Early versus Late Start of Direct Oral Anticoagulants after Acute Ischaemic Stroke Linked to Atrial Fibrillation – an Observational Study

An Individual Patient Data Pooled Analysis

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Abstract

Objective: The optimal timing to start direct oral anticoagulants (DOAC) after an acute ischemic stroke (AIS) related to atrial fibrillation (AF) remains unclear. We aimed to compare early (≤ 5 days of AIS) versus late (>5 days of AIS) DOAC-start.

Methods: This is an individual patient data pooled analysis of 8 prospective European and Japanese cohort studies. We included patients with AIS related to non-valvular AF where a DOAC was started within 30 days. Primary endpoints were 30-day rates of recurrent AIS and ICH.

Results: A total of 2550 patients were included. DOACs was started early in 1362 (53%) patients, late in 1188 (47%). During 212 patient-years, 37 patients had a recurrent AIS (1.5%), 16 (43%) before a DOAC was started; 6 patients (0.2%) had an ICH, all after DOAC-start. In the early DOAC-start group, 23 patients (1.7%) suffered from a recurrent AIS, while 2 patients (0.1%) had an ICH. In the late DOAC-start group, 14 patients (1.2%) suffered from a recurrent AIS; 4 patients (0.3%) suffered from ICH. In the propensity-score adjusted comparison of late versus early DOAC-start groups, there was no statistically significant difference in the hazard of recurrent AIS (aHR=1.2, 95%CI 0.5-2.9, p=0.69), ICH (aHR=6.0, 95%CI 0.6-56.3, p=0.12) or any stroke.

Conclusions: Our results do not corroborate concerns that an early DOAC-start might excessively increase the risk of ICH. The seven-fold higher risk of recurrent AIS than ICH suggests that an early DOAC-start might be reasonable, supporting enrolment into randomized trials comparing an early versus late DOAC start.

Introduction

Among patients with atrial fibrillation, direct oral anticoagulants (DOAC) are at least as effective as vitamin K antagonists (VKA) in preventing acute ischemic strokes (AIS). The main advantage of DOAC over VKA is the lower rate of intracranial hemorrhage (ICH), as shown in four pivotal randomized controlled clinical trials. [1] In these trials, however, patients with AIS were excluded for at least 7 days up to 6 months after AIS, given the fear bleeding into the territory of acute cerebral ischemia. A recent individual patient data analysis of seven prospective observational studies found that the advantage of DOAC over VKA is preserved in the early phase after AIS.[2] It remains unclear how early DOAC can safely be started after AIS. Four randomized-controlled clinical trials are comparing an early to a later DOAC-start after AIS associated with atrial fibrillation (ELAN [NCT03148457], OPTIMAS [EudraCT, 2018- 003859-38], TIMING [NCT0291348], START [NCT03021928]) but results are not available yet.[3] In this individual patient data pooled analysis of prospective observational studies, we compared the 30-day rates of recurrent AIS, ICH and mortality between patients in whom DOAC were started early (≤ 5 days) versus late (>5 days) after an AIS or transient ischemic attack (TIA) associated with atrial fibrillation.

Methods

Selection of the Study Centers and Ethics:

The selection of the study centers has been described in detail previously.[2] Briefly, we contacted the principal investigators of peer-reviewed prospective, observational studies published in English based on real-life cohorts in which DOAC were administered within 3 months after the index stroke. The characteristics of the contributing centers are detailed in Table 1. The NOACISP LONG-TERM registry and the current analysis of pooled individual patient data were approved by the ethics committee in Basel, Switzerland (EKNZ 2014-027). Patients provided written consent for participation in NOACISP LONG-TERM. The requirement for additional local ethical approval differed among participating centers and was acquired by the local principal investigator as well as written informed consent by the patient if necessary. For the other study centers, we invited all the corresponding authors of all the relevant studies in 2017. Patients from the Neurocentro della Svizzera Italiana, Lugano, Switzerland, were included based on the decision of local ethics committee (2017- 02041 CE 3298); accordingly, patients were informed about the anonymization and use of their routinely collected data for research

purposes. Patients who denied use of their data were excluded from the analysis. CROMIS-2 was approved by the National Research Ethics Committee, London Queen Square. Patients with capacity gave informed written consent. When patients could not consent, we obtained written consent from a proxy as defined by relevant local legislation. The SAMURAI-NVAF registry and the collaboration with the joint initiative were approved by the ethics committee in the National Cerebral and Cardiovascular Center (M23-18-3 and M29-077). There is no overlap between the cohort studies studied, i.e. all included patients are unique.

Inclusion and exclusion criteria:

We included patients with: (1) AIS (defined as a focal neurological deficit with acute onset and presence of a corresponding lesion on diffusion weighted magnetic resonance imaging [DWI] or, if no MRI was acquired, signs of early ischemic injury on CT) or TIA (defined as an acute onset focal neurological deficit of presumed ischemic origin without a corresponding lesion on DWI or, if no MRI was acquired, lasting less than 24 hours); (2) diagnosis of non-valvular atrial fibrillation, either known prior to the index event or detected after the event; (3) oral anticoagulation with DOAC, either continued (for those already on anticoagulation on admission), started or resumed within 30 days after the index event; (4) prospective follow-up for at least 30 days after the index event for the presence or absence of recurrent AIS, ICH and death (of any cause). Patients who died prior to the first planned follow-up, i.e. within the first 3 months following the index event, were included.

We excluded patients with (1) mechanical heart valves; (2) rheumatic or severe mitral valve stenosis; (3) oral anticoagulation with VKA; (4) ICH after the index event but prior to DOAC–start; (5) oral anticoagulation started later than 30 days after the index event; or with missing information on the initiation date of oral anticoagulants.

Definition of early and late DOAC-start

Early DOAC-start was defined as ≤5 days from the index event, late DOAC-start as >5 days. The rationale for this cut-off is statistical rather than biological, as 5 days represented the median interval of DOAC-start, leaving us with two groups balanced in size as the published individual patient data study comparing DOAC to VKA after a recent AIS.[2]

As a sensitivity analysis, we assessed whether adherence to the guideline of the European Society of Cardiology (ESC) on the timing of DOAC-start by was associated with the endpoint rate, as recently performed by Eun *et al*. [4] The definition of the guideline-adherent group was as follows: NIHSS<8 and DOAC-start ≥3 days of the index event; or NIHSS ≥ 8

and ≤15 and DOAC-start ≥6 days; or (3) NIHSS≥16 and DOAC-start ≥12 days. Earlier DOAC-starts were defined as non guideline-adherent.[4]

Follow-up

We included only studies with a planned follow-up of at least 30 days after index event for: recurrent AIS (defined as new neurological symptoms and evidence for ischemic stroke on CT or MRI); ICH defined as new neurological symptoms associated with the detection of ICH on CT or MRI as defined within the ISTH criteria[5]; and all-cause mortality (including fatal AIS or ICH).

Endpoint

The co-primary endpoints were the time to occurrence of recurrent AIS, ICH, and any stroke (AIS or ICH).

Statistical analysis

We compared demographic and clinical baseline characteristics among patients in the early versus late DOAC-start using the Pearson $\chi 2$ test for categorical variables and the Mann-Whitney U test for continuous variables. Our main goal was to compare the event rates between the early vs. late DOAC-start groups. Traditional Cox analysis would, however, be biased since the timepoint of the endpoint could have influenced the group allocation. For instance, a recurrent AIS at day 3 – before DOAC-start – may have prompted the treating physicians to start DOAC immediately after the recurrence, with a DOAC-start between day 3 and day 5. Hence, to compare the time-to-events between the early and late DOAC-start groups, we considered only patients who were event-free up to 5 days of the index event (n=2535) – i.e. a landmark analysis. Sensitivity analysis with landmark at 3 and 7 days were performed. We assessed the association between the timepoint of DOAC-start (early vs. late) and the endpoints, using a mixed effects Cox proportional hazards regression model to compute hazard ratios with 95% confidence intervals (95%CI). Landmark analysis was performed for Cox analyses only. Propensity score weighting was used to adjust for confounders – i.e. baseline variables with $p<0.05$ in univariate analysis and intravenous thrombolysis – to compute adjusted hazard ratios (aHR). Only the first outcome event is used and patients who suffered a competing event (e.g. death following ICH) were censored at the day of their first event. To take competing risk into account, we ran a Fine-Gray model.

Concerning the timepoint of death, 22 patients had died within 90 days of the qualifying event but for 15 of these the exact day of death was unknown. For these 15 patients, we used multiple imputations to estimate the time of death. To this end, for each patient a random point between the time of anticoagulation (i.e. the last point the patient was known to be alive) and the point the patient was known to be dead was imputed. We did 100 imputations. For the plots a random imputation was used. The models are fitted on each imputation. Thereafter we used Rubin's rule to pool the estimates.

We assessed treatment effects in the following pre-defined subgroups: (1) patients with minor stroke or TIA (defined as NIHSS≤3)[6]; (2) patients with severe stroke (defined as NIHSS > 15)[7]; (3) elderly patients (defined as aged ≥80 years vs < 80 years); (4) patients with impaired renal function (defined as Creatinine Clearance of <60 ml/min/1.73m^2 using the CKD-EPI equation[8]); (5) patients treated with acute recanalization therapies for the index stroke (intravenous thrombolysis and/or endovascular therapy). Thereby, each binary variable indicating a subgroup was included in a separate model and the interaction term between the covariate and the treatment was estimated. A significant interaction – i.e. $p<0.05$ – term indicates that the estimated difference between treatments differs between the subgroups. The estimated hazard ratios were presented as forest plots. For the subgroup analyses – given the small endpoint numbers – we used the composite of recurrent AIS, ICH and death within 30 days. An α-level of 0.05 was used to determine statistical significance. The statistical analyses were carried out using R.

Data Availability Statement

De-identified participant data will be shared upon written request by qualifying investigators who provide a research protocol.

Results

Baseline data and demographics

The pooled individual patient data cohort comprised 5421 patients, 2871 of which were excluded; flow of patient is showed on figure 1. Five patients were excluded because ICH occurred prior to any DOAC-start; two of these five patients suffered from ICH following acute recanalization therapy. The final cohort included 2550 patients (see Table 2). Overall, the median age was 77 years (IQR 70-84) and 1204 patients were women (47%). Stroke

severity was milder in the early DOAC-start group (NIHSS 4 [IQR 1-8] vs. 6 [IQR 3-12], P<0.001). The index event was AIS in 2455 patients (95.5%), a TIA in 95 (4.5%). Prior to the index event, 773 (37%) patients were on antiplatelet therapy, 506 patients (20%) were on oral anticoagulants. After the index event, DOAC were started early (≤ 5 days of the index event) in 1362 (53%) patients, late (6–30 days of the index event) in 1188 (47%). There were 76 patients who suffered the index stroke under oral anticoagulation and where anticoagulation was continued without pausing (5.6% of the early DOAC-start group). NIHSS on admission was missing in 160 patients (6.3%); renal function in 276 patients (10.8%); information on intravenous thrombolysis in 22 patients (0.9%).

Endpoint analysis for the whole cohort

Between the index event and 30 days follow-up, 37 patients had a recurrent AIS (1.5%), 57% of which happened under DOAC (21/37) and 41% within the first 5 days of the index event (15/37). Six patients had an ICH (0.2%), and 15 patients died within the first 30 days (0.6%). The composite 30-day rate of any stroke was 1.7% (43/2550).

Endpoint analysis for the early DOAC-start group (DOAC started within 5 days of the index event)

In the early DOAC-start group, within 5 days of the index event, 8 patients (0.6%) suffered from a recurrent AIS before DOAC was even started, 15 patients (1.1%) suffered from a recurrent AIS after DOAC-start; only two patients (0.1%) suffered from ICH, all after DOAC-start. The composite 30-day rate of any stroke was 1.8% (25/1362).

Endpoint analysis for the late DOAC-start group (DOAC started between 6–30 days of the index event)

In the late DOAC-start group, within 30 day of the index event, 8 patients (0.7%) suffered from a recurrent AIS before DOAC was started, 6 patients (0.5%) suffered from a recurrent AIS after DOAC-start; four patients (0.3%) suffered from ICH, all after DOAC-start. The composite 30-day rate of any stroke was 1.5% (18/1188)

Endpoint comparison late versus early DOAC-start groups and by adherence to the ESC Guidelines

In the propensity score weighted comparison of late versus early DOAC-groups, no statistically significant difference in the hazard ratios was observed for the endpoint of

recurrent AIS (aHR=1.2, 95%CI 0.5-2.9, p=0.69), ICH (aHR=6.0, 95%CI 0.6-56.4, p=0.12) and any-stroke (aHR=1.44, 95%CI 0.66-3.33, p=0.33) (see figure 2a-c). A Fine-Gray model to take competing risk into account did not change these HRs. The propensity score weights were estimated using the following variables: NIHSS at onset, type of event (AIS vs. TIA), intravenous thrombolysis, any anticoagulation at baseline, antiplatelets at baseline, impaired renal function, current smoking status, CHA_2DS_2-Vasc and HAS-BLED. Sensitivity analyses with Kaplan-Meier curves for the landmark analyses at day 3 and day 7 are presented in Supplemental Figures 1 and 2, respectively.

A sensitivity analysis by adherence to the ESC Guidelines revealed that DOAC-start was guideline-adherent in 1445 patients (57%) and non-adherent in 1105 patients (43%). There was no significant difference in the propensity score adjusted rates for ischemic stroke (aHR 1.15, 95%CI 0.58-2.31, p=0.69), ICH (aHR 1.28, 95%CI 0.22-7.56, p=0.79), and any-stroke (aHR 1.17, 95%CI 0.61-2.23, p=0.64), the Kaplan-Meier curves are presented in the Supplemental Figure 3.

Subgroup analyses

The rate of the composite endpoint (recurrent AIS, ICH and death within 30 days) did not differ significantly across subgroups (Figure 3, no significant interaction term).

Discussion

In this individual patient data pooled analysis of 8 international, prospective cohort studies including 2550 patients treated with DOACs within 30 days of an atrial fibrillation-related AIS or TIA, we found that: (1) the 30-day rate of recurrent AIS (1.5%) was more than 7-fold higher than the rate of ICH (0.2%); (2) 40% of recurrent AIS occurred early – within 5 days of the index event – and 43% of recurrent AIS occurred before any DOAC-start, being thus potentially preventable; (3) both early (≤ 5 days) and late (> 5 days) as well as ESC guideline adherent vs. non-adherent DOAC-starts were similar in terms of recurrent AIS, ICH and any-stroke at 30 day follow-up. Our results do not corroborate the concern that early anticoagulation with DOACs might increase the risk of ICH compared to a delayed strategy. Given the seven times higher risk of recurrent AIS – with almost half occurring in the first five days and before any DOAC-start – our findings suggest that early DOAC-start after atrial fibrillation-related AIS or TIA might be reasonable, and justifies enrolment of patients into ongoing randomized controlled trials.

The risk of a recurrent AIS is front-loaded – it peaks immediately after the index AIS/TIA and drops thereafter: in our study, over the first 5 days, the risk of AIS was 0.12% per day (15 patients with recurrent AIS / 2550 patients / 5 days), whereas – over the following 25 days – the risk of AIS was 0.03% per day (22 patients with recurrent AIS / 2550 patients / 25 days). These event rates are considerably higher than that reported in the subgroup analyses of the four pivotal randomized clinical trials comparing DOACs to VKAs for atrial fibrillation, in which the subgroups of patients with a remote history of cerebrovascular events had a rate of recurrent atrial fibrillation-related AIS between 0.0048% per day in the RE-LY trial (dabigatran group, exclusion of patients up to 6 months after AIS) and 0.0064% per day in ROCKET-AF (rivaroxaban group, exclusion of patients up to 3 months after AIS), i.e. around 10-fold lower than ours. [9, 10]

The rate of a recurrent AIS observed in our study was considerably lower than reported in earlier studies (0.3% and 1.1% per day).[11, 12] One potential reason for this difference is the choice of anticoagulant; in the earlier studies – published between 1984 and 1993 – the anticoagulant of choice was often heparin; in the year 2000, however, the Heparin in Acute Embolic Stroke Trial (HAEST) found no evidence that low-molecular-weight heparin, started within 30 hours from stroke onset, was superior to aspirin at 14 days, adding to the body of evidence that heparin – both fractioned and unfractioned – does not protect effectively against recurrent AIS.[13, 14] Also, the cited studies looked only at the first 14 days following the index AIS, a timeframe with a higher recurrence rate than over a longer follow-up period as in our study (30 days).

The lower AIS-rate in our study is not likely to result from the exclusion of VKA-treated patients, as a recent analysis comparing DOAC to VKA within 3 months of an atrial fibrillation-related AIS showed similarly low rates of recurrent AIS between the DOAC and VKA-groups. [2]

The low 30-day rate of ICH is likely due to the exclusion of VKA-treated patients, as DOAC are associated with a lower ICH-rate than VKA.[2, 15] The low 30-day rate of ICH aligns well with four studies on patients with atrial fibrillation-related AIS with clinical follow-up of ≥3 months, in which the annualized rate of ICH was between 1.2 and 9.5 times lower than the annualized rate of recurrent AIS. [16-19]The study with the highest annualized ICH-rate was

RAF-NOAC (6.4% per year), but most ICH occurred beyond 30 days from AIS onset, making the association between ICH and early DOAC-start uncertain.

In our study, seven patients suffered from ICH between the index AIS/TIA and before DOAC-start, two of them immediately after acute endovascular treatment. In these seven patients, DOAC-start was performed late (>5 days). We excluded these patients because their ICH could not be attributed to the DOAC-start following the index event. Also, including these patients would have resulted in a falsely higher 30-day ICH rate in the late DOAC-start group. “Primary” hemorrhagic transformation – i.e. independent of anticoagulation or recanalization therapies – is a known complication of large AIS, including those due to atrial fibrillation. In comparison, in the aspirin arm of the HAEST trial, symptomatic ICH was reported in 4 patients (1.8%) at 14 days of their atrial fibrillation-related AIS.

Because no routine imaging was performed on follow-up, reported events are confined to symptomatic ICH. Asymptomatic hemorrhagic transformation – albeit more frequent – does not seem to portend symptomatic ICH after DOAC are started: in a recent prospective study on 60 patients with an acute atrial fibrillation-related AIS, baseline MRI showed asymptomatic petechial hemorrhagic transformation in 25 (42%) of patients; rivaroxaban was started in all of the 60 patients, after an average of 3 days, and none developed symptomatic hemorrhagic transformation by day 7. [20]

The optimal time to start DOAC remains controversial. Our data suggest that an early DOAC-start (≤ 5 days) might be reasonable, given that 43% of recurrent AIS were potentially preventable, and that the early DOAC-start group did not show the feared excess in ICH. Similar findings were observed in the recent, comprehensive analysis of the Samurai-NVAF registry.[21] Current guidelines are inconsistent on when to start oral anticoagulation after atrial fibrillation-related AIS, and do not distinguish between use of DOAC and VKA, i.e. they do not take into account the lower ICH-rates observed with DOAC compared to VKA. To shed light on this important question, four randomized clinical trials are comparing different timepoints of DOAC-start: ELAN (NCT03148457; Switzerland/International), OPTIMAS (EudraCT, 2018-003859-38; UK), TIMING (NCT02961348; Sweden), and START (NCT03021928; USA).[3] The event rates we report here might be informative in determining the sample size needed in the ongoing trials to demonstrate a difference in efficacy and safety between early and late DOAC treatment.

Strengths of our study include the international multicenter design, the inclusion of a current, large cohort of patients – all treated with DOACs. The 30-day follow-up focusses on the critical first few days following an AIS, where the complication risk is highest. The main limitation is that this study is not randomized, and residual confounding cannot be ruled out. Propensity scores can only take account for known confounders, not for unknown or unmeasured ones, such as lesion size, location, and hemorrhagic transformation. Also, propensity scores can compensate only in part for the low event rate – the risk of overfitting cannot be ruled out. The immortal time bias also merits discussion: in the early DOAC-start group, eight patients suffered from a recurrent AIS within the first 5 days but prior to any DOAC-start; here, the early DOAC-start is likely to have been a reaction triggered by the recurrent AIS itself; these patients would bias the 30-day recurrent AIS rate (artificially higher in the early DOAC-start or lower in the late DOAC-start group). We addressed this issue with the landmark analysis. The landmark analysis considers only patients who were event-free up to 5 days following the index event, in order to estimate whether the event rates after day 5 differ between the early and late DOAC-start groups. We acknowledge that the selection of the time point of 5 days to discriminate between early and late DOAC initiation may be considered as arbitrary; we tried to compensate this through the analysis on adherence to the ESC-guidelines. The amount of interaction analyses is problematic given the limited number of events – the results are exploratory and shall be viewed with caution. Finally, as in many observational study comparing treatments, the possibility of confounding by indication cannot be ruled out.

In conclusion, our results – based on individual assessments used to select patients to start early versus late – do not corroborate concerns that early anticoagulation with DOACs may increase the risk of ICH. The seven-fold higher risk of recurrent AIS than ICH – with almost half of these occurring before DOAC-start – suggests that early DOAC-start after atrial fibrillation-related AIS might be reasonable. This supports enrolment into ongoing randomized trials comparing an early versus late DOAC anticoagulation after AIS linked to atrial fibrillation.

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<u>Table 1:</u> Single- and multi-center studies participating in the individual patient data analysis

	Study period	**Patients contributed to final cohort, n (%)**	**Maximum follow-up period***
Single Center			
NOACISP (Basel/Switzerland)[16]	2012-2017	376 (14.7)	up to 3.8 years
Verona (Italy)[22]	2013-2015	225 (8.8)	3 months
Erlangen (Germany) [23]	2011-2013	201 (7.9)	up to 1 year
Lugano (Switzerland)	2014-2018	32 (1.3)	3 months
Multi Center			
RAF-NOAC (29 centers in Europe/Asia)[18]	2014-2016	768 (30)	3 months
SAMURAI-NVAF (18 centers in Japan) [24]	2011-2014	439 (17)	up to 3.5 years
CROMIS-2 (80 centers in the UK and 1 in the Netherlands) [25]	2011-2015	436 (17)	up to 5.4 years
RAF (29 centers in Europe/Asia)[26]	2012-2014	73 (2.9)	3 months

*Minimum follow-up period of 3 months for all studies. Because of rounding, percent do not add up to 100%.

Table 2: Baseline Demographic and Clinical Characteristics

	Early[a] Anticoagulation (n=1362)	**Late[a] Anticoagulation (n=1188)**	***p***
Age (median [IQR])	78.0 (71–84)	77.0 (70–83)	0.06
Women	637 (46.8)	567 (47.7)	0.66
AIS as qualifying event	1283 (94.1)	1172 (98.7)	<0.001
Baseline antiplatelet agents	353 of 1035 (34.1)	420 of 1074 (39.1)	<0.001
Baseline Vitamin K Antagonist	222 of 1345 (16.5)	150 of 1181 (12.7)	<0.001
Baseline DOAC	94 of 1345 (7.0)	31 of 1181 (15.5)	<0.001
Baseline statins	172 of 688 (25.0)	102 of 358 (28.5)	0.26
History of intracranial hemorrhage	10 of 1000 (1.0)	8 of 667 (1.2)	0.84
Diabetes mellitus	298 of 1360 (21.9)	275 of 1185 (23.2)	0.47
Hypertension	1026 of 1360 (75.4)	899 of 1182 (76.0)	0.78
Dyslipidemia	421 of 1063 (39.6)	301 of 717 (42.0)	0.33
Impaired renal function[b]	453 of 1231 (36.8)	260 of 1044 (24.9)	<0.001
Current smoking	176 of 1313 (13.4)	260 of 1156 (22.5)	<0.001
NIHSS on admission	4.0 (1–8)	6.0 (3–12)	<0.001
CHA_2DS_2-Vasc	5.0 (4–6)	5.0 (4–6)	0.02
HAS-BLED	3.0 (2–3)	3.0 (2–4)	0.001
Intravenous thrombolysis	324 of 1350 (24.0)	281 of 1180 (23.8)	0.95
Endovascular treatment	43 of 1194 (3.6)	53 of 1128 (4.7)	0.22

Categorical variables are given in number of patients having the characteristic/total patients available for analysis and (%).

Continuous variables are displayed as median and interquartile range (IQR).

[a] Early: ≤5 days of the index event; late: between 6–30 days of the index event

[b] Impaired renal function defined as creatinine clearance of <60ml/min/1.73m^2

AIS = acute ischemic stroke; DOAC = direct oral anticoagulants; NIHSS = National Institute of Health Stroke Severity Scale

Figure Legends

Figure 1: Patient Flow

Figure 2a-c: 30-day Outcomes, landmark analyses at day 5. Figure 2a represents recurrent acute ischemic stroke; 2b intracranial hemorrhage; 2c any stroke

Figure 3: Subgroup Analyses. The endpoint is the composite of recurrent acute ischemic stroke, intracranial hemorrhage and any-cause mortality within 30 days of the index event.

Supplemental Figure 1: Sensitivity Analysis with 30-day Outcomes, landmark analyses at day 3

Supplemental Figure 2: Sensitivity Analysis with 30-day Outcomes, landmark analyses at day 7