Statistical and Epidemiological Analysis Plan for Protocol titled

Pradaxa Initiation Post-Stroke Study: SITS-Pradaxa1. A retrospective analysis of existing data from the SITS-AF Registry on treatment initiation of dabigatran etexilate in non-valvular atrial fibrillation patients hospitalized with acute ischemic stroke

(BI protocol study no. 1160-0235)

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2 RESEARCH QUESTIONS AND OBJECTIVES

2.1 Primary objective:

A. To evaluate the timing of dabigatran treatment initiation in patients with non-valvular atrial fibrillation (NVAF) after hospitalization for first ever ischemic stroke (the index event), in order to prevent secondary stroke.

Meaning: To describe the distribution of dabigatran treatment initiation times after hospitalization for first-ever ischemic stroke (the index event) in patients with non-valvular atrial fibrillation (NVAF) having received dabigatran within the 3 months after index event.

2.2 Secondary objectives:

B. To describe baseline characteristics of patients treated with dabigatran according to time of dabigatran initiation.

C. To describe self-reported factors important for the physician's decision as to the time of dabigatran initiation in the post-ischemic stroke setting.

D. To describe self-reported factors important for physician's decision as to which dabigatran dose was used in the post-ischemic stroke setting.

3 Definitions and Outcome Measurements/Variables

3.1 Definitions:

- **Index event** is defined as the first ever acute ischemic stroke that led to hospital admission for eligible patients (baseline visit).
- **Baseline visit:** day of hospital admission for ischaemic stroke
- The **3 month follow-up data point** for patients is 90 (+/- 10) days after the index event.

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3.2 Primary Outcome Measurements/Variables

A. The time lapsed from the index event to the initiation of the dabigatran treatment within 3 months.(continuous and categorical).

3.3 Secondary outcomes Measurements/Variables

B. The following baseline characteristics are considered as secondary outcomes for patients treated with dabigatran within the 3 months after index event:

- Age
- Gender
- CHA_2DS_2-VASc stroke risk score
- HAS-BLED bleeding risk score

C. Factors important for the physician's decision as to the time of dabigatran initiation. A pre-specified list of self-reported factors important for physician's decision when to initiate dabigatran between day 0 and 3 months post index event, have been included in the SITS-AF database. These are based on the following two questions, with the subsequent possible responses:

Question 1: Reasons to delay start of dabigatran therapy (multiple choices can be selected)

- Reason is not specified
- Severity of stroke
- Location of infarct
- Size of infarct
- Hemorrhagic transformation of infarct
- Intracranial hemorrhage, spontaneous or as a complication of intervention
- Type of intervention used to treat ischemic stroke (e.g. fibrinolysis)
- Coagulation Lab parameters
  - APTT
  - ECT Time
  - Thrombin Time
  - INR
- Patient's Stroke risk factors

- Patient's Bleeding risk factors
- Patient currently in sinus rhythm
- Renal function
- Recommendation from specialist (e.g. Cardiologists)
- Practical considerations (e.g. date of follow up appointment, limitation of appointments or INR)
- Patient preference
- Other
    - Specify other (Reasons to delay start of oral anticoagulation therapy)

Question 2: Reasons for not planned to start oral anticoagulation therapy (multiple choices can be selected)

- Age
- Falling risk
- Dementia
- Cognitive decline
- Patient preference
- Co-morbidity (e.g. fragility index, etc.)
- Other

D. Factors important for physician's decision as to which dabigatran dose was used. A pre-specified list of self-reported factors important for physician's decision which dabigatran dose have been included in the SITS-AF database based the following question and subsequent possible responses:

- Question 1: Reasons for the dose of oral anticoagulation (multiple choices can be selected)Patient age
- Patient gender
- Severity of stroke
- Location of infarct
- Size of infarct
- Hemorrhagic transformation of infarct
- Intracranial hemorrhage, spontaneous or as a complication of intervention
- Type of intervention used to treat ischemic stroke (e.g. fibrinolysis)
- Type of AF (e.g. paroxysmal/ persistent/ permanent)
- Patient's Stroke risk factors
- Patient's Bleeding risk factors
- Coagulation Lab parameters
    - APTT
    - ECT Time
    - Thrombin Time

    - INR
- Patient medical history (e.g. previous GI bleed, etc)
- Patient co-morbidities (e.g. heart failure, diabetes, etc)
- Patient renal function
- History of previous stroke, transient ischemic attack, or systemic embolism
- Co-medication affecting haemorrhagic risk (e.g. ASA, clopidogrel, NSAIDs, verapamil)
- Co-medication other (e.g. antihypertensive, etc.)
- Recommendation from specialist (e.g. Cardiologists)
- Other
    - Specify other (Reasons for the dose of oral anticoagulation)

3.5 Covariates:

The following variables will be considered to characterize the patients in addition to the key variables defined for secondary outcomes B

- Patient demographics (, e.g. weight, smoking)
- Country
- Stroke severity based on National Institute of Health Stroke Scale (NIHSS),
- pre-stroke functional status by mRS
- Signs of current/ acute infarction in the brain imaging scans
- Prior TIA

- Time since AF diagnosis
- Antithrombotic treatment for stroke prevention history prior index event
- Comorbidities (Hypertension, Diabetes, Hyperlipidaemia, Congestive Heart Failure, Systemic embolism, MI, PAD, complex aortic plaque, abnormal kidney function, abnormal liver function,
- Prior Bleeding (history and/or predisposition to bleeding)Relevant comedications at time of index stroke (as listed in Appendix 7.1)
- CHADS2
- Type of Acute Intervention (Intravenous thrombolysis, Intraarterial thrombolysis, Mechanical thrombectomy)
- Time from hospital admission – start and dose of dabigatran treatment for stroke prevention in NVAF (
- ...

4 Study design

Data from the SITS-International AF registry will be extracted for the purpose of analysis. Patients with NVAF presenting with their first ever acute ischemic stroke who are registered in the SITS International Registry from 1 July 2014 until approximately 31 July 2018 and meeting the inclusion and not having the exclusion criteria will be included in the study.

4.1 Inclusion criteria

1.) Patients with non-valvular Atrial Fibrillation (NVAF)
2.) Patients presenting with their first acute ischemic stroke
3.) 18 years of age

4.2 Exclusion criteria

- Documentation that the patient was enrolled or is planned to be enrolled in an investigational clinical trial at the time of the onset of the index event and for the duration of the data collection

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5 Information on Data Extraction, Limitations and Bias

Because for most of the objectives we are only using a sample of subjects that initiated treatment prior to dying, having a second stroke or leaving care, we have a selected sample. Therefore, all findings are conditional on subjects actually initiating treatment within 3 months and subjects living and remaining stroke free long enough to initiate treatment. Since this is not a baseline

characteristic, the baseline associations with time to treatment initiation are not generalizable to the population of subjects that would initiate treatment prior to 3-months if they could, as many subjects will die or have second strokes prior to this. For this reason, all findings are hypothesis generating, and would need to be confirmed in a study that includes all subjects which are eligible to initiate treatment prior to 3 months regardless of their actual treatment.

Weaknesses/ limitations

This is a non-interventional study based on existing data, therefore its quality relies on accuracy of recorded data. Important data may not be available. In the absence of randomization, it can be difficult to control for bias and confounders.

Power:

No formal power calculations have been done as this is a descriptive study.

Selection bias

There is a risk of selection bias at the patient level. Sites might preferentially include "interesting" cases to the SITS study. To minimize selection bias at the patient level, centers were reminded by e-mail every 3 months that all consecutive patients from each site who meet entry criteria must be included in the SITS-Registry.

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6 Planned Analyses

6.1 Primary Analysis

This analysis will be done for NVAF patients presenting with first ischemic acute stroke and treated with dabigatran within 3 months of index event.

To describe the distribution of dabigatran treatment initiation times in patients with non-valvular atrial fibrillation (NVAF) after hospitalization for first-ever ischemic stroke (the index event) treated with dabigatran, we will

1. Create a histogram of initiation times by day.
2. Calculate mean, standard deviation and 95% (Standard Normal) confidence intervals (CI) of the Mean, as well as the median, interquartile ranges, minimum and maximum values.
3. Create frequency table by time periods. Give the absolute count of subjects and the proportion of subjects in each group. The time periods to be considered are 0-24h, >24-72h, >3-7d >7-14d, >14-28d, >28d-3m, however these categories may be revised depending on the distribution of initiation times to ensure sufficient patient numbers in each category.

We do not expect to have any missing values in the time to dabigatran treatment initiation. However, if there are missing values collected, they will be summarized in the frequency table as a separate category. Proportions for all other categories will not include the missing values in the dominator (as this is what has been done in pervious works for all previous SITS-MOST and/or SITS-ISTR publications [P07-00880, P08-11746].). The proportion of missing values will be out of all subjects sampled.

6.2 Secondary Analysis:

These analyses will be done for NVAF patients presenting with first ischemic acute stroke and treated with dabigatran within 3 months of index event.

6.2.1 To describe baseline characteristics for patients treated with dabigatran according to time of dabigatran initiation.

Descriptions will only be done for the subgroups (of time to initiation) consisting of at least 100 patients. We Will:

Provide the mean, SD and 95% (Student's T based or Resampling method based) CI for all continuous or the proportion and Clopper-Pearson 95% CI for all binary or categorical (within each category) for all subject baseline characteristics for all time periods, with time periods defined as in the primary analysis section. We will use the standardized difference < 10% in absolute value as indicating a negligible difference in the mean or prevalence of a covariate between groups. The earlier initiation time category will be used as the reference group for calculation of the standardized differences. No P-values will be provided for these comparisons.

1. run univariate and multivariable regression models with the dependent variable time-to-initiation as a continuous variable in days, the independent variables in these models will include age and baseline stroke severity as measured by NIHSS score at index stroke, pre-stroke functional status by mRS, prior treatment with anticoagulation, Signs of current/ acute infarction in the brain imaging scans, CHA2DS2-VASc stroke risk score as the continuous value and/or categorized into low, intermediate and high risk and HAS-BLED bleeding risk score by the mean and/or or categorized into low or high risk. We will run a linear (or log-linear) regression model. Complete case analysis will be performed (exclusion from the regression of subjects with at least one missing value on any of the predictors or outcome analyzed). P-values

will not be adjusted for multiple comparisons. Other baseline variables, for example those identified in analysis 1, may be included in one or more of the models. However, P-values and confidence intervals will not be reported from these investigations.

2. Make scatter or boxplots of each of time-to-initiation by each baseline characteristics of interest

6.2.2 To describe self-reported factors important for the physician's decision as to the time of dabigatran initiation in the post-ischemic stroke setting.

For Question 1 ("Reasons to delay start of oral anticoagulation therapy"), we will, for NVAF patients presenting with first ischemic acute stroke and treated with dabigatran within 3 months of index event:

1. Make frequency tables of physician responses
2. Make frequency tables of reasons by time period for each physician response with time periods as defined in the primary analysis. Time periods with less than 100 patients will not be considered. Comparisons of the distribution of reasons between different time periods may be made and a standardized difference of 10% or more in absolute value will be considered notable.
3. Make frequency tables of time periods by physician responses (reasons) with time periods as defined in the primary analysis. Reasons with less than 100 patients will not be considered. Comparisons of the distribution of time periods between different reasons may be made and a standardized difference of 10% or more in absolute value will be considered notable.

For Question 2 ("Reasons for not planned to start oral anticoagulation therapy"), a descriptive analysis (frequency tables of physician responses) will be done for NVAF patients presenting with first ischemic acute stroke and not receiving any OAC within 3 months of index event.

6.2.3 To describe self-reported factors important for the physician's decision as to the dose of dabigatran in the post-ischemic stroke setting.

For NVAF patients presenting with first ischemic acute stroke and treated with dabigatran within 3 months of index event, we will:

1. Make frequency tables for physician responses to question "Reasons for the dose of oral anticoagulation"
2. Make frequency tables for physician responses (reasons) for each dose categories 110, or 150 mg 2 times daily. Comparisons of the distribution of reasons between the dose categories may be made and a standardized difference of 10% or more in absolute value will be considered notable. Subgroup analysis for dose will only be performed if there are at least 100 patients in the subgroup
3. Make frequency tables for dose category (110, or 150 mg 2 times daily) for each physician response (reason) with at least 100 patients. Comparisons of the distribution

of dose between the reasons provided may be made and a standardized difference of 10% or more in absolute value will be considered notable.

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7 Appendixes

7.1 Appendix 1

SITS Variables names particularly important for this study

Patient/ file code
Country name
Hospital/ Centre code
Gender
Age At Stroke Onset
Participation In Other Trials
Treatment at baseline
Aspirin
Dipyridamole
Clopidogrel
Other Antiplatelet
Anticoagulants- Yes/ No/ Unknown
If yes, specify Anticoagulants- Not specified/ Warfarin/ Dabigatran/ Apixaban/ Rivaroxaban/ Edoxaban/ Other
If specify Anticoagulant chosen then, dose of Dabigatran as free text
Heparin/ Heparinoids for Stroke Prevention
Heparin/ Heparinoids for Prophylaxis Deep Venous Thrombosis
Anti-diabetic, oral
Insulin
Antihypertensive, IV
Antihypertensive, oral
Statin
Other treatment
NSAIDS
Risk factors at baseline
Hypertension
Diabetes
Hyperlipidaemia
Smoking
Previous Stroke
Previous TIA
Atrial fibrillation' (AF)
• Valvular AF
• Non-valvular AF

• Not specified
Congestive Heart Failure
Systemic embolism
Vascular disease- with sub-classification
If Yes,
• Myocardial infarction,
• Complex aortic plaque
• Peripheral arterial disease (PAD)
Abnormal kidney function (defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L.
Abnormal liver function (defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal)
Bleeding (history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%).
Drugs/alcohol use (concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. If a patient is not on VKA/Warfarin the value for 'labile INRs' will not be assessed)
Modified Rankin Scale (mRS) Before Stroke
NIHSS score
Systolic Blood Pressure
Diastolic Blood Pressure
Plasma glucose
Cholesterol
Temperature
APTT
Weight
Length
Current Infarct CT/MR
ASPECTS Score CT/MR
Time logistics
Time For Pick up
Hospital Arrival Date
Date Time Of Alarm
Date Time Of imaging
Date Time Of Acute intervention
Type of Acute Intervention
Intravenous thrombolysis
Intraarterial thrombolysis
• Dose Of Actilyse
Mechanical thrombectomy
During hospital stay
Rules: Questions below will be activated if;
• Previous stroke or TIA = NO

• Non-valvular Atrial Fibrillation = YES
• Oral anticoagulation (OAC)
○ ☐ Yes ☐ No ☐ Unknown
○ If Yes,
▪ Warfarin derivatives
▪ New OAC (NOAC)
• If NOAC
○ Dabigatran
○ Apixaban
○ Rivaroxaban
2h follow up
Systolic Blood Pressure
Diastolic Blood Pressure
NIHSS
24h follow up
NIHSS
Systolic Blood Pressure
Diastolic Blood Pressure
Current Infarct CT/MR
ASPECTS Score CT/MR
Local Haemorrhage CT/MR
Remote Haemorrhage CT/MR
Cerebral Oedema CT/MR
At discharge/ 7d
Diagnosis of NVAF at (previous, at or during hospital stay)
Oral anticoagulation (OAC) at = YES
▪ Warfarin derivatives
▪ New OAC (NOAC)
• If NOAC
○ Dabigatran
○ Apixaban
○ Rivaroxaban
Date & time of OAC start: DD/MM/YYYY, time: clock
OAC at discharge = No
1) Date of foreseen start of OAC if not started during hospital stay
Date: DD/MM/YYYY
Aspirin
mRS Score
NIHSS
Systolic Blood Pressure
Diastolic Blood Pressure
Date of
Dipyridamole
Clopidogrel
Other Antiplatelet

Anticoagulants Oral
Dabigatran
Dabigatran Dose
Date of Dabigatran Initiation
Anti Diabetic Oral
Antihypertensive Oral
Statin
Other
Type Of Stroke
Type Of Stroke Ischemic
Type Of Stroke Haemorrhagic
Date Time Of Death
Cause Of Death
At 3-months
Modified Rankin Scale score
If mRS=6=Dead, date/time of death
Cause of death
Patients with NVAF at discharge/ 7d but patient has not been prescribed Warfarin or NOAC (Dabigatran, Apixaban, Rivaroxaban at
1) Has the patient been prescribed Dabigatran after discharge?
If YES questions below will also be shown.
2) Date of initiation of Dabigatran for stroke prevention in NVAF
Date: DD/MM/YYYY
Dose:
Patients with NVAF has been prescribed dabigatran at discharge
Is the patient continuing the prescribed Dabigatran at 3 months follow up since start of the treatment?
- Yes/ No/ Unknown
If No, date of stop of treatment:
Reason for stop of treatment:
- Has the OAC treatment been changed?
If Yes,
Which treatment:

7.2 Appendix 2

$CHADS_2$ Stroke Risk Score

$CHADS_2$ components	**Points**
Congestive heart failure	1
Hypertension	1
Age 75 years or older	1
Diabetes mellitus	1
Prior cerebral ischemia (i.e., stroke, TIA)	2
Maximum score	6

$CHADS_2$ score is based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack and 1 point each is assigned for age 75 years or older, hypertension, diabetes, or clinical heart failure or impaired left ventricular systolic function (generally interpreted as an ejection fraction ≤ 40%). A $CHADS_2$ score of 0 identifies patients at low stroke risk, a score of 1 to 2 identifies patients at moderate stroke risk, and a score greater than 2 identifies patients at high stroke risk [Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ; Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 285 (22), 2864 - 2870 (2001)]

7.3 Appendix 3

CHA_2DS_2-VASc Stroke Risk Score

$CHA_2DS_2VAS_c$ score	
Risk factors for stroke and thrombo-embolism in non-valvular AF	
Major risk factors	**Clinically relevant non-major risk factors**
Previous stroke, TIA, or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40 %) Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease
Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VAS_c (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/systemic embolism	2
Vascular disease*	1
Age 65-74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

* myocardial infarction, complex aortic plaque and PAD

The CHA_2DS_2-VASc risk score is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a hypertension, diabetes, cardiac failure, vascular disease and female sex. On the basis of the risk strata defined in previous guidelines, a CHA_2DS_2-VASc score of 0 corresponds to "low risk", a score of 1 corresponds to "intermediate risk", and a score of 2 or more corresponds to "high risk" [Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM; Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 137 (2), 263 - 272 (2010)]

7.4 Appendix 4

HAS-BLED Bleeding Risk SCORE

Clinical characteristics comprising the HAS-BLED bleeding risk score		
Letter	**Clinical characteristic**	**Points awarded**
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
Maximum score		**9**

Hypertension is defined as history of hypertension and current uncontrolled systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. If a patient is not on VKA the value for 'labile INRs' will not be assessed and will therefore be set to 0.

A HAS-BLED score of ≥3 indicates 'high risk' for AF patients to develop a bleed and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy [Pisters R, Lane DA, Nieuwlaat R, Vos CB de, Crijns HJGM, Lip GYH; A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 138 (5), 1093 - 1100 (2010).]