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Dabigatran initiation in patients with non-valvular AF and first acute ischemic stroke: an analysis from the SITS registry

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Title: Dabigatran initiation in patients with non-valvular AF and first acute ischemic stroke: an analysis from the SITS registry

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ABSTRACT

Background and objective: The optimal timing for initiation of dabigatran after acute ischemic stroke (AIS) is not established. We aimed to evaluate initiation timing and clinical outcomes of dabigatran in AIS patients with non-valvular atrial fibrillation (NVAF).

Design: We analyzed patients registered in SITS Thrombolysis and Thrombectomy Registry, (NCT03258645) from July 2014 to July 2018.

Participants: European NVAF patients (≥18 years) hospitalized after first-ever ischemic stroke (index event).

Setting: A multinational, prospective, observational monitoring register.

Intervention: Dabigatran initiation within 3 months after the index event.

Primary and secondary outcomes: The primary outcome was time from index event to dabigatran initiation. Additional outcomes included physicians' reasons for delaying dabigatran initiation beyond acute hospital discharge and outcomes within 3 months of index event.

Methods: We identified patients with NVAF that received Dabigatran within 3 months of index. We

Results: In total, 1489 patients with NVAF received dabigatran after AIS and of these 1240 patients had available initiation time. At baseline, median age was 75 years; 53% of patients were female, 15% were receiving an oral anticoagulant, 29% acetylsalicylic acid, and 4% clopidogrel. Most patients (82%) initiated dabigatran within 14 days after the index event. Patients initiating earlier had lower stroke severity: from median NIHSS 8 (IQR 6-13) if initiated within 7 days, to NIHSS 15 (9-19) if initiated between 28 days and 3 months. Most common reasons for delaying initiation were hemorrhagic transformation or intracranial hemorrhage, stroke severity, and infarct size. Few thrombotic/hemorrhagic events occurred within 3 months post–index event (20 of 926 patients, 2.2% with available data).

Conclusions: Our findings, together with previous observational studies, indicate that dabigatran initiated within the first days after AIS is safe, also in patients treated with intravenous thrombolysis, endovascular thrombectomy or both.

Strengths and limitations of this study:

- This study shows real-world clinical practice in a wide range of centers and countries.
- To our knowledge, this is the first study of dabigatran for secondary stroke prevention in patients treated with reperfusion therapies.
- The study is observational and based on a retrospective analysis of an ongoing database, with all the limitations of this type of study design.
- Another major limitation is that we are only reporting cases deemed by participating clinicians to be eligible for OAC for secondary prevention

Keywords: ischemic stroke, atrial fibrillation, prevention, anticoagulation.

INTRODUCTION

Cardioembolic stroke, the most severe ischemic stroke subtype, related mostly to NVAF accounts for 13% to 26% of all ischemic strokes.[1] Its recurrence rate within the first 14 days without anticoagulation is around 5%.[2] Anticoagulation using heparin decreases the risk of ischemic stroke recurrence to 3.0%, but at the cost of 1.8% increase risk of the absolute risk of intracranial bleeding.[3] Meanwhile, the rate of ischemic stroke recurrence may decrease to as low as 2.8% within 90 days when a direct oral anticoagulant (DOAC) is prescribed.[4] For clinicians, the decision of when to initiate anticoagulation after an acute ischemic stroke (AIS) is still a challenge, mainly due to perceived risk of early intracerebral hemorrhage.

The latest Cochrane systematic review in 2015 concluded that early anticoagulant therapy is not associated with net short- or long-term benefit in patients with AIS.[5] Moreover, neither national nor international stroke guidelines give firm recommendations. The AHA-ASA 2018 guidelines state that starting oral anticoagulation (OAC) within 4-14 days after AIS is reasonable for most patients, and the European Society of Cardiology (ESC) 2016 and European Heart Rhythm Association (EHRA) 2018 guidelines, endorsed by the European Stroke Organisation (ESO), recommend starting OAC 1, 3, 6 and 12 days, respectively, after transient ischemic attack, minor, moderate and severe strokes. [6, 7, 8]
Clinical practice is therefore to delay anticoagulation by up to 14 days. As the risk of recurrence during this time is around 5%, many clinicians anticoagulate earlier, guided by the approximate size of the infarct and absence or presence of any hemorrhagic transformation.

The lower overall risk of intracranial hemorrhage with DOACs compared to vitamin K antagonists (VKA) may facilitate earlier anticoagulation using DOACs in these patients.[9] Recent observational studies indicate that the risk of symptomatic intracranial hemorrhage (SICH) in patients treated with DOACs within the first 5 days of ischemic stroke is low.[10,11,12] A pooled individual patient data analysis of 7 observational studies concluded that DOACs started early after AIS were associated with reduced risk of poor clinical outcomes compared with VKA, mainly due to lower risk of ICH.[13]

Regarding dabigatran, patients were randomized to RE-LY trial no sooner than 14 days after AIS.[14] More recently, a smaller trial including 301 patients with TIA or minor ischemic stroke (NIHSS < 9) showed that dabigatran and aspirin had similar safety, with a non-significant trend for fewer early recurrent ischemic strokes in the dabigatran arm.[15,16]

The primary aim of this observational study was to evaluate the timing of dabigatran initiation in acute ischemic stroke patients with NVAF treated with IV thrombolysis, mechanical thrombectomy, or both. Secondary aims were: (1) to report physicians' reasons to delay OAC and (2) to evaluate clinical outcomes at 3 month follow-up.

MATERIAL AND METHODS

Patients presenting with first ever acute ischemic stroke and NVAF recorded in the SITS-AF registry between July 2014 and July 2018 were included.

The SITS-AF registry is a subset of the SITS-ISTR, an ongoing, prospective, academic-driven, multinational, register for clinical centers treating patients with acute stroke. The methodology of the SITS-ISTR, including procedures for data collection and management, patient identification and verification of source data, has been described previously.[17]

In the present study, patients were included if they presented with stroke symptoms and were treated with intravenous alteplase (Actilyse, Boehringer Ingelheim, Germany) within or outside license criteria, and/or with endovascular thrombectomy. Data collection in this study was done under the umbrella of SITS-MOST II study which was approved by the Stockholm Ethics committee. Need for ethical approval or patient consent for participation in the SITS-ISTR varied among participating countries. Ethics approval and patient consent were obtained in countries that required this; other countries approved the register for conduct as an anonymized audit.

We collected baseline and demographic characteristics, premorbid modified Rankin Scale (mRS), variables required for CHA_2DS_2-VASc and HAS-BLED scores, stroke severity per the NIHSS, medication history, imaging data at admission and follow up, time interval in days between index event and start of dabigatran and physicians' reasons for delaying dabigatran initiation beyond acute hospital discharge. Follow-up

period for this study was 3 months during which we collected information on any new clinical events, functional outcome using the mRS and death. All assessments of imaging studies, neurological, and functional status were done according to clinical routine at centers participating in the SITS-ISTR.

Outcomes

The primary outcome was the time from index event to dabigatran initiation. Additional outcomes included physicians' reasons for delaying dabigatran initiation beyond acute hospital discharge, and clinical outcomes within 3 months of index event. The timing of initiation was at the discretion of the treating physicians. The clinical outcomes were stroke or systemic embolism, ICH or major bleeding defined according to the International Society on Thrombosis and Hemostasis, all within 3 months after the index event.[18]

Statistical analysis

We performed descriptive statistics for baseline, imaging, and demographic data. For continuous variables, median and interquartile range values were obtained. For categorical variables, we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases.[16] Comparisons were made using Mann–Whitney U test and $\chi 2$ test, as appropriate. Pearson correlation coefficient was used to correlate dabigatran initiation time with continuous variables. A multivariable regression model including potential confounders was used to establish association between baseline variables and dabigatran initiation time. Because of the low number of events, no inferential analysis was performed. To calculate incidence rates we used the number of patient-years (number of included patients multiplied by the follow-up time in years).

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

RESULTS

The dataset comprised 14695 patients with first-ever AIS and NVAF, diagnosed either pre-stroke or within 3 months after the event. Of these, 1489 patients received dabigatran treatment for secondary prevention. Information regarding dabigatran initiation timing was available in 1240 patients, who were the study population for primary outcome (figure 1). Baseline and demographic characteristics in aggregate are presented in table 1. Baseline characteristics according to time of dabigatran initiation are presented in Supplementary Tables 1. Median age was 75 (69-82) years, 656 (53%) patients were female. Median NIHSS at admission was 10 (6-16). The median time from index stroke to dabigatran initiation was 8 (4-12) days. About 82% of patients initiated dabigatran within 14 days after the index stroke (supplementary figure 1).

Univariate analysis showed that higher NIHSS score at baseline and higher pre-stroke mRS were associated with a delay of dabigatran initiation ($p < 0.001$ and 0.01 respectively). Multivariate regression analysis showed that older age ($p=0.02$), higher diastolic blood pressure at admission ($p=0.002$), higher previous CHA_2DS_2-VASc score ($p=0.04$) and a history of or predisposition to bleeding ($p=0.03$) were independently associated with a delay of dabigatran initiation.

Reasons for delaying anticoagulation

Regarding reasons for delaying dabigatran initiation beyond the period of acute hospitalization, a total of 268 reasons were reported in 203 patients (one reason in 160 patients, more than one in 43). Table 2 shows the distribution of physician responses. Of all reasons given, 65.3% were related to the index event, the most frequent being stroke severity (22.8%), size of infarct (19.4%) and hemorrhagic transformation (14.9%).

Follow-up

In total, 926 patients had available information at 3 month follow-up regarding clinical events since discharge, resulting in a cumulative follow-up time of 231.5 patient-years. Of these, in 702 patients information about dabigatran initiation time was available. Among 926 patients, 101 experienced at least one event, with a total of 107 events reported. Of these, 20 (2.2%) were considered events of interest (embolism or

hemorrhage, defined as new stroke, myocardial infarct, pulmonary embolism or systemic embolism, as well as intracranial hemorrhage, and major extracranial hemorrhage). 13 of these events were embolic/ischemic (7 new stroke since discharge [3.02%/y], 3 myocardial infarction, 2 pulmonary embolism and 1 systemic embolism) and 7 were hemorrhagic (1 intracranial hemorrhage [0.43%/y] and 6 major extracranial hemorrhage). There were no differences in the distribution of events of interest and initiation time.

Data on mRS at 3 months after the index event were available in 1018 patients. A total of 697 patients (68.5%) were functionally independent (mRS 0-2), and 31 (3%) had died.

DISCUSSION

This large observational study shows that dabigatran in clinical practice is most commonly initiated early (82% patients within first 14 days) after an AIS. The rate of ischemic or hemorrhagic complications during the first three months after early initiation of dabigatran is low.

Our findings suggest that the safety profile of dabigatran for secondary stroke prevention in clinical practice is similar to the findings in the RE-LY trial.[14]

We have compared our results with those in recently published observational studies (tables 3 & 4). At a median age of 76, the patients in our series were older than in other studies, with the exception of the NOACISP.[10,11,12,19] Importantly, our patients had a much higher stroke severity than those in previous publications due to the fact that they received intravenous and/or endovascular reperfusion therapies, with an expectedly higher median NIHSS score, (median NIHSS 10 in our patients vs. 2 – 7 in previous observational studies).[10,11,12,19] The higher NIHSS score and older age had likely a major influence on our finding that dabigatran was initiated at median 8 days, compared to 2-4 days in previous studies.[10,11,19]. Both stroke severity, and reperfusion treatment, are associated with an elevated hemorrhagic risk. In spite of this, the rate of large parenchymal hematoma (PH2-PHr2) in our study was 1% compared to 2.7% to 5.1% previously reported in IVT patients and the rate of ICH within 3 months from index event was even lower, at 0.1%, compared to 5.1% at 90 days in a meta-analysis of endovascular thrombectomy (EVT).[20,21,22] However, these findings should be interpreted

with caution due to potential selection bias, as patients with early severe symptomatic bleeding after acute treatment may have died, or if alive, may have been too severely disabled to be considered for OAC initiation – potentially removing bleeding-prone patients from the treatment-eligible population.

According to the RAF-NOAC study, the period of DOAC initiation with the lowest rates of ischemic recurrence and major bleeding events would be 3 to 14 days after the index event (2.1% for composite AIS, TIA, symptomatic systematic embolism and major bleeding).[12] Although our numbers of events were too low for significance testing between periods, the period with the lowest rate of safety events was 3-7 days after AIS (1.7% for composite AIS, TIA, symptomatic systematic embolism and major bleeding). When comparing safety events in our study and the dabigatran subgroup of RAF-NOAC, the rate of the composite outcome is similar (2.2% vs 2.4%), but in our series the rates of stroke or TIA and ICH were lower.

We further described physicians' reasons to delay anticoagulation. Previous registry studies have shown an underutilization of OAC both in primary prevention and in patients after AIS.[23,24,25] Several reasons might explain this: lack of knowledge of current guidelines, physician concern for the risk of bleeding, and clinical factors, such as poor functional outcome after stroke, advanced age or the risk of falling. In our study, physicians' reasons for the delay of dabigatran initiation were mostly related to the index event and its putative high hemorrhagic risk.[26]

Our study has some limitations. The main one is that our series only includes patients treated with IVT and/or endovascular thrombectomy. Thus, there is a matter of selection of cases eligible for such therapies (whether treated on- or off-label and within or outside guidelines). These cases are likely to have more severe strokes, may have a lower pre-morbid score on mRS and other differences, compared to an unselected NVAF stroke population. Another limitation is that on 16% of patients initiating dabigatran within 3 months from index event there was no available information on exact initiation timing. A sensitivity analysis (supplementary table II) comparing clinical characteristics between patients with and without initiation timing showed that the latter group had higher NIHSS scores and glucose levels at baseline, less frequent history of previous AF and more frequently had endovascular treatment. These

differences could potentially have biased our findings to some extent in the direction of earlier dabigatran initiation.

Moreover, we are only reporting cases deemed by participating clinicians to be eligible for OAC for secondary prevention. In 4 cases of events of interest, information about dabigatran initiation timing was not available, but sensitivity analysis has been performed under different distribution assumptions and showed non-statistical significance regarding time initiation groups.

The strengths of our study are that it shows real-world clinical practice in a wide range of centers and countries, in which the timing of OAC was not standardized across the study but left to the discretion of the individual physicians and centers. It is also, to our knowledge, the first study of dabigatran for secondary stroke prevention in patients treated with IVT and or EVT, a population in which there may be even more controversy about when to start OAC due to a potentially elevated risk of hemorrhage. In addition, our data add important safety information on dabigatran, as the population in this study was not included in the pivotal dabigatran trial RE-LY (patients with a recent acute stroke were excluded).

Four large randomized controlled trials, OPTIMAS (EudraCT, 2018-003859-38; UK), TIMING (NCT02961348; Sweden), START (NCT03021928; USA) and ELAN (NCT03148457; Switzerland), are investigating the benefit of early DOAC administration in patients with AF-related ischemic stroke. The results of these trials are expected in the coming years; in the meantime, clinicians have to rely on data from observational studies.

Conclusions

Our findings, together with previous observational studies, suggest that dabigatran initiated within the first days after AIS is safe in patients treated with intravenous thrombolysis, endovascular thrombectomy, or both.

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ETHICAL APPROVAL

Data collection in this study was done under the umbrella of SITS-MOST II study which was approved by the Stockholm Ethics committee.

DATA SHARING STATEMENT: All data relevant to the study are included in the article or uploaded as supplementary.

CONFLICT OF INTEREST / DISCLOSURES

Niaz Ahmed is chair of SITS International, which receives a grant from Boehringer Ingelheim for the SITS-ISTR.
Michael Mazya is International Network and Research Executive at SITS International, which receives a grant from Boehringer Ingelheim for the SITS-ISTR.

CONTRIBUTORSHIP

MM and NA were involved in protocol development. MM and IEM were involved in data analysis. IEM and NA wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Figure legend

Figure 1. Flowchart of the study.

Tables

	Dabigatran patients with available time of initiation N = 1240
Age (Mean, SD) (Median, IQR)	75 ± 10 (69-82)
Gender (N, %, Female)	656 (52.9%)
NIHSS baseline (Median, IQR)	10 (6-16)
SBP (mm Hg, Mean, SD)	153 ± 23
DBP (mm Hg, Mean, SD)	85 ± 15
Glucose (mmol/dl, Mean, SD)	7.3 ± 2.3
Weight (kg, Mean, SD)	78 ± 15
Hypertension (N, %)	955 (77%)
Diabetes (N, %)	216 (17.4%)
Hyperlipidemia (N, %)	349 (28.1%)
Previous TIA (N, %)	65 (5.3%)
Current smoker (N, %)	88 (7.1%)
Previous smoker (N, %)	107 (8.8%)
Congestive heart failure (N, %)	134 (10.9%)
Vascular disease (N, %)	149 (12%)
Renal impairment (N, %)	30 (2.6%)
Abnormal liver function (N, %)	16 (1.4%)
Alcohol use (N, %)	37 (3.2%)
History of / predisposition to bleeding (N, %)	30 (2.6%)
Labile INR (N, %)	39 (3.5%)
Previous AF (N,%)	720 (58.6%)
Previous mRS (Median, IQR)	0 (0-0)
Previous CHA2DS2-VASc (Mean) (Median, IQR)	3.1 3 (2-4)
Previous HAS-BLED (Mean) (Median, IQR)	1.7 1 (1-2)
CHA2DS2-VASc Discharge (Mean) (Median, IQR	5,1 5 (4-6)
HAS-BLED Discharge (Mean) (Median, IQR)	2.7 3 (2-3)
IVT (N, %)	1055 (85.1%)
EVT (N, %)	68 (5.5%)
IVT+EVT (N, %)	117 (9.4%)

Table 1. Baseline characteristics of dabigatran patients included in the study.

Reasons for delay	N	Percent
Severity of stroke	61	22.8%
Size of infarct	52	19.4%
Hemorrhagic transformation	40	14.9%
ICH	8	3.0%
Reason not specified	27	10.1%
Patient bleeding risk factors	18	6.7%
Location of infarct	14	5.2%
Practical considerations	14	5.2%
Intervention used to treat ischemic stroke	8	3.0%
Patient stroke risk factors	6	2.2%
Recommendation from specialist	6	2.2%
Altered coagulation parameters	5	1.9%
Other reasons	5	1.9%
Patient preference	4	1.5%
Total	**268**	**100%**

Table 2. Distribution of physician reasons to delay dabigatran initiation until after discharge from acute stroke care.

	Dabigatran SITS **N=1240**	NOACISP (all patients) **N=204**	Gioia et al[19] **N=60**	SAMURAI (NOACs) **N=475**	RAF-NOAC (Dabigatran group) **N=381**
Median/ Mean* age	**76 (69-82)**	79 (73-84)	73.5 +/- 13.2*	74.4 +/- 9.2*	73.6+/- 9.9*
Median/ Mean* NIHSS (at admission)	**10 (6-16)**	4 (2-8)	2 (0-4) at Rivaroxaban initiation	4 (1-13)	7.7 +/- 6.2*
Median delay (days)	**8 (4-12)**	5 (3-11) (Dabigatran group)	3 (1.5-6)	4 (2-7)	8 (3-14)

Table 3. Comparison of our results with previous observational studies with NOACs with 90 days follow-up.

	Dabigatran (N=926)	RAF-NOAC (Dabigatran N=381)
All safety events	**20 (2.2%)**	9 (2.4%)
Embolism	**13 (1.4%)**	**7 (1.8%)**
Stroke/TIA	**7 (0.8%)**	7 (1.8%)
Other thromboembolic events (MI, PE, or SE)	**6 (0.7%)**	0
Major hemorrhage	**7 (0.8%)**	**2 (0.5%)**
ICH	**1 (0.1%)**	2 (0.5%)

Table 4. Comparison of our results with dabigatran patients from a previous observational study with 90 days follow-up.

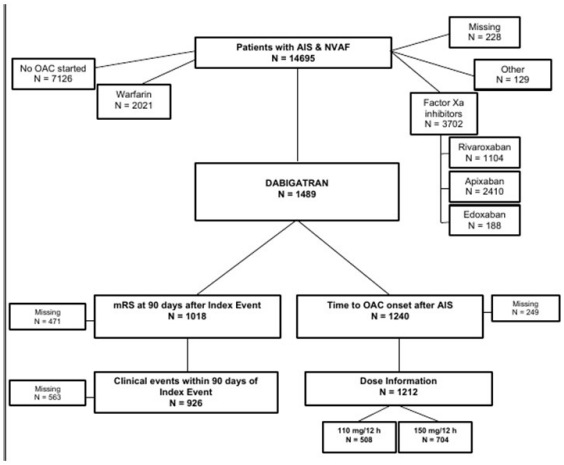

Figure 1. Flowchart of the study.

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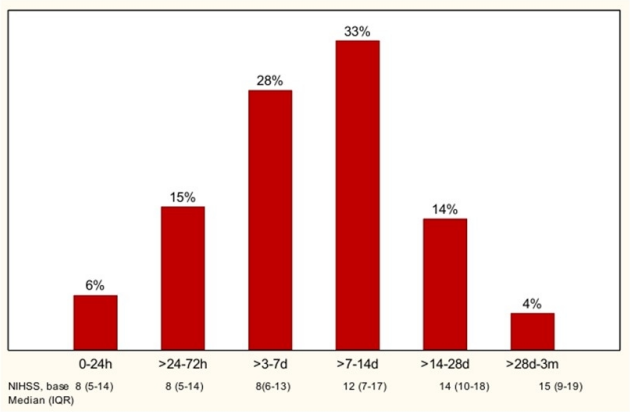
	< 24 h n=73	> 24 – 72 h n=190	> 3 – 7 d n=344	> 7 – 14 d n=410	> 14 – 28 d n=174	>28d – 3m n=49
Age (Mean, SD) (Median, IQ)	72 ± 11 (69-75)	74 ± 10 (73-76)	75 ± 9 (73-76)	75 ± 9 (74-77)	76 ± 9 (74-78)	77 ± 10 (73-80)
Gender (N, %, Female)	29 (39.7%)	95 (50%)	175 (50.9%)	225 (54.9%)	99 (56.9%)	33 (67.3%)
NIHSS baseline (Median, IQ)	8 (5-14)	8 (5-14)	8 (6-13)	12 (7-17)	14 (10-18)	15 (9-19)
SBP (mm Hg, Mean, SD)	156 ± 22	150 ± 21	154 ± 22	155 ± 23	152 ± 22	157 ± 29
DBP (mm Hg, Mean, SD	87 ± 12	83 ± 15	84 ± 14	85 ± 15	85 ± 17	91 ± 16
Glucose (mmol/dl, Mean, SD)	6.8 ± 1	7.1 ± 3	7.3 ± 2	7.8 ± 3	7.4 ± 2	7.1 ± 2
Weight (kg, Mean, SD)	84 ± 16	79 ± 15	77 ± 15	78 ± 15	77 ± 16	77 ± 17
Hypertension (%)	75.3%	77.9%	74.9%	79.9%	76.3%	77.6%
Diabetes (%)	15.1%	17.4%	16.9%	18.1%	16.9%	22.4%
Hyperlipidemia (%)	29.6%	33.5%	25.5%	34.4%	21.9%	26.5%
Previous TIA (%)	5.5%	6.8%	6.2%	3.4%	5.8%	6.1%
Current smoker (%)	5.8%	8.6%	7.1%	8.9%	5.4%	6.3%
Previous smoker (%)	8.7%	8.0%	10.8%	10.5%	6.8%	10.9%
Congestive heart failure (%)	12.3%	7.4%	8.7%	13.2%	11.6%	14.3%
Vascular disease (%)	12.3%	10.6%	13.9%	12.5%	10.5%	8.3%
Renal impairment (%)	2.0%	2.8%	2.1%	3.5%	1.2%	2.2%
Abnormal liver function (%)	0.0%	0.6%	2.1%	1.5%	1.2%	0.0%
Alcohol use (%)	8.5%	2.3%	4.0%	2.1%	4.3%	2.2%
History of / predisposition to bleeding (%)	2.1%	1.1%	3.0%	3.0%	1.8%	4.4%
Labile INR (%)	0.0%	4.8%	3.1%	2.7%	5.8%	4.5%
Previous AF (%)	20.5%	22.2%	27.9%	19.1%	22.5%	42.9%
Previous mRS (Median, IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0-1)
Previous CHA2DS2-VASc (Mean, 95%CI) (Median, IQ)	2.9 (2.5-3.2) 3 (1-5)	3.2 (3-3.4) 3 (1-5)	3.2 (3-3.3) 3 (1-5)	3.2 (3.1-3.4) 3 (1-5)	3.3 (3.-3.5) 3 (1-5)	3.4 (3.1-3.8) 3.5 (2.5-4.5)
Previous HAS-BLED (Mean, 95%CI) (Median, IQ)	1.1 (0.9-1.3) 1 (0-3)	1.3 (1.2-1.3) 1 (0-2)	1.2 (1.2-1.3) 1 (0-2)	1.3 (1.2-1.4) 1 (0-1)	1.2 (1-1.3) 1 (1-1)	1.2 (1.1-1.4) 1 (0-2)
CHA2DS2-VASc (Mean, 95%CI) (Median, IQ)	4.7 (3.1-6.3) 5 (4-6)	5 (3.7-6.3) 5 (4-6)	5 (3.6-6-4) 5 (4-6)	5.2 (3.8-6.6) 5 (4-6)	5.2 (3.8-6.6) 5 (4-6)	5.3 (4.2-6.4) 5 (4-6)
HAS-BLED (Mean, 95%CI) (Median, IQ)	1.7 (0.9-2.5) 3 (2-3)	1.7 (1-2.4) 3 (2-3)	1.7 (0.9-2.5) 3 (2-3)	1.8 (1.1-2.5) 3 (2-3)	1.7 (1-2.4) 3 (2-3)	1.8 (1.2-2.4) 3 (2-3)
Signs of acute infarct (N, %)	11 (15.9%)	23 (14.5%)	33 (12%)	36 (11.3%)	22 (15.9%)	3 (17.1%)

Supplementary Table I. Baseline characteristics according to time initiation.

	Dabigatran patients with available time of initiation N = 1240	Dabigatran patients NO timing information N= 249	P value
Age (Mean, SD) (Median, IQR)	75 ± 10 (69-82)	74 ± 10 (69-80)	0.15
Gender (N, %, Female)	656 (52.9%)	132 (53%)	0.97
NIHSS baseline (Median, IQR)	10 (6-16)	14 (9-19)	<0.001
SBP (mm Hg, Mean, SD)	153 ± 23	154 ± 25	0.31
DBP (mm Hg, Mean, SD)	85 ± 15	84 ± 14	0.23
Glucose (mmol/dl, Mean, SD)	7.3 ± 2.3	7.8 ± 5.1	<0.001
Weight (kg, Mean, SD)	78 ± 15	77 ± 13	0.004
Hypertension (N, %)	955 (77%)	189 (75.9%)	0.63
Diabetes (N, %)	216 (17.4%)	48 (19.3%)	0.5
Hyperlipidemia (N, %)	349 (28.1%)	75 (30.1%)	0.04
Previous TIA (N, %)	65 (5.3%)	10 (4%)	0.48
Current smoker (N, %)	88 (7.1%)	15 (6%)	0.051
Previous smoker (N, %)	107 (8.8%)	30 (12.3%)	0.048
Congestive heart failure (N, %)	134 (10.9%)	24 (9.6%)	0.57
Vascular disease (N, %)	149 (12%)	33 (13.3%)	0.6
Renal impairment (N, %)	30 (2.6%)	5 (2.4%)	0.88
Abnormal liver function (N, %)	16 (1.4%)	1 (0.5%)	0.5
Alcohol use (N, %)	37 (3.2%)	9 (4.3%)	0.44
History of / predisposition to bleeding (N, %)	30 (2.6%)	12 (5.7%)	0.02
Labile INR (N, %)	39 (3.5%)	5 (2.5%)	0.46
Previous AF (N,%)	720 (58.6%)	110 (44.4%)	<0.001
Previous mRS (Median, IQR)	0 (0-0)	0 (0-0)	0.98
Previous CHA2DS2-VASc (Mean) (Median, IQR)	3.1 3 (2-4)	3.1 3 (2-4)	0.31
Previous HAS-BLED (Mean) (Median, IQR)	1.7 1 (1-2)	1.7 1 (1-2)	0.64
CHA2DS2-VASc Discharge (Mean) (Median, IQR)	5,1 5 (4-6)	5.1 5 (4-6)	0.53
HAS-BLED Discharge (Mean) (Median, IQR)	2.7 3 (2-3)	2.8 3 (2-3)	0.73
IVT (N, %)	1055 (85.1%)	180 (72.3%)	<0.001
EVT (N, %)	68 (5.5%)	23 (9.2%)	<0.001
IVT+EVT (N, %)	117 (9.4%)	46 (18.5%)	<0.001

Supplementary Table II. Baseline characteristics of patients initiating dabigatran after the index event.

Legend Supplementary Figure 1. Histogram of initiation time periods, showing proportion of patients and median NIHSS at baseline for each group



Legend Supplementary Figure 1. Histogram of initiation time periods, showing proportion of patients and median NIHSS at baseline for each group

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, table
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables
		(*b*) Report category boundaries when continuous variables were categorized	Table
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,111
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Dabigatran initiation in patients with non-valvular AF and first acute ischemic stroke: a retrospective observational study from the SITS registry

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Title: Dabigatran initiation in patients with non-valvular AF and first acute ischemic stroke: a retrospective observational study from the SITS registry

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ABSTRACT

Background and objective: The optimal timing for initiation of dabigatran after acute ischemic stroke (AIS) is not established. We aimed to evaluate initiation timing and clinical outcomes of dabigatran in AIS patients with non-valvular atrial fibrillation (NVAF).

Design: Retrospective study based on prospectively collected data in SITS Thrombolysis and Thrombectomy Registry, (NCT03258645) from July 2014 to July 2018.

Participants: European NVAF patients (≥18 years) hospitalized after first-ever ischemic stroke.

Setting: A multinational, observational monitoring register.

Intervention: Dabigatran initiation within 3 months after the ischemic stroke.

Primary and secondary outcomes: The primary outcome was time from first-ever ischemic stroke (index event) to dabigatran initiation. Additional outcomes included physicians' reasons for delaying dabigatran initiation beyond acute hospital discharge and outcomes within 3 months of index event.

Methods: We identified patients with NVAF who received Dabigatran within 3 months of index event. We performed descriptive statistics for baseline and demographic data and clinical outcomes after dabigatran initiation.

Results: In total, 1489 patients with NVAF received dabigatran after AIS treated with thrombolysis and/or thrombectomy. Of these, 1240 had available initiation time. At baseline, median age was 75 years; 53% of patients were female, 15% were receiving an oral anticoagulant, 29% acetylsalicylic acid, and 4% clopidogrel. Most patients (82%) initiated dabigatran within 14 days after the index event. Patients initiating earlier had lower stroke severity: from median NIHSS 8 (IQR 6-13) if initiated within 7 days, to NIHSS 15 (9-19) if initiated between 28 days and 3 months. Most common reasons for delaying initiation were hemorrhagic transformation or intracranial hemorrhage, stroke severity, and infarct size. Few thrombotic/hemorrhagic events occurred within 3 months post–index event (20 of 926 patients, 2.2% with available data).

Conclusions: Our findings, together with previous observational studies, indicate that dabigatran initiated within the first days after an AIS is safe in patients treated with intravenous thrombolysis, endovascular thrombectomy or both.

Strengths and limitations of this study:

- This study shows real-world clinical practice in a wide range of centers and countries.
- To our knowledge, this is the first study of dabigatran for secondary stroke prevention in patients treated with reperfusion therapies.
- The study is observational and based on a retrospective analysis of an ongoing database, with all the limitations of this type of study design.
- Another limitation is that we are only reporting cases deemed by participating clinicians to be eligible for OAC for secondary prevention

Keywords: ischemic stroke, atrial fibrillation, secondary prevention, anticoagulation, intravenous thrombolysis, thrombectomy

INTRODUCTION

Cardioembolic stroke, the most severe ischemic stroke subtype, related mostly to NVAF, accounts for 13% to 26% of all ischemic strokes.[1] Its recurrence rate within the first 14 days without anticoagulation is around 5%.[2] Anticoagulation using heparin decreases the risk of ischemic stroke recurrence to 3.0%, but at the cost of 1.8% increase risk of the absolute risk of intracranial bleeding.[3] Meanwhile, the rate of ischemic stroke recurrence may decrease to as low as 2.8% within 90 days when a direct oral anticoagulant (DOAC) is prescribed.[4] For clinicians, the decision on when to initiate anticoagulation after an acute ischemic stroke (AIS) is still a challenge, mainly due to perceived risk of early intracerebral hemorrhage.

The latest Cochrane systematic review in 2015 concluded that early anticoagulant therapy is not associated with net short- or long-term benefit in patients with AIS.[5] Moreover, neither national nor international stroke guidelines give firm recommendations. The AHA-ASA 2018 guidelines state that starting oral anticoagulation (OAC) within 4-14 days after AIS is reasonable for most patients, and the European Society of Cardiology (ESC) 2016 and European Heart Rhythm Association (EHRA) 2018 guidelines, endorsed by the European Stroke Organisation (ESO), recommend starting OAC 1, 3, 6 and 12 days, respectively, after transient ischemic attack, minor, moderate and severe strokes. [6, 7, 8]
Clinical practice is therefore to delay anticoagulation by up to 14 days. As the risk of recurrence during this time is around 5%, many clinicians anticoagulate earlier, guided by the approximate size of the infarct and absence or presence of any hemorrhagic transformation.

The lower overall risk of intracranial hemorrhage with DOACs compared to vitamin K antagonists (VKA) may facilitate earlier anticoagulation using DOACs in these patients.[9] Recent observational studies indicate that the risk of symptomatic intracranial hemorrhage (SICH) in patients treated with DOACs within the first 5 days of ischemic stroke is low.[10,11,12] A pooled individual patient data analysis of 7 observational studies concluded that DOACs started early after AIS were associated with reduced risk of poor clinical outcomes compared with VKA, mainly due to lower risk of ICH.[13]

Regarding dabigatran, patients were randomized in the RE-LY trial no sooner than 14 days after AIS.[14] More recently, a smaller trial including 301 patients with TIA or minor ischemic stroke (NIHSS < 9) showed that dabigatran and aspirin had similar safety, with a non-significant trend for fewer early recurrent ischemic strokes in the dabigatran arm.[15,16]

The optimal timing of anticoagulation after an AIS is not established, and until results of ongoing randomized controlled trials are published, observational studies are needed to provide recommendations for clinical practice.

The primary aim of this observational study was to evaluate the timing of dabigatran initiation in acute ischemic stroke patients with NVAF treated with IV thrombolysis, mechanical thrombectomy, or both. Secondary aims were: (1) to report physicians' reasons to delay OAC and (2) to evaluate clinical outcomes at 3-month follow-up.

MATERIAL AND METHODS

Patients presenting with first ever acute ischemic stroke and NVAF recorded in the SITS-AF registry between July 2014 and July 2018 were included.
The SITS-AF registry is a subset of the SITS-ISTR, an ongoing, prospective, academic-driven, multinational, register for clinical centers treating patients with acute stroke. The methodology of the SITS-ISTR, including procedures for data collection and management, patient identification and verification of source data, has been described previously.[17]

In the present study, patients were included if they presented with stroke symptoms and were treated with intravenous alteplase (Actilyse, Boehringer Ingelheim, Germany) within or outside license criteria, and/or with endovascular thrombectomy. Data collection in this study was done under the umbrella of SITS-MOST II study which was approved by the Stockholm Ethics committee. Need for ethical approval or patient consent for participation in the SITS-ISTR varied among participating countries. Ethics approval and patient consent were obtained in countries that required this; other countries approved the register for conduct as an anonymized audit.

We collected baseline and demographic characteristics, premorbid modified Rankin Scale (mRS), variables required for CHA_2DS_2-VASc and HAS-BLED scores, stroke severity per the NIHSS, medication history, imaging data at admission and follow up, time interval in days between index event and start of dabigatran and physicians' reasons for delaying dabigatran initiation beyond acute hospital discharge. Follow-up period for this study was 3 months, during which we collected information on any new clinical events, functional outcome using the mRS, and death. All assessments of imaging studies, neurological, and functional status were done according to clinical routine at centers participating in the SITS-ISTR.

Outcomes

The primary outcome was the time from index event (first-ever ischemic stroke) to dabigatran initiation. Secondary outcomes included: physicians' reasons for delaying dabigatran initiation beyond acute hospital discharge and clinical outcomes of interest within 3 months of index event. Clinical outcomes of interest include death, stroke or systemic embolism, ICH or major bleeding defined according to the International Society on Thrombosis and Hemostasis, all within 3 months after the index event.[18] The timing of initiation was at the discretion of the treating physicians.

Statistical analysis

We performed descriptive statistics for baseline, imaging, and demographic data. For continuous variables, median and interquartile range values were obtained. For categorical variables, we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases.[16] Comparisons were made using Mann–Whitney U test and $\chi 2$ test, as appropriate. Pearson correlation coefficient was used to correlate dabigatran initiation time with continuous variables. A multivariable regression model including potential confounders (clinically relevant variables and variables based on a univariate significance of $p < 0.05$) was used to establish association between baseline variables and dabigatran initiation time. Because of the low number of events, no inferential analysis was performed. To calculate annualized incidence rates we calculated the number of patient-years (number of included patients multiplied by the follow-up time in years). Incidence

rates were expressed per 100 person-years. The 95% CIs for incidence rates were calculated using Fisher's exact test.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research

RESULTS

The dataset comprised 14695 patients with first-ever AIS and NVAF, diagnosed either before the stroke or within 3 months after the event. Of these, 1489 patients received dabigatran treatment for secondary prevention. Information regarding dabigatran initiation timing was available in 1240 patients, who were the study population for primary outcome (figure 1). Baseline and demographic characteristics in aggregate are presented in table 1. Baseline characteristics according to time of dabigatran initiation are presented in Supplementary Tables 1. Median age was 75 (69-82) years, 656 (53%) patients were female. Median NIHSS at admission was 10 (6-16). The median time from index stroke to dabigatran initiation was 8 (4-12) days. About 82% of patients initiated dabigatran within 14 days after the index stroke (supplementary figure 1). Univariate analysis showed that higher NIHSS score at baseline and higher pre-stroke mRS were associated with a delay of dabigatran initiation ($p < 0.001$ and 0.01 respectively). Multivariate regression analysis including clinically significant variables (age, gender, baseline NIHSS, systolic blood pressure on admission, glucose level at admission) showed that older age ($p=0.02$), higher diastolic blood pressure on admission ($p=0.002$), higher previous CHA_2DS_2-VASc score ($p=0.04$) and a history of, or predisposition to bleeding ($p=0.03$) were independently associated with a delay of dabigatran initiation.

Reasons for delaying anticoagulation

Regarding reasons for delaying dabigatran initiation beyond the period of acute hospitalization, a total of 268 reasons were reported in 203 patients (one reason in 160 patients, more than one in 43). Table 2 shows the distribution of physician responses. Of all reasons given, 65.3% were related to the index event, the most frequent being

stroke severity (22.8%), size of infarct (19.4%) and hemorrhagic transformation (14.9%).

Follow-up

In total, 926 patients had available information at 3-month follow-up regarding clinical events since discharge, resulting in a cumulative follow-up time of 231.5 patient-years. Of these 926, information about the primary outcome (timing of dabigatran initiation) was only available for 702 patients.

Among 926 patients, 101 experienced at least one event, with a total of 107 events reported. Of these, 20 (2.2%) were considered events of interest (embolism or hemorrhage, defined as new stroke, myocardial infarct, pulmonary embolism or systemic embolism, as well as intracranial hemorrhage, and major extracranial hemorrhage). 13 of these events were embolic/ischemic (7 new stroke since discharge [3.02%/y, 95% CI 1.22-6.23], 3 myocardial infarction, 2 pulmonary embolism and 1 systemic embolism) and 7 were hemorrhagic (1 intracranial hemorrhage [0.43%/y, 95% CI 0.01-2.13] and 6 major extracranial hemorrhage). There were no differences in the distribution of events of interest and initiation time.

Data on mRS at 3 months after the index event were available in 1018 patients. A total of 697 patients (68.5%) were functionally independent (mRS 0-2), and 31 (3%) had died. Causes of death were recorded as follows: 10 (32%) due to index cerebral infarction, 1 (3.2%) patient due to ICH, 2 (6.5%) patients due to pneumonia, 2 (6.5%) patients due to pulmonary embolism, 6 (19.4%) patients due to other causes and 10 (32%) patients had an unknown cause.

Tables 3 and 4 show comparisons of our results with previously reported observational studies. Patients in our study were older and had a higher stroke severity. Our findings regarding events of interest are in line with those previously reported.

DISCUSSION

This large observational study shows that dabigatran in clinical practice is most commonly initiated early (82% patients within first 14 days) after an AIS. The rate of ischemic or hemorrhagic complications during the first three months after early initiation of dabigatran is low. Our findings suggest that the safety profile of dabigatran

for secondary stroke prevention in clinical practice is similar to findings in the RE-LY trial.[14]

We have compared our results with those in recently published observational studies (tables 3 & 4). At a median age of 76, the patients in our series were older than in other studies, with the exception of the NOACISP.[10,11,12,19] Importantly, our patients had a much higher stroke severity than those in previous publications, due to the fact that they received intravenous and/or endovascular reperfusion therapies, median NIHSS 10 in our patients vs. 2 – 7 in previous observational studies.[10,11,12,19] The higher NIHSS score and older age likely had a major influence on our finding that dabigatran was initiated at median 8 days, compared to 2-4 days in previous studies.[10,11,19]. Both stroke severity and reperfusion treatment, are associated with an elevated hemorrhagic risk. In spite of this, the rate of large parenchymal hematoma (PH2-PHr2) in our study was 1% compared to 2.7% to 5.1% previously reported in IVT patients and the rate of ICH within 3 months from index event was even lower, at 0.1%, compared to 5.1% at 90 days in a meta-analysis of endovascular thrombectomy (EVT).[20,21,22] However, these findings should be interpreted with caution due to potential selection bias, as patients with early severe symptomatic bleeding after acute treatment may have died, or if alive, may have been too severely disabled to be considered for OAC initiation – potentially removing bleeding-prone patients from the treatment-eligible population.

According to the RAF-NOAC study, the period of DOAC initiation with the lowest rates of ischemic recurrence and major bleeding events would be 3 to 14 days after the index event (2.1% for composite AIS, TIA, symptomatic systematic embolism and major bleeding).[12] Although our numbers of events were too low for significance testing between periods, the period with the lowest rate of safety events was 3-7 days after AIS (1.7% for composite AIS, TIA, symptomatic systematic embolism and major bleeding). When comparing safety events in our study and the dabigatran subgroup of RAF-NOAC, the rate of the composite outcome is similar (2.2% vs 2.4%), but in our series the rates of stroke or TIA and ICH were lower.

Our study adds new data to the recent observational studies regarding anticoagulation after AIS. This literature together with guideline recommendations and patients'

individual embolic and hemorrhagic risks should guide the decision on when to start OAC therapy.

We have described physicians' reasons to delay anticoagulation. Previous registry studies have shown an underutilization of OAC both in primary prevention and after AIS.[23,24,25] Several reasons could explain this: lack of knowledge of current guidelines, physician concern for the risk of bleeding, and clinical factors, such as poor functional outcome after stroke, advanced age or the risk of falling. In our study, reasons for the delay of dabigatran initiation were mostly related to the index event and its putative high hemorrhagic risk.[26]

Our study has some limitations. The main one, is that it only includes patients treated with IVT and/or endovascular thrombectomy. Thus, there is a matter of selection of cases eligible for such therapies (whether treated on- or off-label and within or outside guidelines). These cases are likely to have more severe strokes, may have a lower pre-morbid score on mRS and other differences, compared to an unselected NVAF stroke population. Another limitation is that 16% of patients initiating dabigatran within 3 months from index event had no available information on exact initiation timing. A sensitivity analysis (supplementary table II) comparing clinical characteristics between patients with and without known initiation time showed that the latter group had higher NIHSS scores and glucose levels at baseline, less frequent history of previous AF and more frequently had endovascular treatment. These differences could potentially have biased our results to some extent in favor of earlier dabigatran initiation. Moreover, we are only reporting cases deemed by participating clinicians to be eligible for OAC treatment. In 4 cases of events of interest, information about dabigatran initiation timing was not available, but sensitivity analysis has been performed under different distribution assumptions and showed no statistical significance regarding time initiation groups.

The strengths of our study are that it shows real-world clinical practice in a wide range of centers and countries, in which the timing of OAC was not standardized across the study but left to the discretion of the individual physicians and centers. It is also, to our knowledge, the first study of dabigatran for secondary stroke prevention in patients treated with IVT and or EVT, a population in which there may be even more

controversy about when to start OAC due to a potentially elevated risk of hemorrhage. In addition, our data add important safety information on dabigatran, as the population in this study was not included in the pivotal dabigatran trial RE-LY (patients with a recent acute stroke were excluded).

Four large randomized controlled trials, OPTIMAS (EudraCT, 2018-003859-38; UK), TIMING (NCT02961348; Sweden), START (NCT03021928; USA) and ELAN (NCT03148457; Switzerland), are investigating the benefit of early DOAC administration in patients with AF-related ischemic stroke. The results of these trials are expected in the coming years; in the meantime, clinicians have to rely on data from observational studies.

Conclusions

Our findings, together with previous observational studies, suggest that dabigatran initiated within the first days after AIS is safe in patients treated with intravenous thrombolysis, endovascular thrombectomy, or both.

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ETHICAL APPROVAL

Data collection in this study was done within the framework of SITS-MOST II study which was approved by the Stockholm Ethics committee.

DATA SHARING STATEMENT: All data relevant to the study are included in the article or uploaded as supplementary.

CONFLICT OF INTEREST / DISCLOSURES

Niaz Ahmed is chair of SITS International, which receives a grant from Boehringer Ingelheim for the SITS-ISTR.

Michael Mazya is International Network and Research Executive at SITS International, which receives a grant from Boehringer Ingelheim for the SITS-ISTR.

CONTRIBUTORSHIP

MM and NA were involved in protocol development. MM and IEM were involved in data analysis. IEM and NA wrote the first draft of the manuscript. CT, NL, ZG, LB, WF, MK, AK, GK, APN, KP, AP, PS, AV and DT reviewed and edited the manuscript and approved the final version of the manuscript.

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Figure legend

Figure 1. Flowchart of the study.

Tables

	Dabigatran patients with available time of initiation N = 1240
Age (Mean, SD) (Median, IQR)	75 ± 10 (69-82)
Gender (N, %, Female)	656 (52.9%)
NIHSS baseline (Median, IQR)	10 (6-16)
SBP (mm Hg, Mean, SD)	153 ± 23
DBP (mm Hg, Mean, SD)	85 ± 15
Glucose (mmol/dl, Mean, SD)	7.3 ± 2.3
Weight (kg, Mean, SD)	78 ± 15
Hypertension (N, %)	955 (77%)
Diabetes (N, %)	216 (17.4%)
Hyperlipidemia (N, %)	349 (28.1%)
Previous TIA (N, %)	65 (5.3%)
Current smoker (N, %)	88 (7.1%)
Previous smoker (N, %)	107 (8.8%)
Congestive heart failure (N, %)	134 (10.9%)
Vascular disease (N, %)	149 (12%)
Renal impairment (N, %)	30 (2.6%)
Abnormal liver function (N, %)	16 (1.4%)
Alcohol use (N, %)	37 (3.2%)
History of / predisposition to bleeding (N, %)	30 (2.6%)
Labile INR (N, %)	39 (3.5%)
Previous AF (N,%)	720 (58.6%)
Previous mRS (Median, IQR)	0 (0-0)
Previous CHA2DS2-VASc (Mean) (Median, IQR)	3.1 3 (2-4)
Previous HAS-BLED (Mean) (Median, IQR)	1.7 1 (1-2)
CHA2DS2-VASc Discharge (Mean) (Median, IQR	5,1 5 (4-6)
HAS-BLED Discharge (Mean) (Median, IQR)	2.7 3 (2-3)

IVT (N, %)	1055 (85.1%)
EVT (N, %)	68 (5.5%)
IVT+EVT (N, %)	117 (9.4%)

Table 1. Baseline characteristics of dabigatran patients included in the study.

Reasons for delay	**N**	**Percent**
Severity of stroke	61	22.8%
Size of infarct	52	19.4%
Hemorrhagic transformation	40	14.9%
ICH	8	3.0%
Reason not specified	27	10.1%
Patient bleeding risk factors	18	6.7%
Location of infarct	14	5.2%
Practical considerations	14	5.2%
Intervention used to treat ischemic stroke	8	3.0%
Patient stroke risk factors	6	2.2%
Recommendation from specialist	6	2.2%
Altered coagulation parameters	5	1.9%
Other reasons	5	1.9%
Patient preference	4	1.5%
Total	**268**	**100%**

Table 2. Distribution of physician reasons to delay dabigatran initiation until after discharge from acute stroke care.

	Dabigatran SITS **N=1240**	NOACISP (all patients) **N=204**	Gioia et al[19] **N=60**	SAMURAI (NOACs) **N=475**	RAF-NOAC (Dabigatran group) **N=381**
Median/ Mean* age	**76 (69-82)**	79 (73-84)	73.5 +/- 13.2*	74.4 +/- 9.2*	73.6+/- 9.9*
Median/ Mean* NIHSS (at admission)	**10 (6-16)**	4 (2-8)	2 (0-4) at Rivaroxaban initiation	4 (1-13)	7.7 +/- 6.2*
Median delay (days)	**8 (4-12)**	5 (3-11) (Dabigatran group)	3 (1.5-6)	4 (2-7)	8 (3-14)

Table 3. Comparison of our results with previous observational studies of NOACs with 90 days of follow-up.

	Dabigatran (N=926)	RAF-NOAC (Dabigatran N=381)
All safety events	**20 (2.2%)**	9 (2.4%)
Embolism	**13 (1.4%)**	**7 (1.8%)**
Stroke/TIA	**7 (0.8%)**	7 (1.8%)
Other thromboembolic events (MI, PE, or SE)	**6 (0.7%)**	0
Major hemorrhage	**7 (0.8%)**	**2 (0.5%)**
ICH	**1 (0.1%)**	2 (0.5%)

Table 4. Comparison of our results with dabigatran treated patients from a previous observational study with 90 days of follow-up.

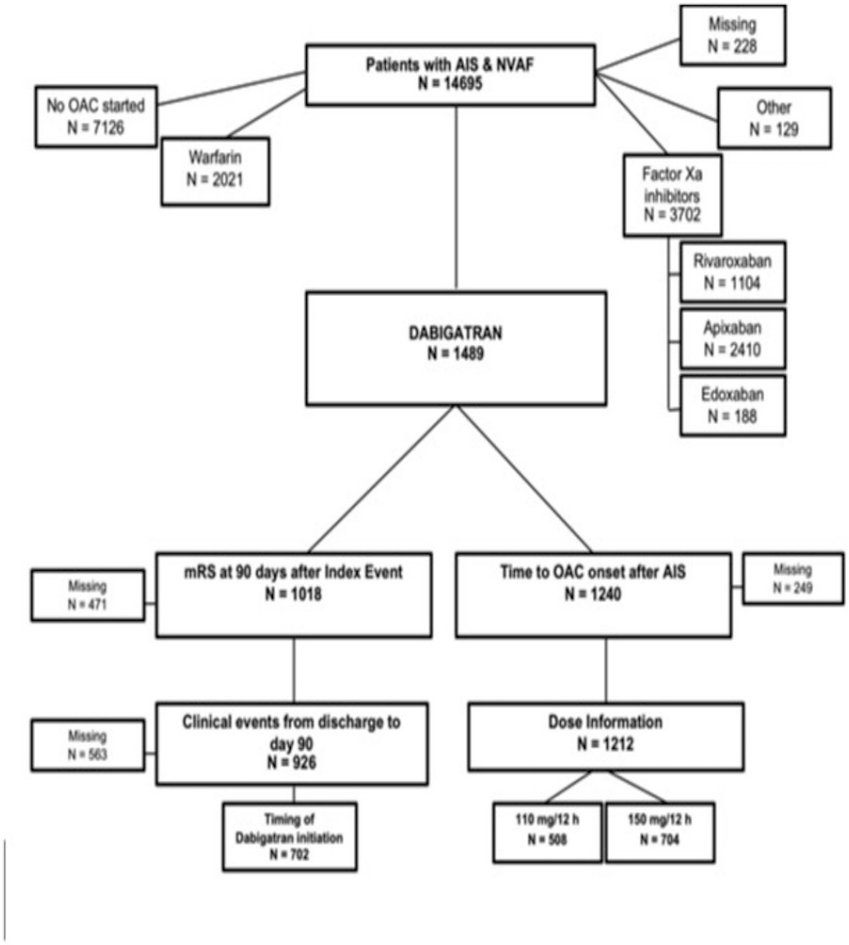
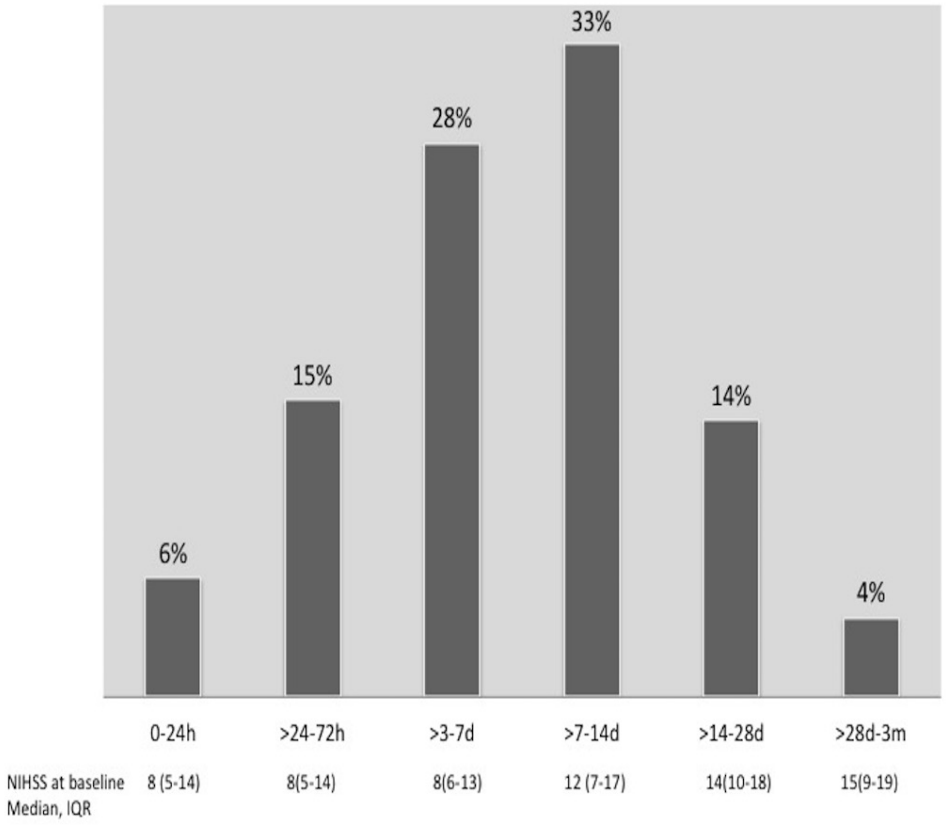


Figure 1. Flowchart of the study.

90x90mm (300 x 300 DPI)



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	< 24 h n=73	> 24 – 72 h n=190	> 3 – 7 d n=344	> 7 – 14 d n=410	> 14 – 28 d n=174	>28d – 3m n=49
Age (Mean, SD) (Median, IQ)	72 ± 11 (69-75)	74 ± 10 (73-76)	75 ± 9 (73-76)	75 ± 9 (74-77)	76 ± 9 (74-78)	77 ± 10 (73-80)
Gender (N, %, Female)	29 (39.7%)	95 (50%)	175 (50.9%)	225 (54.9%)	99 (56.9%)	33 (67.3%)
NIHSS baseline (Median, IQ)	8 (5-14)	8 (5-14)	8 (6-13)	12 (7-17)	14 (10-18)	15 (9-19)
SBP (mm Hg, Mean, SD)	156 ± 22	150 ± 21	154 ± 22	155 ± 23	152 ± 22	157 ± 29
DBP (mm Hg, Mean, SD	87 ± 12	83 ± 15	84 ± 14	85 ± 15	85 ± 17	91 ± 16
Glucose (mmol/dl, Mean, SD)	6.8 ± 1	7.1 ± 3	7.3 ± 2	7.8 ± 3	7.4 ± 2	7.1 ± 2
Weight (kg, Mean, SD)	84 ± 16	79 ± 15	77 ± 15	78 ± 15	77 ± 16	77 ± 17
Hypertension (%)	75.3%	77.9%	74.9%	79.9%	76.3%	77.6%
Diabetes (%)	15.1%	17.4%	16.9%	18.1%	16.9%	22.4%
Hyperlipidemia (%)	29.6%	33.5%	25.5%	34.4%	21.9%	26.5%
Previous TIA (%)	5.5%	6.8%	6.2%	3.4%	5.8%	6.1%
Current smoker (%)	5.8%	8.6%	7.1%	8.9%	5.4%	6.3%
Previous smoker (%)	8.7%	8.0%	10.8%	10.5%	6.8%	10.9%
Congestive heart failure (%)	12.3%	7.4%	8.7%	13.2%	11.6%	14.3%
Vascular disease (%)	12.3%	10.6%	13.9%	12.5%	10.5%	8.3%
Renal impairment (%)	2.0%	2.8%	2.1%	3.5%	1.2%	2.2%
Abnormal liver function (%)	0.0%	0.6%	2.1%	1.5%	1.2%	0.0%
Alcohol use (%)	8.5%	2.3%	4.0%	2.1%	4.3%	2.2%
History of / predisposition to bleeding (%)	2.1%	1.1%	3.0%	3.0%	1.8%	4.4%
Labile INR (%)	0.0%	4.8%	3.1%	2.7%	5.8%	4.5%
Previous AF (%)	20.5%	22.2%	27.9%	19.1%	22.5%	42.9%
Previous mRS (Median, IQR)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0-1)
Previous CHA2DS2-VASc (Mean, 95%CI) (Median, IQ)	2.9 (2.5-3.2) 3 (1-5)	3.2 (3-3.4) 3 (1-5)	3.2 (3-3.3) 3 (1-5)	3.2 (3.1-3.4) 3 (1-5)	3.3 (3.-3.5) 3 (1-5)	3.4 (3.1-3.8) 3.5 (2.5-4.5)
Previous HAS-BLED (Mean, 95%CI) (Median, IQ)	1.1 (0.9-1.3) 1 (0-3)	1.3 (1.2-1.3) 1 (0-2)	1.2 (1.2-1.3) 1 (0-2)	1.3 (1.2-1.4) 1 (0-1)	1.2 (1-1.3) 1 (1-1)	1.2 (1.1-1.4) 1 (0-2)
CHA2DS2-VASc (Mean, 95%CI) (Median, IQ)	4.7 (3.1-6.3) 5 (4-6)	5 (3.7-6.3) 5 (4-6)	5 (3.6-6-4) 5 (4-6)	5.2 (3.8-6.6) 5 (4-6)	5.2 (3.8-6.6) 5 (4-6)	5.3 (4.2-6.4) 5 (4-6)
HAS-BLED (Mean, 95%CI) (Median, IQ)	1.7 (0.9-2.5) 3 (2-3)	1.7 (1-2.4) 3 (2-3)	1.7 (0.9-2.5) 3 (2-3)	1.8 (1.1-2.5) 3 (2-3)	1.7 (1-2.4) 3 (2-3)	1.8 (1.2-2.4) 3 (2-3)
Signs of acute infarct (N, %)	11 (15.9%)	23 (14.5%)	33 (12%)	36 (11.3%)	22 (15.9%)	3 (17.1%)

Supplementary Table I. Baseline characteristics according to time initiation.

	Dabigatran patients with available time of initiation N = 1240	Dabigatran patients NO timing information N= 249	P value
Age (Mean, SD) (Median, IQR)	75 ± 10 (69-82)	74 ± 10 (69-80)	0.15
Gender (N, %, Female)	656 (52.9%)	132 (53%)	0.97
NIHSS baseline (Median, IQR)	10 (6-16)	14 (9-19)	<0.001
SBP (mm Hg, Mean, SD)	153 ± 23	154 ± 25	0.31
DBP (mm Hg, Mean, SD)	85 ± 15	84 ± 14	0.23
Glucose (mmol/dl, Mean, SD)	7.3 ± 2.3	7.8 ± 5.1	<0.001
Weight (kg, Mean, SD)	78 ± 15	77 ± 13	0.004
Hypertension (N, %)	955 (77%)	189 (75.9%)	0.63
Diabetes (N, %)	216 (17.4%)	48 (19.3%)	0.5
Hyperlipidemia (N, %)	349 (28.1%)	75 (30.1%)	0.04
Previous TIA (N, %)	65 (5.3%)	10 (4%)	0.48
Current smoker (N, %)	88 (7.1%)	15 (6%)	0.051
Previous smoker (N, %)	107 (8.8%)	30 (12.3%)	0.048
Congestive heart failure (N, %)	134 (10.9%)	24 (9.6%)	0.57
Vascular disease (N, %)	149 (12%)	33 (13.3%)	0.6
Renal impairment (N, %)	30 (2.6%)	5 (2.4%)	0.88
Abnormal liver function (N, %)	16 (1.4%)	1 (0.5%)	0.5
Alcohol use (N, %)	37 (3.2%)	9 (4.3%)	0.44
History of / predisposition to bleeding (N, %)	30 (2.6%)	12 (5.7%)	0.02
Labile INR (N, %)	39 (3.5%)	5 (2.5%)	0.46
Previous AF (N,%)	720 (58.6%)	110 (44.4%)	<0.001
Previous mRS (Median, IQR)	0 (0-0)	0 (0-0)	0.98
Previous CHA2DS2-VASc (Mean) (Median, IQR)	3.1 3 (2-4)	3.1 3 (2-4)	0.31
Previous HAS-BLED (Mean) (Median, IQR)	1.7 1 (1-2)	1.7 1 (1-2)	0.64
CHA2DS2-VASc Discharge (Mean) (Median, IQR)	5,1 5 (4-6)	5.1 5 (4-6)	0.53
HAS-BLED Discharge (Mean) (Median, IQR)	2.7 3 (2-3)	2.8 3 (2-3)	0.73
IVT (N, %)	1055 (85.1%)	180 (72.3%)	<0.001
EVT (N, %)	68 (5.5%)	23 (9.2%)	<0.001
IVT+EVT (N, %)	117 (9.4%)	46 (18.5%)	<0.001

Supplementary Table II. Baseline characteristics of patients initiating dabigatran after the index event.

Legend Supplementary Figure 1. Histogram of initiation time periods, showing proportion of patients and median NIHSS at baseline for each group

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, table
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables
		(*b*) Report category boundaries when continuous variables were categorized	Table
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,111
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.