiplatelet therapy of conditions other than AF; concomitant use of potent P-gp inhibitor(s) or drugs with known interaction with dabigatran; uncontrolled hypertension; significant kidney impairment with estimated creatinine clearance (CrCl) ≤30 mL/min; liver dysfunction of Child Pugh Stage B or C; pregnancy or if there is child-baring 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 summarized in figure 1, For patients randomized 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 twice daily, whereas those with CrCl between 30 to 50 ml/min will receive dabigatran 110 mg twice daily. For patients previously on warfarin randomized 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 randomized 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 i.e., 2 days after termination of dabigatran to minimise potential impact of remaining dabigatran levels in elevating the INR. On the other hand, for those randomized to receive warfarin, INR will be measured at least every 8 weeks with target INR of 2.0 to 3.0. The time in therapeutic range (TTR) will be calculated for each study participant using Rosendaal method,[24] 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 randomization and then every 4 months during the study period of 1 year (Table 2).

Outcomes

The primary outcome is a composite of stroke or systemic embolism at 1 year. Secondary outcomes are ischemic stroke, systemic embolism, hemorrhagic 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 (trauma, infection, vasculitis). Stroke will be further classified as ischemic stroke and hemorrhagic stroke according to computerized axial tomography or magnetic resonance imaging of the brain. Intracranial hemorrhage (ICH) consists of hemorrhagic stroke (intra-cerebral hemorrhage and cerebellar hemorrhage), subdural hemorrhage, and subarachnoid hemorrhage, and will be confirmed with computerized axial tomography or magnetic resonance imaging 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 hemoglobin level of at least 2 g/dL, 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 hemoglobin drop of at least 5 g/dL, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or requiring surgery. All outcomes will be adjudicated by 2 independent investigators in a blinded fashion.

Randomization

Randomization 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 will generate the random-number table. The codes will remain securely in the Department of Pharmacy, QMH until study completion and analysis of results.

Patient 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. 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.

Sample Size Calculation

The primary analysis is to test whether dabigatran is noninferior to warfarin for ischemic 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 noninferior in patients with AF and moderate or severe MS. The noninferiority 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 ischemic stroke risk of patients with AF and MS receiving vitamin K antagonist and NOAC are 4.19%/year and 2.22%/year respectively. Accordingly, 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 noninferiority hypothesis with the upper boundary of the one-sided 95% confidence interval (CI) (or equivalent with a 90% two-sided CI) and the Hazard ratio (HR) of the primary outcome below the noninferiority margin of 1.49.

Patient and public involvement

No patient and public involved in the research plan of this study.

Statistical Analysis

Baseline data will be reported as means and standard deviations 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 randomization included in the analysis. Clinical events that occur after randomization 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 (version 12.0).

Storage and Security

To minimise lost or misplaced data collection sheets, each document will contain clear contact information for each study site. An Excel file containing study data will be kept in de-identified form for 5 years. Data will be kept on a password-protected data files on a local computer drive at the study sites, accessible only by the study investigators. Back-up discs will be encrypted and kept locked securely. All paper records will be de-identified and stored securely in a locked cabinet for 5 years. Presented and published data will not allow identification of any study subject.

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, 2] While patients with AF have in general an increased risk of stroke, 4 subgroups are at particularly high risk necessitating long-term anticoagulation therapy. These include (1) patients with non-valvular AF and high CHA_2DS_2-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 CHA_2DS_2-VASc score. In the 4 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 term 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 randomizing 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 randomized to dabigatran, rendering the study prematurely terminated.[25]

On the other hand, international guidelines do not recommend NOACs for patients with AF and moderate or severe mitral stenosis 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 amongst patients with AF and MS is only second to those with mechanical valvular replacement ranging from 4 to 17%. Second, previous epidemiological studies[12,13, 14, 21, 26, 27] and sub-analyses of the pivotal NOAC trials[15-17] have consistently reported a much higher nominal risk of ICH amongst Asians than non-Asians, favouring NOACs over warfarin therapy. More importantly, the notoriously poor time in therapeutic range (TTR) for warfarin in Asian populations observed in real world data[18, 27-31] and pivotal NOAC trials[15-17] substantially undermines the overall clinical benefits of warfarin therapy. In fact, the annual incidence of ICH amongst 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 approved indication for stroke prevention in non-valvular AF patients from the United States Food and Drug Administration in 2009. In the pivotal study, the

RE-LY study,[32] patients with non-valvular AF with CHADS2≥1 were randomly assigned to two doses of dabigatran: 110 mg or 150 mg twice daily; 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 substantially lower risk of major bleeding and ICH.[32] On the other hand, the standard dose dabigatran (150mg BD) is superior to warfarin in reducing the primary composite endpoint and ICH, with a comparable risk of major bleeding.[32] 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 AF patients from territory-wide registries from Asia Pacific region. Plausible explanations include suboptimal quality of warfarin therapy with low time in therapeutic range and higher risk of ICH in Asian populations.[18, 23, 28, 33, 34] 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.

Conclusion

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.

Contributors

Mi ZHOU is the investigator of a local site and is responsible for the study design, study dataset and website establishment, and study execution.

Esther W. CHAN, Jojo HAI, Chun-Ka WONG, Yuk-Ming LAU, Duo HUANG, Cheung-Chi LAM, Chor-Cheung TAM, Yiu-Tung WONG, See-Yue YUNG, Ki-Wan CHAN, Yingqing FENG, Ning TAN, Ji-Yan CHEN, Chi-Yui YUNG, Kwok-Lun LEE, Chun-Wai CHOI, Ho LAM, Andrew NG, Katherine FAN, Man-Hong JIM, Kai-Hang YIU, those people above are the investigator of a local site.

Bryan P. YAN is the principal investigator of the whole study responsible for study design.

Chung-Wah SIU is the principal investigator of the whole study responsible for study design, study execution, manuscript drafting, and study site recruitment.

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LEGENDS:

Figure 1. Design for the DAVID-MS study.

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

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
• Patients with AF documented with standard 12-lead ECG documented AF on the day of screening or randomization • Patients with age >18 years • Patients with moderate or severe MS i.e., MVA <1.5 cm^2 • Patients should be able to provide a written, informed consent. • Patients should have all 4 inclusion-criteria fulfilled to be qualified for the study.
Exclusion criteria
• Patients with prosthetic valve, or with active endocarditis • Patients with planned valvular intervention within 1 year • Patients with left atrial appendage occlusive device • Patients with planned AF ablation • Patients with history of intracranial, intraocular, spinal, or retroperitoneal bleeding • Unexplained anemia (hemoglobin level <10 g/dL) or thrombocytopenia (platelet count <100×10^9/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 mmHg and/or diastolic blood pressure >100 mmHg) • 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 (e.g. drug addiction, alcohol abuse).

Abbreviations: AF: atrial fibrillation; MS: mitral stenosis; MVA: mitral valvular area

Table 2. 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 & exclusion criteria		X									
Randomization		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 randomized to receive warfarin

**UNS (unplanned visit): (X) The marked item is optimal and performed according to the judgment of researchers.

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

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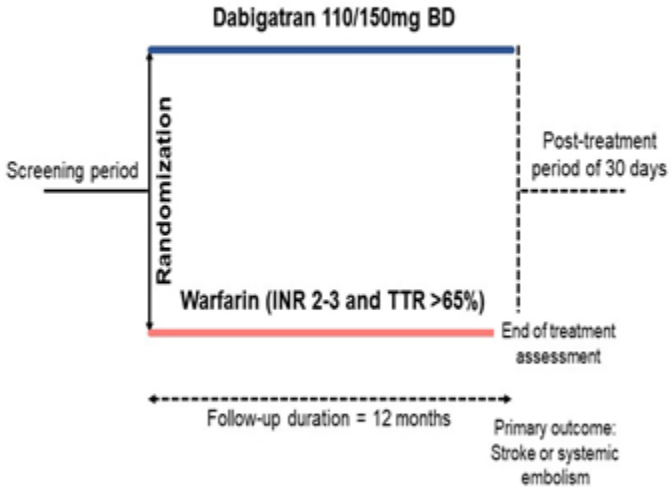

Figure 1. Design for the DAVID-MS study

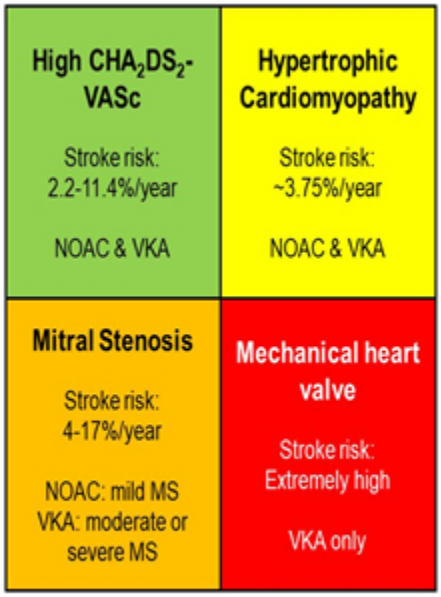

Figure 2. Four main groups of patients with AF requiring long-term anticoagulation therapy. MS: mitral stenosis; NOAC: non-vitamin K oral anticoagulant; and VKA: vitamin K antagonist.

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Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study

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Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study

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ABSTRACT

Introduction: Current international guidelines recommend non-vitamin K oral anticoagulants (NOACs) for stroke prevention amongst 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 remain disproportionately prevalent in Asian countries compared with the developed countries. This prospective, randomized, 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 mitral stenosis not planned for valvular intervention in the coming 12 months will be randomized in a 1:1 ratio to receive dabigatran 110 mg or 150 mg twice daily or warfarin with INR 2-3 in an open-label design. Patients with estimated creatinine clearance <30 ml/min, or with a concomitant indication for anti-platelet therapy will be excluded. The primary outcome is a composite of stroke and systemic embolism. Secondary outcomes are ischaemic stroke, systemic embolism, hemorrhagic stroke, intracranial haemorrhage, major bleeding, and death. The estimated required sample size is approximately 686 participants.

Ethics and dissemination: The study protocol of DAVID-MS has been approved by the Institutional Review Board of The University of Hong Kong, and Hong Kong West Cluster, Hospital Authority, Hong Kong. Results will be published in peer-reviewed journals.

Registration details: ClinicalTrials.gov (NCT04045093).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first investigator-initiated, open-label, randomized clinical trial to compare 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 generalizability 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 (OAC) for thromboprophylaxis is the cornerstone in AF management. In previous randomized 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 K 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 amongst 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-anticoagulated[7] and the highest recurrences.[8] However, patients with AF and underlying MS are typically excluded in randomized 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 7,357 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 annualized risk of 2.22%/year, compared to that of 4.19%/year for patients treated with warfarin, (adjusted HR: 0.28; 95% confidence interval (CI): 0.18 to 0.45), suggesting a potential role of NOAC amongst patients with AF and underlying MS.[8 10 11]

This is of particular importance for Asian AF patients, 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 undermines the benefits of warfarin therapy.[12,13 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 sub-analyses of pivotal randomized controls trials[15-17] as well as in studies using real-world data.[18-23] To our knowledge, this is the first multicentre randomized control trial aims to comparing NOAC to 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 (SPIRIT).[24] [25] The underlying protocol follows the Consolidated Standards of Reporting Trials (CONSORT). [26] [27] The study is registered with the www.ClinicalTrials.gov (NCT04045093).

Study Design

This is an investigator-initiated, open-label, randomized clinical trial to compare effectiveness and safety of dabigatran 150 mg or 110 mg twice daily according to kidney function with warfarin therapy with target international normalized 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 SAR China and Mainland China. Written informed consent will be obtained from all study participants. Table 1 summarizes 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 electrocardiography (ECG) performed at screening or randomization and moderate or severe MS as defined as the mitral valvular area (MVA) of 1.0-1.5 cm^2 and <1.0 cm^2, 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 or retroperitoneal haemorrhage; unexplained anaemia with haemoglobin level <10 g/dL, or thrombocytopenia with platelet count $<100\times10^9$/L; need for anticoagulant or antiplatelet therapy of conditions other than AF; concomitant use of potent P-gp inhibitor(s) or drugs with a known interaction with dabigatran; uncontrolled hypertension; significant kidney impairment with estimated creatinine clearance (CrCl) ≤30 mL/min by the Cockcroft-Gault Formula; [28] liver dysfunction of Child-Pugh Stage B or C; [29] pregnancy or if there is child-baring 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 summarized in figure 1, For patients randomized 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 twice daily, whereas those with CrCl between 30 to 50 ml/min will receive dabigatran 110 mg twice daily. For patients previously on warfarin randomized 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 randomized 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 i.e., 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 randomized to receive warfarin, INR will be measured at least every 8 weeks with a target INR of 2.0 to 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 randomization and then every 4 months during the study period of 1 year (Table 2). 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 randomized 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, hemorrhagic 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 will be further

classified as ischaemic stroke and hemorrhagic stroke according to computerized axial tomography or magnetic resonance imaging of the brain. Intracranial haemorrhage (ICH) consists of hemorrhagic stroke (intra-cerebral haemorrhage and cerebellar haemorrhage), subdural haemorrhage , and subarachnoid haemorrhage , and will be confirmed with computerized axial tomography or magnetic resonance imaging 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 2 g/dL, 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 5 g/dL, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or requiring surgery. All outcomes will be adjudicated by 2 independent investigators in a blinded fashion.

Sample Size Calculation

The primary analysis is to test whether dabigatran is noninferior 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 noninferior in patients with AF and moderate or severe MS. The noninferiority 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, 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 noninferiority hypothesis with the upper boundary of the one-sided 95% confidence interval (CI) (or equivalent with a 90% two-sided CI) and the Hazard ratio (HR) of the primary outcome below the noninferiority margin of 1.49. Hierarchical analysis for superiority will be performed if noninferiority is established.

Statistical Analysis

Baseline data will be reported as means and standard deviations 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 randomization included in the analysis. Clinical events that occur after randomization 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 (version 12.0).

Randomization

Randomization 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 are blinded to this

study will generate the random-number table. Study staff responsible for enrolment will be informed of randomization assignment by phone. Subjects and clinicians will not be blinded to the randomization assignment. Data staff responsible for data entry will be blinded from randomization 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. Approvals at other participating sites will be subsequently obtained before recruitment begins. Written informed consents will be obtained from all study participants by study staff responsible for recruitment (Supplementary File 1). Important protocol modifications will be 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, 4 subgroups are at particularly high risk necessitating long-term anticoagulation therapy. These include (1) patients with non-valvular AF and high CHA_2DS_2-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 CHA_2DS_2-VASc score. In the 4 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 randomizing 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 randomized 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 mitral stenosis 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 amongst patients with AF and MS is only second to those with mechanical valvular replacement ranging from 4 to 17%. Second, previous epidemiological studies[12,13 14 21 33 34] and sub-analyses of the pivotal NOAC trials[15-17] have consistently reported a much higher nominal risk of ICH amongst Asians than non-Asians, favouring NOACs over warfarin therapy. More importantly, the notoriously poor time in therapeutic range (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 amongst 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 non-valvular AF patients 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 twice daily; 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 (150mg BD) 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 AF patients from territory-wide registries from Asia Pacific region. Plausible explanations include suboptimal quality of warfarin therapy with low time in therapeutic range 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.

Author contributions:

MZ, EWC, JH, CKW, BPY and CWS contributed to the conception and design of the study. MZ, EWC, JH, CKW, YML, DH, CCL, CCT, AYTW, ASYY, KKWC, YF, NT, JYC, CYY, KLL, CWC, HL, AN, KF, MHJ, KHY, BPY and CWS contributed to the acquisition of data. Data analysis and interpretation will be conducted by MZ, EWC, JH, CKW, BPY and CWS. MZ, EWC, JH, CKW, BPY and CWS wrote first draft of the protocol and revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published.

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Legends:

Figure 1. Design of the DAVID-MS study.

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

Supplementary Files:

Supplementary File 1: Model consent form in English

Tables:

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
• Patients with AF documented with standard 12-lead ECG documented AF on the day of screening or randomization • Patients with age >18 years • Patients with moderate or severe MS i.e., MVA <1.5 cm^2 • Patients should be able to provide a written, informed consent. • Patients should have all 4 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 anemia (haemoglobin level <10 g/dL) or thrombocytopenia (platelet count <100×10^9/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 mmHg and/or diastolic blood pressure >100 mmHg) • 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 (e.g. drug addiction, alcohol abuse).

Abbreviations: AF: atrial fibrillation; MS: mitral stenosis; MVA: mitral valvular area

Table 2. 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 & exclusion criteria		X									
Randomization		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 randomized to receive warfarin

**UNS (unplanned visit): (X) The marked item is optimal and performed according to the judgment of researchers.

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

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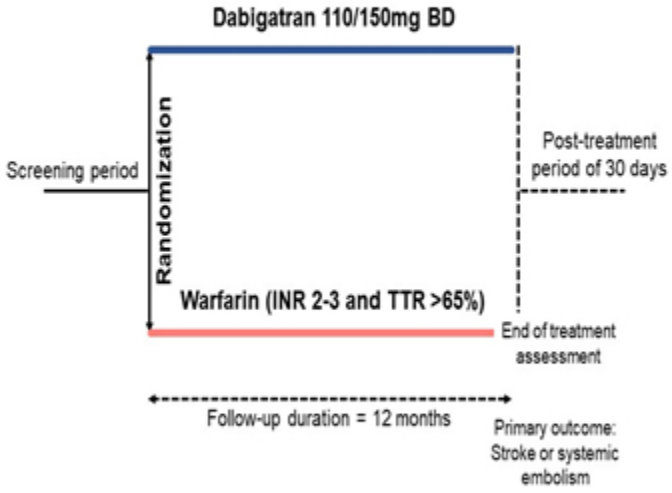

Figure 1. Design for the DAVID-MS study

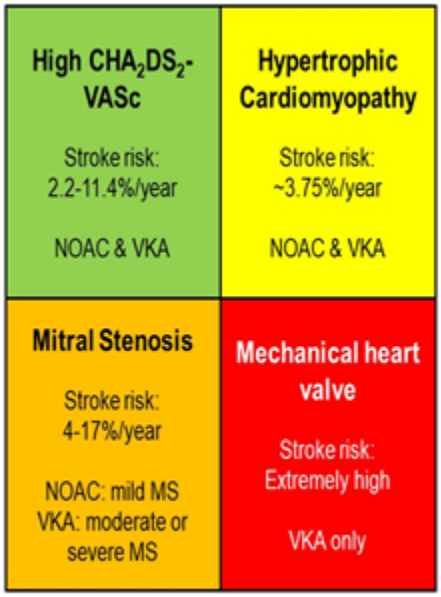

Figure 2. Four main groups of patients with AF requiring long-term anticoagulation therapy. MS: mitral stenosis; NOAC: non-vitamin K oral anticoagulant; and VKA: vitamin K antagonist.

Information sheet

Study Name: **Rationale and design of Dabigatran for Mitral Stenosis Atrial Fibrillation Trial**

Version no.: v.1.2 (18/Nov/2019)

Protocol no.: DAMS-01
Protocol version no.: v.1.2 (18/Nov/2019)
Study site: Queen Mary Hospital
Study Principal Investigator: Prof. SIU Chung Wah David

You are being invited to take part in a research study. Before you decide, it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask the study doctor or research staff any questions you may have before signing the attached consent form.

About This Study

The purpose of our study is to find out the efficacy and safety of non-vitamin K oral anticoagulants (NOACs), the drugs used to prevent ischemic stroke for atrial fibrillation (AF) patients.

Why have I been chosen?

You are suffering from atrial fibrillation, a heart disease associated with 5-fold increase in ischemic stroke risk. Currently, NOAC is one of the most effective drug groups in preventing ischemic stroke under this condition. Among these AF patients, some have underlying valvular heart diseases with particularly high risk for stroke for those with mitral stenosis (MS) and the annual stroke rate ranges from 4% to 17% if left un-anticoagulated.

However, there's lack of research-based evidence to indicate the efficacy and safety of NOACs for patients with both AF and MS. As a result, there're still no standard guidelines for stroke prevention management regarding to NOACs for AF patients with underlying moderate to severe MS. On the other hand, there's recent foreign study suggesting the potential role of NOACs amongst AF patients with underlying MS in stroke prevention.

Concerning the very high risk for stroke for AF patients with underlying MS, also higher baseline risk of intracranial haemorrhage and higher ischemic stroke risk in Asian populations, we launch this study aiming at comparing the efficacy and safety of one of the NOACs – Dabigatran (150mg or 110mg according to subjects' renal function) – with normal warfarin

therapy in AF patients with moderate or severe MS. We plan to recruit a total of 686 subjects randomizing into 2 groups of investigational Dabigatran and warfarin in a 1:1 ratio. Since you have carried both heart problems, you are invited into our study.

What will happen to me if I take part?

If you meet the criteria of this study and are being enrolled, our investigator(s) shall have a short interview with you (less than 10 minutes) to explain the benefits and potential side effects of NOACs. Enough time will be given for understanding and solving any queries raised, and written consent has to be signed for agreement of study participation. You will then be randomized into either Dabigatran or warfarin group, which is open to your notice.

Study period of individual participants will be around 1 year. We will obtain medical history directly from you, hospital record as well as electronic medical record under Hospital Authority. Within the study time frame, you will have the first follow-up at 2-week interval after randomization. After that, we will arrange regular follow-ups of every 4 months for you to monitor the effect and safety of the drug prescribed until the study ends. We will perform certain investigations during study visits, including physical examination, echocardiography (during the first visit only) and blood sampling via venipuncture. You will be responsible to comply with the scheduled study visits, study procedures and prescription plan, and report to us as soon as possible for any adverse effects appear.

There are no extra expenses anticipated for participating in the clinical trial. You simply need to pay for the regular specialty follow-up fee and the regular medication fee under Hospital Authority policy as usual for each time scheduled or unscheduled follow-ups. On the other hand, there will not have reimbursement in any forms from the study.

What are the benefits of participating?

NOAC is currently a self-financing item under Hospital Authority. That means patients need to purchase the drug themselves or only patients meet certain medical criteria will the item be free. In this study, according to randomization, you will be given free-of-charged NOAC for stroke prevention secondary to AF, which is significantly safe and efficacious over the traditional warfarin therapy. Close monitoring by experienced medical staff will be held to ensure your safety.

Besides, your contribution is important to provide valuable information for stroke prevention strategy for patients with mitral stenosis and that may be immediately translatable to real clinical practice. It may also provide necessary evidence for establishing relevant universal guidelines.

What if something goes wrong?

Both dabigatran and warfarin are registered medications under the Pharmacy and Poisons Ordinance (Cap. 138) in Hong Kong Special Administrative Region. They have been overseen for their safety, efficacy and quality. Being randomized into either group (a 50/50 chance like flipping a coin) in this study, you will be prescribed corresponding anticoagulant with dosage adjustment based on your coagulation or renal blood-check result, according to standard medical guidelines.

As with all other researches regarding to clinical trial, there may involve harms and risks that are already known or currently unknown and unforeseen with the drug treatment. You are free to raise queries and concerns to our investigators prior to consenting and at any time during the study. Our medical staff will closely monitor your condition throughout the whole study period and you are responsible to tell our research staff as soon as possible for any changes in medical condition. Below are listed known side effects of the two anticoagulants.

Side effects of Dabigatran:

Common – nausea / diarrhea / indigestion / stomach upset / stomach pain / stomach burn / unexpected bruising / minor bleeding

Less common or rare – allergy / skin rash / itchiness / headache / dizziness / weakness / unexpected or uncontrollable bleeding / coffee-ground vomiting / brown urine / black stool / swelling / pain

Side effects of Warfarin:

Common – unexpected bruising / minor bleeding / bloating / nausea / vomiting / diarrhea / loss of appetite

Less common or rare – allergy / skin rash / itchiness / headache / dizziness / weakness / unexpected or uncontrollable bleeding / coffee-ground vomiting / brown urine / black stool / swelling / pain

Facts between Dabigatran and Warfarin:

Dabigatran	Warfarin
No need for regular blood-check	Regular blood-check
Fixed dosage	Regular dosage adjustment based on blood result
Not much food avoidance	A number of food that can affect drug efficacy has to be avoided

We indeed do not expect significant harms related to your participation to the study. In the

unlikely event of harm resulting directly from your participation in this study, medical treatment will be provided. Discontinuation of study treatment depends on discretion of investigator based on your medical condition, subsequent management and alternative medication use. Your willingness will be taken into consideration and prioritize. We are open to discussion to your concern and you definitely have the rights at any time to informedly withdraw from the study.
There are no special compensation arrangements provided to you in this study. If you are harmed due to someone's negligence, you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspects of the way you have been approached or treated during the course of this study, the normal health service complaint mechanisms will be available to you.

If you have any queries related to the insurance coverage from your own insurer(s) for your participation in the study, please discuss with your insurance consultant(s).

What are the alternatives for treatment?
Your participation in this study is absolutely voluntary. You may choose not to participate in this study by simply telling our research staff. If you decline this study, your medical appointments and medications will remain unchanged, or you may have to take alternative medical advice from doctor(s). You also have the rights at any time to withdraw from the study. In this case, we may arrange a final study visit for assessing and monitoring your health status. Your future follow-up appointments will be scheduled and conducted as directed by your physician. Your decision will not in any way affect your medical care or treatments.

What if new information becomes available?
During the course of the study, if any new information becomes available that may affect investigators' medical decision and/or relate to your willingness to continue to participate in this study, your research doctor will tell you about it in a timely manner and discuss with you. You would have the rights of access to personal data and known study results, if and when needed.

There are no foreseeable circumstances that the study will be ended unintentionally. Unless there is safety concern of the investigational drug from relative studies or from drug manufacturers, the study will be held according to protocol. In case of official mid-way termination of study, participants will be arranged similarly as of study discontinuation, with additional medical assessment and treatments as required to ensure patient safety.

Will my participation in this study be kept confidential?
As a subject in this research study, all your information will be kept confidential. Your name or your personal identity will not be used for any public purposes, publications, or transmitted

outside of the medical centre. Under the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance (Cap. 486), you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding to the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study.

By consenting to participate in this study, you expressly authorize the access to, the use of, and the retention of your personal data by the investigator(s) and members of his research team, representatives of the sponsor, and Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) for the purposes and in the manner described in this informed consent process.

By consenting to participate in this study, you also expressly authorize relevant government agencies (e.g. Hong Kong Department of Health) to get access to your personal data for the purpose of checking and verifying the integrity of study data and assessing compliance with the study protocol and other relevant requirements.

For any queries, you should consult the Privacy Commissioner for Personal Data or his office (tel no.: 852-2827-2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

Who should I contact if have questions?

If you have any questions regarding to this study, you may contact Dr. Siu Chung Wah at 852-2255-3597. If you have any queries regarding to your rights in the study, you may contact the Secretary of HKU/HA HKU IRB at 852-2255-4086.

Consent Form

Study Name: **Rationale and design of Dabigatran for Mitral Stenosis Atrial Fibrillation Trial**

Study Principal Investigator: Prof. SIU Chung Wah David

By signing below, I agree that:

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

Participant's signature	Participant's name	Date
Witness's signature	Witness's name	Date
Investigator's signature	Investigator's name	Date

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 7
	2b	All items from the World Health Organization Trial Registration Data Set	Uploaded to BMJ Open server
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	18

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8, Table
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9 Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11-12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12-13

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO Trial Registration Data Set

1. Primary Registry and Trial Identifying Number	Clinicaltrial.gov NCT04045093
2. Date of Registration in Primary Registry	First posted on August 5, 2019
3. Secondary Identifying Numbers	None
4. Source(s) of Monetary or Material Support	None
5. Primary Sponsor	None
6. Secondary Sponsor(s)	None
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	Fax: (852) 2818-6304, E-mail: cwdsiu@hku.hk & bryanyan@cuhk.edu.hk.
9. Public Title	Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study
10. Scientific Title	Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study
11. Countries of Recruitment	Hong Kong (China) and China
12. Health Condition(s) or Problem(s) Studied	Atrial fibrillation, mitral stenosis
13. Intervention	Experimental Arm: Dabigatran 150mg or Dabigatran 110mg (twice daily) according to creatinine clearance level, twice daily) Active Comparator Arm: Warfarin with dosage adjustment according to INR level (targeting to INR 2-3)
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: • Patients with atrial fibrillation documented with standard 12-lead ECG documented atrial fibrillation on the day of screening or randomization • Patients with age 18 years old or above • Patients with moderate or severe mitral stenosis, i.e. mitral valvular area (MVA) <1.5cm2

	• Patients should be able to provide a written informed consent • Patients should have all 4 inclusion-criteria fulfilled to be qualified for the study <u>Exclusion criteria:</u> • Patients with prosthetic valve, or with active endocarditis • Patients with planned valvular intervention within 1 year • Patients with left atrial appendage occlusive device • Patients with planned AF ablation • Patients with history of intracranial, intraocular, spinal, or retroperitoneal bleeding • Unexplained anemia (haemoglobin level <10g/dL) or thrombocytopenia (platelet count <100x10*9/L) • Need for anticoagulant therapy of disorders other than atrial fibrillation • Patients receiving antiplatelet therapy for disorders other an atrial fibrillation • Uncontrolled hypertension (systolic blood pressure >180mmHg and/or diastolic blood pressure >100mmHg) • Estimated creatinine clearance equal to or less than 30mL/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 e.g. drug addiction, alcohol abuse)
15. Study Type	Study Type: Interventional (Clinical Trial) Participants Allocation: Randomized (details in protocol manuscript) Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Prevention
16. Date of First Enrollment	June 1, 2020
17. Target Sample Size	686
18. Recruitment Status	Pending
19. Primary Outcome(s)	1. Stroke, time frame: 1 year 2. Systemic embolism, time frame: 1 year
20. Key Secondary Outcome(s)	1. Ischemic stroke, time frame: 1 year 2. Hemorrhagic stroke, time frame: 1 year 3. Intracranial haemorrhage, time frame: 1 year 4. Major bleeding, time frame: 1 year 5. Death, time frame: 1 year

BMJ Open

Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) : A Randomized, Open-label study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Valvular heart disease < CARDIOLOGY, CLINICAL PHARMACOLOGY, Adult cardiology < CARDIOLOGY

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Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS): A Randomized, Open-label study

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ABSTRACT

Introduction: Current international guidelines recommend non-vitamin K oral anticoagulants (NOACs) for stroke prevention amongst 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 remain disproportionately prevalent in Asian countries compared with the developed countries. This prospective, randomized, 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 mitral stenosis not planned for valvular intervention in the coming 12 months will be randomized in a 1:1 ratio to receive dabigatran 110 mg or 150 mg twice daily or warfarin with INR 2-3 in an open-label design. Patients with estimated creatinine clearance <30 ml/min, or with a concomitant indication for anti-platelet therapy will be excluded. The primary outcome is a composite of stroke and systemic embolism. Secondary outcomes are ischaemic stroke, systemic embolism, hemorrhagic 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.

Registration details: ClinicalTrials.gov (NCT04045093).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first investigator-initiated, open-label, randomized clinical trial to compare 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 generalizability 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 (OAC) for thromboprophylaxis is the cornerstone in AF management. In previous randomized 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 K 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 amongst 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-anticoagulated[7] and the highest recurrences.[8] However, patients with AF and underlying MS are typically excluded in randomized 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 7,357 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 annualized risk of 2.22%/year, compared to that of 4.19%/year for patients treated with warfarin, (adjusted HR: 0.28; 95% confidence interval (CI): 0.18 to 0.45), suggesting a potential role of NOAC amongst patients with AF and underlying MS.[8 10 11]

This is of particular importance for Asian AF patients, 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 undermines the benefits of warfarin therapy.[12,13 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 sub-analyses of pivotal randomized controls trials[15-17] as well as in studies using real-world data.[18-23] To our knowledge, this is the first multicentre randomized control trial aims to comparing NOAC to 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 (SPIRIT).[24] [25] The underlying protocol follows the Consolidated Standards of Reporting Trials (CONSORT). [26] [27] The study is registered with the www.ClinicalTrials.gov (NCT04045093).

Study Design

This is an investigator-initiated, open-label, randomized clinical trial to compare effectiveness and safety of dabigatran 150 mg or 110 mg twice daily according to kidney function with warfarin therapy with target international normalized 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 SAR China and Mainland China. Written informed consent will be obtained from all study participants. Table 1 summarizes 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 electrocardiography (ECG) performed at screening or randomization and moderate or severe MS as defined as the mitral valvular area (MVA) of 1.0-1.5 cm^2 and <1.0 cm^2, 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 or retroperitoneal haemorrhage; unexplained anaemia with haemoglobin level <10 g/dL, or thrombocytopenia with platelet count $<100\times10^9$/L; need for anticoagulant or antiplatelet therapy of conditions other than AF; concomitant use of potent P-gp inhibitor(s) or drugs with a known interaction with dabigatran; uncontrolled hypertension; significant kidney impairment with estimated creatinine clearance (CrCl) ≤30 mL/min by the Cockcroft-Gault Formula; [28] liver dysfunction of Child-Pugh Stage B or C; [29] pregnancy or if there is child-baring 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 summarized 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 110mg two times per day was recommended in patients with creatinine clearance in the range 30-49 ml/min. For patients randomized 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 twice daily, whereas those with CrCl between 30 to 50 ml/min will receive dabigatran 110 mg twice daily. For patients previously on warfarin randomized 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 randomized 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 i.e., 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 randomized to receive warfarin, INR will be measured at least every 8 weeks with a target INR of 2.0 to 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 randomization and then every 4 months during the study period of 1 year (Table 2). 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 randomized 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, hemorrhagic 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 will be further classified as ischaemic stroke and hemorrhagic stroke according to computerized axial tomography or magnetic resonance imaging of the brain. Intracranial haemorrhage (ICH) consists of hemorrhagic stroke (intra-cerebral haemorrhage and cerebellar haemorrhage), subdural haemorrhage , and subarachnoid haemorrhage , and will be confirmed with computerized axial tomography or magnetic resonance imaging 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 2 g/dL, 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 5 g/dL, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or

requiring surgery. All outcomes will be adjudicated by 2 independent investigators in a blinded fashion.

Sample Size Calculation

The primary analysis is to test whether dabigatran is noninferior 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 noninferior in patients with AF and moderate or severe MS. The noninferiority 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 noninferiority hypothesis with the upper boundary of the one-sided 95% confidence interval (CI) (or equivalent with a 90% two-sided CI) and the Hazard ratio (HR) of the primary outcome below the noninferiority margin of 1.49. Hierarchical analysis for superiority will be performed if noninferiority is established.

Statistical Analysis

Baseline data will be reported as means and standard deviations 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 randomization included in the analysis. Clinical events that occur after randomization 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 (version 12.0).

Randomization

Randomization 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 are blinded to this study will generate the random-number table. Study staff responsible for enrolment will be informed of randomization assignment by phone. Subjects and clinicians will not be blinded to the randomization assignment. Data staff responsible for data entry will be blinded from randomization 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 (Supplementary File 1). Important protocol modifications will be 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, 4 subgroups are at particularly high risk necessitating long-term anticoagulation therapy. These include (1) patients with non-valvular AF and high CHA_2DS_2-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 CHA_2DS_2-VASc score. In the 4 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 randomizing 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 randomized 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 mitral stenosis 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 amongst patients with AF and MS is only second to those with mechanical valvular replacement ranging from 4 to 17%. Second, previous epidemiological studies[12,13 14 21 33 34] and sub-analyses of the pivotal NOAC trials[15-17] have consistently reported a much higher nominal risk of ICH amongst Asians than non-Asians, favouring NOACs over warfarin therapy. More importantly, the notoriously poor time in therapeutic range (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 amongst 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 non-valvular AF patients 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 twice daily; 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 (150mg BD) 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 AF patients from territory-wide registries from Asia Pacific region. Plausible explanations include suboptimal quality of warfarin therapy with low time in therapeutic range 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.

Author contributions:

MZ, EWC, JH, CKW, BPY and CWS contributed to the conception and design of the study. MZ, EWC, JH, CKW, YML, DH, CCL, CCT, AYTW, ASYY, KKWC, YF, NT, JYC, CYY, KLL, CWC, HL, AN, KF, MHJ, KHY, BPY and CWS contributed to the acquisition of data. Data analysis and interpretation will be conducted by MZ, EWC, JH, CKW, BPY and CWS. MZ, EWC, JH, CKW, BPY and CWS wrote first draft of the protocol and revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published.

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None declared.

Legends:

Figure 1. Design of the DAVID-MS study.

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

Supplementary Files:

Supplementary File 1: Model consent form in English

Tables:

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
• Patients with AF documented with standard 12-lead ECG documented AF on the day of screening or randomization • Patients with age >18 years • Patients with moderate or severe MS i.e., MVA <1.5 cm^2 • Patients should be able to provide a written, informed consent. • Patients should have all 4 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 anemia (haemoglobin level <10 g/dL) or thrombocytopenia (platelet count <100×10^9/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 mmHg and/or diastolic blood pressure >100 mmHg) • 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 (e.g. drug addiction, alcohol abuse).

Abbreviations: AF: atrial fibrillation; MS: mitral stenosis; MVA: mitral valvular area

Table 2. 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 & exclusion criteria		X									
Randomization		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 randomized to receive warfarin

**UNS (unplanned visit): (X) The marked item is optimal and performed according to the judgment of researchers.

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

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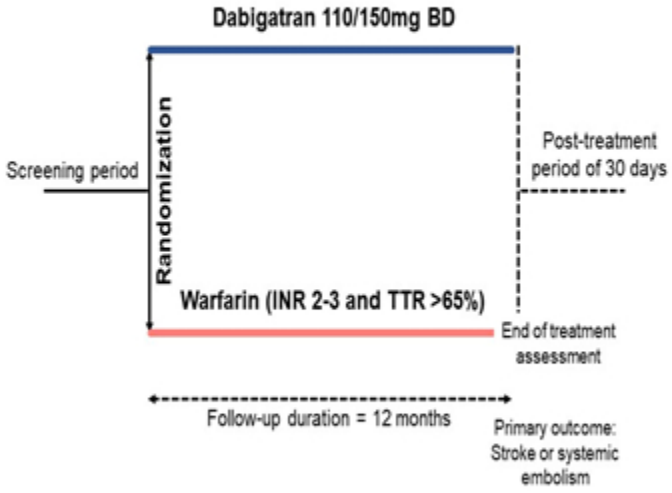

Figure 1. Design for the DAVID-MS study

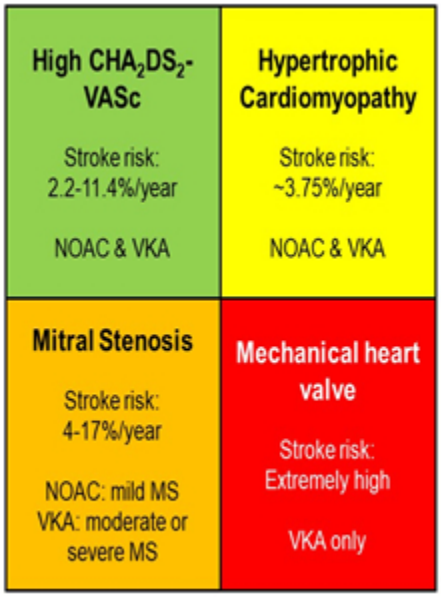

Figure 2. Four main groups of patients with AF requiring long-term anticoagulation therapy. MS: mitral stenosis; NOAC: non-vitamin K oral anticoagulant; and VKA: vitamin K antagonist.

Information sheet

Study Name: **Rationale and design of Dabigatran for Mitral Stenosis Atrial Fibrillation Trial**

Version no.: v.1.2 (18/Nov/2019)

Protocol no.: DAMS-01

Protocol version no.: v.1.2 (18/Nov/2019)

Study site: Queen Mary Hospital

Study Principal Investigator: Prof. SIU Chung Wah David

You are being invited to take part in a research study. Before you decide, it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask the study doctor or research staff any questions you may have before signing the attached consent form.

About This Study

The purpose of our study is to find out the efficacy and safety of non-vitamin K oral anticoagulants (NOACs), the drugs used to prevent ischemic stroke for atrial fibrillation (AF) patients.

Why have I been chosen?

You are suffering from atrial fibrillation, a heart disease associated with 5-fold increase in ischemic stroke risk. Currently, NOAC is one of the most effective drug groups in preventing ischemic stroke under this condition. Among these AF patients, some have underlying valvular heart diseases with particularly high risk for stroke for those with mitral stenosis (MS) and the annual stroke rate ranges from 4% to 17% if left un-anticoagulated.

However, there's lack of research-based evidence to indicate the efficacy and safety of NOACs for patients with both AF and MS. As a result, there're still no standard guidelines for stroke prevention management regarding to NOACs for AF patients with underlying moderate to severe MS. On the other hand, there's recent foreign study suggesting the potential role of NOACs amongst AF patients with underlying MS in stroke prevention.

Concerning the very high risk for stroke for AF patients with underlying MS, also higher baseline risk of intracranial haemorrhage and higher ischemic stroke risk in Asian populations, we launch this study aiming at comparing the efficacy and safety of one of the NOACs – Dabigatran (150mg or 110mg according to subjects' renal function) – with normal warfarin

therapy in AF patients with moderate or severe MS. We plan to recruit a total of 686 subjects randomizing into 2 groups of investigational Dabigatran and warfarin in a 1:1 ratio. Since you have carried both heart problems, you are invited into our study.

What will happen to me if I take part?

If you meet the criteria of this study and are being enrolled, our investigator(s) shall have a short interview with you (less than 10 minutes) to explain the benefits and potential side effects of NOACs. Enough time will be given for understanding and solving any queries raised, and written consent has to be signed for agreement of study participation. You will then be randomized into either Dabigatran or warfarin group, which is open to your notice.

Study period of individual participants will be around 1 year. We will obtain medical history directly from you, hospital record as well as electronic medical record under Hospital Authority. Within the study time frame, you will have the first follow-up at 2-week interval after randomization. After that, we will arrange regular follow-ups of every 4 months for you to monitor the effect and safety of the drug prescribed until the study ends. We will perform certain investigations during study visits, including physical examination, echocardiography (during the first visit only) and blood sampling via venipuncture. You will be responsible to comply with the scheduled study visits, study procedures and prescription plan, and report to us as soon as possible for any adverse effects appear.

There are no extra expenses anticipated for participating in the clinical trial. You simply need to pay for the regular specialty follow-up fee and the regular medication fee under Hospital Authority policy as usual for each time scheduled or unscheduled follow-ups. On the other hand, there will not have reimbursement in any forms from the study.

What are the benefits of participating?

NOAC is currently a self-financing item under Hospital Authority. That means patients need to purchase the drug themselves or only patients meet certain medical criteria will the item be free. In this study, according to randomization, you will be given free-of-charged NOAC for stroke prevention secondary to AF, which is significantly safe and efficacious over the traditional warfarin therapy. Close monitoring by experienced medical staff will be held to ensure your safety.

Besides, your contribution is important to provide valuable information for stroke prevention strategy for patients with mitral stenosis and that may be immediately translatable to real clinical practice. It may also provide necessary evidence for establishing relevant universal guidelines.

What if something goes wrong?

Both dabigatran and warfarin are registered medications under the Pharmacy and Poisons Ordinance (Cap. 138) in Hong Kong Special Administrative Region. They have been overseen for their safety, efficacy and quality. Being randomized into either group (a 50/50 chance like flipping a coin) in this study, you will be prescribed corresponding anticoagulant with dosage adjustment based on your coagulation or renal blood-check result, according to standard medical guidelines.

As with all other researches regarding to clinical trial, there may involve harms and risks that are already known or currently unknown and unforeseen with the drug treatment. You are free to raise queries and concerns to our investigators prior to consenting and at any time during the study. Our medical staff will closely monitor your condition throughout the whole study period and you are responsible to tell our research staff as soon as possible for any changes in medical condition. Below are listed known side effects of the two anticoagulants.

Side effects of Dabigatran:

Common – nausea / diarrhea / indigestion / stomach upset / stomach pain / stomach burn / unexpected bruising / minor bleeding

Less common or rare – allergy / skin rash / itchiness / headache / dizziness / weakness / unexpected or uncontrollable bleeding / coffee-ground vomiting / brown urine / black stool / swelling / pain

Side effects of Warfarin:

Common – unexpected bruising / minor bleeding / bloating / nausea / vomiting / diarrhea / loss of appetite

Less common or rare – allergy / skin rash / itchiness / headache / dizziness / weakness / unexpected or uncontrollable bleeding / coffee-ground vomiting / brown urine / black stool / swelling / pain

Facts between Dabigatran and Warfarin:

Dabigatran	Warfarin
No need for regular blood-check	Regular blood-check
Fixed dosage	Regular dosage adjustment based on blood result
Not much food avoidance	A number of food that can affect drug efficacy has to be avoided

We indeed do not expect significant harms related to your participation to the study. In the

unlikely event of harm resulting directly from your participation in this study, medical treatment will be provided. Discontinuation of study treatment depends on discretion of investigator based on your medical condition, subsequent management and alternative medication use. Your willingness will be taken into consideration and prioritize. We are open to discussion to your concern and you definitely have the rights at any time to informedly withdraw from the study.
There are no special compensation arrangements provided to you in this study. If you are harmed due to someone's negligence, you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspects of the way you have been approached or treated during the course of this study, the normal health service complaint mechanisms will be available to you.

If you have any queries related to the insurance coverage from your own insurer(s) for your participation in the study, please discuss with your insurance consultant(s).

What are the alternatives for treatment?
Your participation in this study is absolutely voluntary. You may choose not to participate in this study by simply telling our research staff. If you decline this study, your medical appointments and medications will remain unchanged, or you may have to take alternative medical advice from doctor(s). You also have the rights at any time to withdraw from the study. In this case, we may arrange a final study visit for assessing and monitoring your health status. Your future follow-up appointments will be scheduled and conducted as directed by your physician. Your decision will not in any way affect your medical care or treatments.

What if new information becomes available?
During the course of the study, if any new information becomes available that may affect investigators' medical decision and/or relate to your willingness to continue to participate in this study, your research doctor will tell you about it in a timely manner and discuss with you. You would have the rights of access to personal data and known study results, if and when needed.

There are no foreseeable circumstances that the study will be ended unintentionally. Unless there is safety concern of the investigational drug from relative studies or from drug manufacturers, the study will be held according to protocol. In case of official mid-way termination of study, participants will be arranged similarly as of study discontinuation, with additional medical assessment and treatments as required to ensure patient safety.

Will my participation in this study be kept confidential?
As a subject in this research study, all your information will be kept confidential. Your name or your personal identity will not be used for any public purposes, publications, or transmitted

outside of the medical centre. Under the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance (Cap. 486), you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding to the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study.

By consenting to participate in this study, you expressly authorize the access to, the use of, and the retention of your personal data by the investigator(s) and members of his research team, representatives of the sponsor, and Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) for the purposes and in the manner described in this informed consent process.

By consenting to participate in this study, you also expressly authorize relevant government agencies (e.g. Hong Kong Department of Health) to get access to your personal data for the purpose of checking and verifying the integrity of study data and assessing compliance with the study protocol and other relevant requirements.

For any queries, you should consult the Privacy Commissioner for Personal Data or his office (tel no.: 852-2827-2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

Who should I contact if have questions?

If you have any questions regarding to this study, you may contact Dr. Siu Chung Wah at 852-2255-3597. If you have any queries regarding to your rights in the study, you may contact the Secretary of HKU/HA HKU IRB at 852-2255-4086.

Consent Form

Study Name: **Rationale and design of Dabigatran for Mitral Stenosis Atrial Fibrillation Trial**

Study Principal Investigator: Prof. SIU Chung Wah David

By signing below, I agree that:

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

Participant's signature	Participant's name	Date
Witness's signature	Witness's name	Date
Investigator's signature	Investigator's name	Date

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 7
	2b	All items from the World Health Organization Trial Registration Data Set	Uploaded to BMJ Open server
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	18

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8, Table
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9 Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11-12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12-13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12-13

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO Trial Registration Data Set

1. Primary Registry and Trial Identifying Number	Clinicaltrial.gov NCT04045093
2. Date of Registration in Primary Registry	First posted on August 5, 2019
3. Secondary Identifying Numbers	None
4. Source(s) of Monetary or Material Support	None
5. Primary Sponsor	None
6. Secondary Sponsor(s)	None
7. Contact for Public Queries	Prof Chung-Wah SIU, MD Cardiology Division, Department of Medicine, The University of Hong Kong, Hong Kong SAR, China Tel: (852) 2255-4694, Fax: (852) 2818-6304, E-mail: cwdsiu@hku.hk & bryan.yan@cuhk.edu.hk.
8. Contact for Scientific Queries	Prof Chung-Wah SIU, MD Cardiology Division, Department of Medicine, The University of Hong Kong, Hong Kong SAR, China Tel: (852) 2255-4694,

	Fax: (852) 2818-6304, E-mail: cwdsiu@hku.hk & bryanyan@cuhk.edu.hk.
9. Public Title	Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study
10. Scientific Title	Protocol for Rationale and Design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS) study
11. Countries of Recruitment	Hong Kong (China) and China
12. Health Condition(s) or Problem(s) Studied	Atrial fibrillation, mitral stenosis
13. Intervention	Experimental Arm: Dabigatran 150mg or Dabigatran 110mg (twice daily) according to creatinine clearance level, twice daily) Active Comparator Arm: Warfarin with dosage adjustment according to INR level (targeting to INR 2-3)
14. Key Inclusion and Exclusion Criteria	Inclusion criteria: • Patients with atrial fibrillation documented with standard 12-lead ECG documented atrial fibrillation on the day of screening or randomization • Patients with age 18 years old or above • Patients with moderate or severe mitral stenosis, i.e. mitral valvular area (MVA) <1.5cm2

	• Patients should be able to provide a written informed consent • Patients should have all 4 inclusion-criteria fulfilled to be qualified for the study <u>Exclusion criteria:</u> • Patients with prosthetic valve, or with active endocarditis • Patients with planned valvular intervention within 1 year • Patients with left atrial appendage occlusive device • Patients with planned AF ablation • Patients with history of intracranial, intraocular, spinal, or retroperitoneal bleeding • Unexplained anemia (haemoglobin level <10g/dL) or thrombocytopenia (platelet count <100x10*9/L) • Need for anticoagulant therapy of disorders other than atrial fibrillation • Patients receiving antiplatelet therapy for disorders other an atrial fibrillation • Uncontrolled hypertension (systolic blood pressure >180mmHg and/or diastolic blood pressure >100mmHg) • Estimated creatinine clearance equal to or less than 30mL/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 e.g. drug addiction, alcohol abuse)
15. Study Type	Study Type: Interventional (Clinical Trial) Participants Allocation: Randomized (details in protocol manuscript) Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Prevention
16. Date of First Enrollment	June 1, 2020
17. Target Sample Size	686
18. Recruitment Status	Pending
19. Primary Outcome(s)	1. Stroke, time frame: 1 year 2. Systemic embolism, time frame: 1 year
20. Key Secondary Outcome(s)	1. Ischemic stroke, time frame: 1 year 2. Hemorrhagic stroke, time frame: 1 year 3. Intracranial haemorrhage, time frame: 1 year 4. Major bleeding, time frame: 1 year 5. Death, time frame: 1 year