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Early Versus Late Initiation of Direct Oral Anticoagulants After Ischemic Stroke in People With Atrial Fibrillation and HemorrhagicTransformation: Prespecified Subanalysis of the Randomized-controlled ELAN Trial

Running Title: *Rohner et al.; ELAN hemorrhagic transformation*

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Abstract

Background: Whether hemorrhagic transformation (HT) modifies the treatment effect of early versus late initiation of direct oral anticoagulation (DOAC) in people with ischemic stroke and atrial fibrillation is unknown.
Methods: This is a post-hoc analysis of the ELAN trial. The primary outcome was a composite of recurrent ischemic stroke, symptomatic intracranial hemorrhage (sICH), major extracranial bleeding, systemic embolism, or vascular death within 30 days. Secondary outcomes were the individual components, 30- and 90-day functional outcome. We estimated outcomes based on HT, subclassified as hemorrhagic infarction (HI) or parenchymal hemorrhage (PH) on pre-randomization imaging (core-lab rating) using adjusted risk differences (aRD) between treatment arms.
Results: Overall, 247/1970 (12.5%) participants had HT (114 HI 1, 77 HI 2, 34 PH 1, 22 PH 2). For the primary outcome, the estimated aRD (early versus late) was −2.2% (−7.8 to 3.5%) in people with HT (HI: −4.7%, −10.8 to 1.4%; PH: 6.1%, −8.4 to 20.7%), and −0.9% (−2.6 to 0.8%) in people without. Numbers of sICH were identical in people with and without HT. With early treatment, the estimated aRD for poor 90-day functional outcome (mRS 3–6) was 11.4% (−0.9 to 23.7%) in participants with HT (HI: 7.2%, −6.6 to 21.0%; PH: 25.1%, 0.2 to 50.0%), and −2.6% (−7.1 to 1.8%) in people without HT.
Conclusions: We found no evidence of major treatment effect heterogeneity or safety concerns with early versus late DOAC initiation in people with and without HT. However, early DOAC initiation may worsen functional outcomes in people with PH.
URL: http://www.clinicaltrials.gov/study/NCT03148457**;** NCT03148457

Key Words: ischemic stroke – direct oral anticoagulants - hemorrhagic transformation – treatment start

Non-standard Abbreviations and Acronyms

AF	Atrial fibrillation
CI	Confidence intervals
CT	Computed tomography
DOAC	Direct oral anticoagulation
HI	Hemorrhagic infarction
HT	Hemorrhagic transformation
MRI	Magnetic resonance imaging
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke scale
PH	Parenchymal hemorrhage
RCT	Randomized-controlled trials
sICH	Symptomatic intracranial hemorrhage

Clinical Perspective

What is new?

- In this post-hoc analysis of the ELAN trial, we estimated the treatment effect heterogeneity on safety and efficacy of early versus late initiation of direct oral anticoagulants (DOACs) in ischemic stroke people with and without hemorrhagic transformation (HT). HT was subclassified as hemorrhagic infarction (HI) or parenchymal hemorrhage (PH).
- We identified no major treatment effect heterogeneity or safety concerns in people with and without HT.
- Outcome was similar in people with and without HI, but we observed a 25% higher risk for poor 90-day functional outcome in participants with PH and early versus late DOAC treatment.

What are the clinical implications?

- Early initiation of DOACs (<48h after ischemic stroke for minor and moderate stroke, 6–7 days for major stroke) in people with HT does not increase rates of sICH and might be beneficial in people with HI type 1 and 2.
- In people with PH, early anticoagulation treatment may worsen functional outcomes, but confirmation based on data from ongoing trials is needed.

Introduction

Atrial fibrillation (AF) is a common cause of acute ischemic stroke, carrying a high risk of early recurrence. For people with ischemic stroke and AF, targeted secondary prevention using direct oral anticoagulants (DOACs) appears particularly beneficial in the initial days post-event.[1-3] However, the optimal timing for initiating DOACs remains a subject of ongoing debate, primarily due to concerns about hemorrhagic transformation (HT) of the ischemic lesion.[4-6] HT peaks within the first days after stroke and could potentially offset the presumed benefits of anticoagulation therapy.[2,7] Recently published data from observational studies and two randomized-controlled trials (RCTs) indicate that initiating anticoagulation treatment early, as opposed to later guideline-based initiation, is not only safe but contributes to a reduction in recurrent ischemic events.[6,8-10]

However, it remains unclear whether early initiation of DOAC therapy is also advantageous in people known to have HT at treatment start, as earlier studies either did not provide information on HT or had few participants with this condition.[6,8,9] This information carries considerable clinical relevance, as clinicians frequently postpone the initiation of anticoagulation therapy when HT is detected on post-stroke neuroimaging.[4,11]

In this post-hoc analysis utilizing data from the ELAN trial, we aimed to assess whether the presence of HT on pre-randomization imaging modifies the estimated treatment effect heterogeneity on safety and efficacy of early versus late DOAC initiation in people with acute ischemic stroke and AF.

Methods

The data that support the findings of this study will be accessible upon reasonable request and after approval by the ELAN trial steering committee. Data can be requested via urs.fischer@insel.ch.

This study is a post-hoc analysis of the international, multi-center, randomized-controlled ELAN trial,[9] which was designed to compare early (<48h after ischemic stroke for minor and moderate stroke, 6–7 days for major stroke) versus late (> 48h for minor, 3–4 days for moderate, 12–14 days for major stroke) initiation of DOACs in people with acute ischemic stroke and AF. The ELAN trial was conducted from November 2017 to September 2022 and included more than 2000 participants at 103 stroke centers in Europe, the Middle East, and Asia. The study protocol, main results of the trial and information on data collection have been published previously.[10,12,13]

In brief, participants were eligible if they presented with an acute ischemic stroke and had a history of AF or were diagnosed with AF during the index hospitalization. Individuals with transient ischemic attacks or a particularly high risk of intracranial bleeding (e.g. multiple cerebral microbleeds) were not included in the study. Participants were randomly allocated in a 1:1 ratio to either the early treatment group (=intervention group) or the late treatment group (=guideline-based control group). In the present study, we included all participants from the ELAN trial with available pre-randomization brain imaging (either magnetic resonance imaging [MRI] or computed tomography [CT]). Participants with insufficient imaging quality to assess HT were excluded from the study.

The study protocol received approval from all relevant ethics committees and written informed consent was given either by participants, next of kin or other legal representatives, or an independent physician. All study data were gathered by local investigators and collected in a secuTrial© database hosted by the Clinical Trials Unit (CTU) Bern.

Neuroimaging assessment

All neuroimaging studies obtained during the trial period were transferred to the imaging core-lab at the Support Center for Advanced Neuroimaging (SCAN, Inselspital Bern) by the local site investigators. The core-lab consisted of two board-certified neuroradiologists (SF,

BRK) who were supported by a neurologist with ample experience in neuroimaging (MK, MR-based ratings) and a neuroradiology resident proficient in neuroimaging diagnostics (RR, CT-based ratings).

Pre-randomization imaging studies were assessed for the presence and extent of HT using either plain CT scans or MR-based images (1.5 or 3 Tesla) that included susceptibility-weighted sequences. If both modalities were available, MR-based images were analyzed due to their higher sensitivity for petechial HT.[14]

HT was classified according to the European Cooperative Acute Stroke Study (ECASS) II criteria.[15] ECASS II distinguishes between two types of petechial hemorrhagic infarction (HI) without mass effect: HI 1, characterized by small petechiae, and HI 2, characterized by confluent petechiae. Parenchymal hematomas (PH) were also categorized into two types: PH 1 denotes a hematoma occupying less than 30% of the infarcted tissue, whereas PH 2 refers to intracerebral hemorrhages affecting 30% or more of the infarct area.[15] We also documented intracerebral hemorrhages occurring remotely from the infarcted tissue (**Supplemental Figure 1**).

According to the ELAN trial protocol, people with PH or remote hemorrhages were intended to be excluded from participation.[12] The decision on whether a patient fulfilled the HT inclusion criteria was made at the discretion of the local site investigators. For this post-hoc analysis, all pre-randomization images underwent re-evaluation by the ELAN trial imaging core-lab. In cases where HT was identified or discrepancies between two raters occurred, a senior, board-certified neuroradiologist with special expertise in neurovascular imaging (AH) and 16 years of neuroimaging experience reviewed the images and had the deciding vote. All raters were blinded to clinical data.

Outcomes

The primary outcome used in this study was the same as in the main ELAN trial analysis and comprised the composite of symptomatic intracranial hemorrhage (sICH), major extracranial bleeding, recurrent ischemic stroke, systemic embolism, or vascular death within 30 days after stroke. sICH was defined as any occurrence of intracranial bleeding that resulted in clinical deterioration and had to be determined by the treating physician.[12] Secondary outcomes included the same composite endpoint at 90 days post-stroke and the individual components of the primary outcome as well as functional outcome according to the modified Rankin Scale (mRS) at 30 and 90 days post-stroke.

Statistical analysis

Statistical analyses were performed by MB using Stata version 17.0 (2021) and R version 4.3.1 (2023) based on a statistical analysis plan written by MK, RR, AH, MB, SA, JD, and UF. For the primary analysis, participants were categorized based on the presence of HT on pre-randomization imaging (any HT versus no HT) as assessed by the imaging core-lab. Treatment allocation (early versus late initiation of anticoagulation) was determined according to a modified intention-to-treat strategy, as described previously.[10] Descriptive statistics were employed to analyze and compare baseline clinical characteristics. Categorical variables are presented as number and percentage, while continuous variables are presented as mean and standard deviation, or median and upper/lower quartile (lq, uq).

For binary outcomes, we performed uni- and multivariable Firth penalized logistic regression to account for the small number of outcome events. Ordinally scaled outcomes were assessed with ordinal logistic regression. Multivariable regressions were adjusted for age (per year), hypertension (binary), infarct location (anterior versus posterior circulation), infarct size (minor versus moderate versus major), pre-stroke mRS score, National Institutes of Health Stroke scale (NIHSS) at admission, and acute treatment (intravenous thrombolysis and/or endovascular treatment) utilizing the inverse probability weighting method. The

results of the models were displayed using relative and absolute differences using the Odds ratio with 95% confidence interval (CI) and marginal risk differences with 95% CI, respectively. The marginal risk differences were obtained based on the predicted responses from the logistic model for both groups from which then the difference was calculated.

Sensitivity analysis

We performed three sensitivity analyses: First, participants with HT were dichotomized into those with HI (HI 1 and HI 2) and those with PH (PH 1 and PH 2). Individual participants with intracranial hemorrhage outside the infarcted brain tissue (remote hemorrhage) were included in the PH 2 group. Second, participants were stratified according to imaging modality (CT and MRI). In the third sensitivity analysis, we excluded all participants who had undergone thrombolysis and / or thrombectomy, but had no follow-up images prior randomization available. Efficacy and safety of early versus late DOAC treatment stratified by the presence of HT (primary analysis), its subgroups and imaging modality (sensitivity analyses) were presented using adjusted odds ratios (aOR) and adjusted risk differences (aRD). Owing to the small number of outcome events and, consequently, limited statistical power, this study provides hypothesis-generating evidence, presenting point estimates and 95% confidence intervals (CI) without reporting p-values. Furthermore, the interaction between the presence and the absence of HT and the randomization group was calculated using the firth logistic regression model including the variables and their interaction, while the different ORs were derived from the sub-set of the data separately.

Interrater reliabilities and procedures for handling missing data

Interrater reliabilities for the presence of HT and its subtypes on pre-randomization neuroimaging among different raters in the core imaging lab were assessed using Gwet's AC1 and Cohen's kappa.

The statistical analysis plan prespecified performance of multivariable multiple imputation by chained equations if the total number of missing outcomes in one group was >5%. This was not required for the present analysis, given the high data completeness (missingness <5%).

Results

For this post-hoc analysis of the ELAN trial, 43 of 2013 participants (2.1%) had to be excluded due to insufficient brain imaging quality. Another 37 participants were excluded from the primary analysis, as their primary outcome was missing (24 participants died from a non-vascular cause during follow-up, 12 withdrew consent, and one was lost to follow-up), leading to a final study cohort of 1933 participants with ischemic stroke and AF (median age: 77 years, 45.5% female) (**Figure 1**). Of all included participants, 247 (12.5%) showed HT on pre-randomization imaging, of whom 114 had HI 1, 77 HI 2, 34 PH 1, and 22 PH 2. Core imaging lab interrater reliabilities for the presence of HT were 0.79 (0.70 to 0.87) using Gwet's AC1 and 0.63 (0.49 to 0.76) using Cohen's kappa.

Baseline characteristics

Age, pre-stroke disability and comorbidities were well-balanced between the subgroups. The median CHA2DS2-VASc score was 5 points in most groups. Median NIHSS scores before randomization in people with HT were 6 (interquartile range [IQR] 2 to 12 with early treatment) and 5 (IQR 2 to 11) with late treatment. In participants without HT, median NIHSS scores were 2 (IQR 1 to 6) with early treatment and 3 (IQR 1 to 6) with late treatment. Based on infarct size, HT was frequently observed in participants with major (30.4%, early treatment; 22.7%, late treatment) and moderate (14.8%, early treatment; 14.4%, late treatment) stroke. Participants with minor strokes showed low rates of HT (1.6%, early treatment; 1.9%, late treatment). At the screening visit, single antiplatelet therapy (mostly

aspirin) was used in 53 (40.5%) participants with HT in the early and in 57 (49.1%) in the late treatment arm. In the non-HT group, 420 (49.3%) participants were treated with single antiplatelet in the early and 500 (57.4%) in the late treatment group (for details see **Table 1** and **Supplemental Table 1**).

Primary outcome

The primary composite outcome at 30 days was observed in 5 (3.8%) participants with HT in the early versus 7 (6.0%) participants in the late treatment group (aOR: 0.65, 95% CI: 0.20–2.00). In the non-HT groups, 24 (2.8%) primary outcome events occurred in the early versus 33 (3.8%) in the late treatment arm (aOR: 0.75, 0.44–1.28). This resulted in an estimated aRD between the early and late groups of −2.15% (95% CI: −7.78 to 3.48%) in HT and −0.92% (−2.63 to 0.78%) in participants without HT (**Table 2** and **Figure 2**).

Secondary outcomes

Recurrent ischemic stroke was the most frequently observed primary outcome component in all groups: In the HT subgroups, it occurred in 2 (1.6%) participants in the early and 6 (5.2%) in the late group (aOR: 0.34, 0.06–1.35). Of the participants without HT, 12 (1.5%) in the early and 18 (2.1%) in the late treatment arm (aOR: 0.68, 0.32–1.39) had recurrent ischemic strokes. The numbers of sICH were identical in participants with early versus late DOAC initiation. Although no sICH was identified in participants with HT either in the early (0/131, 0%) or in the late (0/116, 0%) treatment arm, in the non-HT group, 2/852 (0.2%) participants in the early and 2/871 (0.2%) in the late treatment group had sICH (**Figure 2**).

Functional outcome

Poor 90-day functional outcome (mRS 3–6) was observed in 107 (43.3%) participants with HT (HI: 73/191, 38.2%; PH: 34/56, 60.7%) and in 546 (32.0%) participants without (aOR 1.60, 0.59–3.62) (**Supplemental Table 2**). Comparing treatment arms, a poor 90-day outcome was present in 63 (48.1%) participants with HT in the early and in 44 (37.9%) in the

late group, yielding an aOR of 1.59 (0.96–2.65) and an estimated aRD of 11.36% (−0.94 to 23.65%). In the group without HT, a poor functional outcome at 90 days was seen in 260 (30.5%) participants in the early and 291 (33.4%) in the late treatment arm, with an aOR of 0.89 (0.72–1.09) and an estimated aRD of −2.64% (−7.07 to 1.78%).

Similar results were observed for functional outcomes at 30 days post-stroke (**Table 2** and **Supplemental Tables 3 and 4**). A stronger opposite effect between early and late treatment within the HT and non-HT groups was observed for the functional outcome at both 30 and 90 days (i.e. interaction effect).

Sensitivity analyses

HI was the most prevalent HT subtype, observed in 191 (9.7%) participants. This included participants with HI 1 (n=114, 5.8%) and HI 2 (77, 3.9%). PH/remote hemorrhages were identified in 56 (2.8%) participants. PH 1 (n=34, 1.7%) was seen more often than PH 2 (n=22, 1.1%). Of those, ten participants had a hemorrhage remote from the infarcted brain tissue (0.5%) seen on pre-randomization imaging. Baseline characteristics are shown in **Supplemental Table 5**.

The numbers of participants with the composite primary outcome were low in both the HI subgroup (early treatment: n=2, 2.0%; late treatment: n=6, 6.7%), and in the PH/remote hemorrhage subgroup (early treatment: n=3, 10.3%, late treatment: n=1, 3.7%), favoring early treatment in the HI subgroup (aOR: 0.32, 0.06–1.32) with an estimated aRD of −4.69% (−10.81 to 1.43%). In participants with PH, the aOR for the primary outcome was 2.24 (0.35–24.11) with an estimated aRD of 6.13% (−8.44 to 20.69%). Notably, sICH was neither observed in the HI nor in the PH groups (**Supplemental Table 6**)

Functional outcome

For participants with HI, the aOR for poor functional outcome at 90 days (early versus late treatment) was 1.36 (0.76–2.45) with an estimated aRD of 7.24% (−6.55 to 21.03%). The

group with PH had a higher proportion of participants with poor 90-day functional outcome in the early than in the late treatment group (aOR: 2.92, 1.01–8.91) with an increased estimated risk of 25.06% (0.18 to 49.95%) (**Figure 3** and **Supplemental Table 7**). Within the group of participants with PH, the estimated aRD for a poor outcome at 90 days was 13.81% (−19.28 to 46.90%) in those with PH 1 and 37.88% (−0.58 to 76.34%) in those with PH 2/remote hemorrhage, favoring late treatment. Results at 30 days were similar to those at 90 days post-stroke (**Supplemental Table 8 and Supplemental Figures 2 and 3**).

Results were also similar when analyzes were stratified by imaging modality (CT and MRI) **(Supplemental Tables 9 and 10 and Supplemental Figure 4)** and when participants without pre-randomization follow-up imaging after thrombolysis or thrombectomy (n=112) were excluded **(Supplemental Table 11)**.

Discussion

In this post-hoc analysis of data from the ELAN trial, we investigated the estimated treatment effect heterogeneity on safety and efficacy of early versus late, guideline-based, initiation of DOACs in participants with HT. We found neither major safety concerns nor any treatment effect heterogeneity between people with and without HT and ischemic stroke randomized to early versus late DOAC initiation. Outcome in both treatment arms was similar in people with and without HI, but we observed a 25% higher risk for a poor 90-day functional outcome in participants with PH and early versus late DOAC treatment.

The randomized-controlled Swedish TIMING trial and the Swiss ELAN trial have recently described numerically lower rates of event recurrence in people with ischemic stroke and AF who underwent early compared to late DOAC initiation.[9,10] No safety concerns were reported in either of the trials[9,10] nor in pooled data analyses of prospective observational studies and small RCTs.[6,8,16] However, there is a lack of data on early DOAC initiation in

people with HT, a condition that leads most clinicians to postpone anticoagulation treatment due to concerns about bleeding complications. [6,8-11,16-18] This post-hoc analysis of data from the ELAN trial[10] on the timing of DOAC initiation in people with asymptomatic HT provides no evidence that delaying DOAC initiation is safer or more effective in people with HT than early initiation of anticoagulation. In contrast, delaying DOAC treatment is likely to increase event recurrences. For people with HI, the number needed to treat (based on the adjusted risk difference point estimate) was 21 to avoid one outcome event within 30 days after the index stroke. No symptomatic intracranial bleeding complications were observed in participants who underwent early DOAC treatment. These data suggest that early DOAC initiation (<48h after ischemic stroke for minor and moderate stroke, 6–7 days for major stroke) is reasonable in people with HI.

However, not all HT subgroups appear to benefit from earlier anticoagulation treatment. Although people with PH are known to have an unfavorable post-stroke prognosis,[19] a fact reinforced by our findings (61% of participants with PH had a 90-day mRS of 3–6), our results indicate that early DOAC treatment, as opposed to late initiation, independently raises the probability of a poor 90-day functional outcome by 25%. These findings are surprising given the absence of symptomatic intracranial bleeding in participants with PH. In this context, recent observations of a 20% rate of HT progression in people after early post-stroke DOAC initiation should be taken into consideration.[8] Although in that study, HT worsening did not lead to abrupt clinical deterioration and sample size was too small to report on outcomes,[8] subclinical HT progression with associated local effects that may impact on regeneration processes represents the most likely pathomechanism behind our findings.[20-22]

Notably, presence of PH 2 or remote hemorrhage were the primary contributors to the heightened risk of unfavorable post-stroke outcomes in the PH group if treated early (risk difference for PH 2/remote hemorrhage: 38% favoring late treatment). In the early phase after stroke, the initiation of DOAC treatment is likely to be harmful in people with PH 2/remote hemorrhage. However, our results may not endorse the avoidance of early DOAC therapy in people with PH 1. Rather, they point toward a subgroup of people for whom an individualized benefit-risk assessment might be appropriate. It should be borne in mind that, according to the ELAN trial study protocol, PH was an exclusion criterion and was only identified based on the present post-hoc analysis by the imaging core-lab. This underscores the challenges associated with determining PH within acute stroke populations. Moreover, the selection of erroneously included PH participants might therefore not be representative for a routine stroke population and we observed imbalances between the PH groups (early versus late, **Supplemental Table 5**). Our results must therefore be interpreted cautiously and regarded as hypothesis generating.

Nevertheless, the effect of early DOAC treatment in people with ischemic stroke and PH warrants further attention and appears to be a promising target for a sub-analyses of ongoing trials that regularly include participants with PH (i.e., OPTIMAS [Optimal Timing of Anticoagulation After Acute Ischemic Stroke], NCT03759938) and a planned individual participant data meta-analysis from four trials (i.e. TIMING, ELAN, OPTIMAS, START).[9,10,23,24]

Moreover, the substantial proportion of misclassifications of HT subtypes (i.e., underestimation of HT severity) by local investigators underscores the importance of careful neuroimaging interpretation in clinical practice.

Further limitations may have influenced our results: 1) The present study was a post-hoc analysis of a trial[10] that was not originally designed to assess the impact of asymptomatic

HT on outcome. Consequently, we lacked follow-up brain imaging investigations and, as a result, cannot provide information on the proportion of people with subclinical progression of HT. 2) Infarct volumes were unavailable, and since infarct size is the primary determinant of HT, the absence of volumetric adjustments may have led to some imprecision in our analysis. Volumetric analyses, particularly in people with HT, are complex and time-consuming processes.[25] Nevertheless we were able to address infarct size by categorizing it into three groups (minor, moderate, major), which should have minimized any potential bias. 3) MRI is the gold standard for identifying small petechial HI as it has a higher sensitivity than CT.[14] In the present analysis, MRI-based images were available in 43% of participants. Therefore, in people who had undergone CT but not MRI, small HI might not have been detected, which should be considered when interpreting our results. However, results remained unchanged in sensitivity analysis stratified by imaging modality (CT and MRI). 4) In severely affected people with acute ischemic stroke, a clinical deterioration might be difficult to assess, and sICH could have potentially been missed in few cases. However, the liberal definition of sICH, encompassing any intracranial hemorrhage that leads to a clinical worsening, along with the meticulous review of all bleeding events and all serious adverse events by an independent clinical event committee,[12] should have avoided a substantial underreporting of sICH in the present study. 5) For this study, the most recent imaging prior to randomization was utilized to classify HT. According to the ELAN trial protocol,[12] a pre-randomization follow-up imaging after thrombolysis and / or thrombectomy was strongly encouraged but not mandatory. Consequently, in some participants (n=112) there were no images available after reperfusion treatment and before randomisation. However, in a sensitivity analysis excluding these participants with missing follow-up images, study outcomes remained unchanged.

In conclusion, among people with ischemic stroke and AF, we did not observe any major treatment effect heterogeneity or identify any major safety concerns according to the presence of HT and early versus late DOAC initiation. Whereas outcome in both treatment arms was similar in people with and without HI, in participants with PH, early DOAC treatment increased the risk for a poor 90-day functional outcome. Our results suggest that early initiation of DOACs in people with HI is acceptable on the balance of risks and benefits. In people with PH, the potential negative impact of early treatment on functional outcomes remains to be confirmed and requires further data from ongoing trials.

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Supplemental Materials

Supplemental Tables 1-11

Supplemental Figures 1-4

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Tables

Table 1: Baseline Characteristics According to the Presence of Hemorrhagic Transformation (HT) and Treatment Arm.

	Early - No HT (N=852)	Late - No HT (N=871)	Early - HT (N=131)	Late - HT (N=116)
Demographics				
Age, median [lq, uq]	77 [70, 84]	78 [71, 84]	78 [72, 82]	78 [71, 83]
Female - n (%)	385 (45.2)	407 (46.7)	65 (49.6)	40 (34.5)
Pre-stroke mRS - n (%)				
mRS 0-2	746 (87.6)	780 (89.6)	122 (93.1)	100 (86.2)
mRS 3-5	105 (12.3)	90 (10.3)	9 (6.9)	16 (13.8)
Comorbidities				
Prior ischemic stroke - n (%)	113 (13.3)	125 (14.4)	14 (10.7)	13 (11.2)
Prior systemic embolism - n (%)	14 (1.6)	26 (3.0)	5 (3.8)	5 (4.3)
Prior myocardial infarction - n (%)	69 (8.1)	67 (7.7)	8 (6.1)	15 (12.9)
Hypertension - n (%)	582 (68.3)	583 (66.9)	93 (71.0)	81 (69.8)
Diabetes - n (%)	149 (17.5)	134 (15.4)	31 (23.7)	23 (19.8)
Dyslipidemia - n (%)	380 (44.6)	370 (42.5)	52 (39.7)	49 (42.2)
Smoking (current) - n (%)	86 (10.1)	76 (8.7)	12 (9.2)	5 (4.3)
CHA2DS2-VASc Score - Median [lq, uq]	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	6.0 [4.0, 6.0]	5.0 [4.0, 6.0]
Stroke severity				
NIHSS at admission - median [lq, uq]	4.0 [2.0, 10]	5.0 [2.0, 11]	11 [4.0, 18]	8.0 [4.0, 16]
NIHSS before randomisation - median [lq, uq]	2.0 [1.0, 6.0]	3.0 [1.0, 6.0]	6.0 [2.0, 12]	5.0 [2.0, 11]
Acute recanalization therapy - n (%)				
Thrombolysis	328 (38.5)	320 (36.7)	57 (43.5)	51 (44.0)
Thrombectomy	154 (18.1)	179 (20.6)	50 (38.2)	48 (41.4)

Stroke size - n (%)				
Minor	367 (43.1)	359 (41.2)	6 (4.6)	7 (6.0)
Moderate	329 (38.6)	332 (38.1)	57 (43.5)	56 (48.3)
Major	156 (18.3)	180 (20.7)	68 (51.9)	53 (45.7)
Antiplatelets pre-randomization - n (%)				
Aspirin	396 (46.5)	482 (55.3)	49 (37.4)	53 (45.7)
Dual antiplatelet therapy	15 (1.8)	21 (2.4)	1 (0.8)	0 (0.0)
Other	54 (6.3)	60 (6.9)	6 (4.6)	4 (3.4)

lq, lower quartile; uq, upper quartile; mRS, modified Rankin Scale; NIHSS, national institutes of health stroke scale; sICH

Table 2: Multivariable regression model comparing early versus late initiation of direct oral anticoagulation according to the presence of hemorrhagic transformation (HT)

	No HT adjusted OR (95%-CI)	HT adjusted OR (95%-CI)	P for int.
Outcomes at 30 days			
Composite outcome (n=69)	0.75 (0.44 to 1.28)	0.65 (0.20 to 2.00)	0.803
mRS (ordinal)	0.83 (0.70 to 0.98)	1.44 (0.93 to 2.24)	0.021
mRS (3-6) (n=736)	0.92 (0.76 to 1.12)	1.54 (0.93 to 2.55)	0.061
Recurrent ischemic stroke (n=38)	0.68 (0.32 to 1.39)	0.34 (0.06 to 1.35)	0.349
Systemic embolism (n=13)	0.64 (0.18 to 2.04)	0.17 (0.00 to 2.08)	0.163
Major extracranial bleeding (n=8)	0.48 (0.08 to 2.06)	2.71 (0.15 to 395.04)	0.150
sICH (n=4)	1.07 (0.17 to 6.95)	0.85 (0.00 to 157.86)	1.000
Vascular Death (n=21)	1.20 (0.46 to 3.14)	0.88 (0.13 to 5.89)	0.783
Non-major bleeding (n=56)	1.50 (0.80 to 2.88)	0.62 (0.23 to 1.61)	0.124
Outcomes at 90 days			
Composite outcome (n=89)	0.67 (0.42 to 1.07)	0.66 (0.22 to 1.88)	0.957
mRS (ordinal)	0.86 (0.72 to 1.02)	1.36 (0.87 to 2.12)	0.060
mRS (3-6) (n=658)	0.89 (0.72 to 1.09)	1.59 (0.96 to 2.65)	0.034
Recurrent ischemic stroke (n=47)	0.65 (0.33 to 1.24)	0.47 (0.11 to 1.71)	0.629
Systemic embolism (n=14)	0.56 (0.16 to 1.70)	0.16 (0.00 to 2.04)	0.183
Major extracranial bleeding (n=11)	0.34 (0.06 to 1.32)	0.84 (0.07 to 9.72)	0.511
sICH (n=4)	1.06 (0.17 to 6.90)	0.84 (0.00 to 155.02)	1.000
Vascular Death (n=33)	1.19 (0.57 to 2.54)	0.61 (0.10 to 3.22)	0.451
All-cause death (n=92)	1.09 (0.70 to 1.69)	0.32 (0.06 to 1.27)	0.085
Non-major bleeding (n=79)	1.12 (0.67 to 1.89)	0.66 (0.27 to 1.59)	0.307

mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage

[+] The p for interaction represents the interaction between the presence or absence of HT within the treatment groups (early and late)

Figure Legends

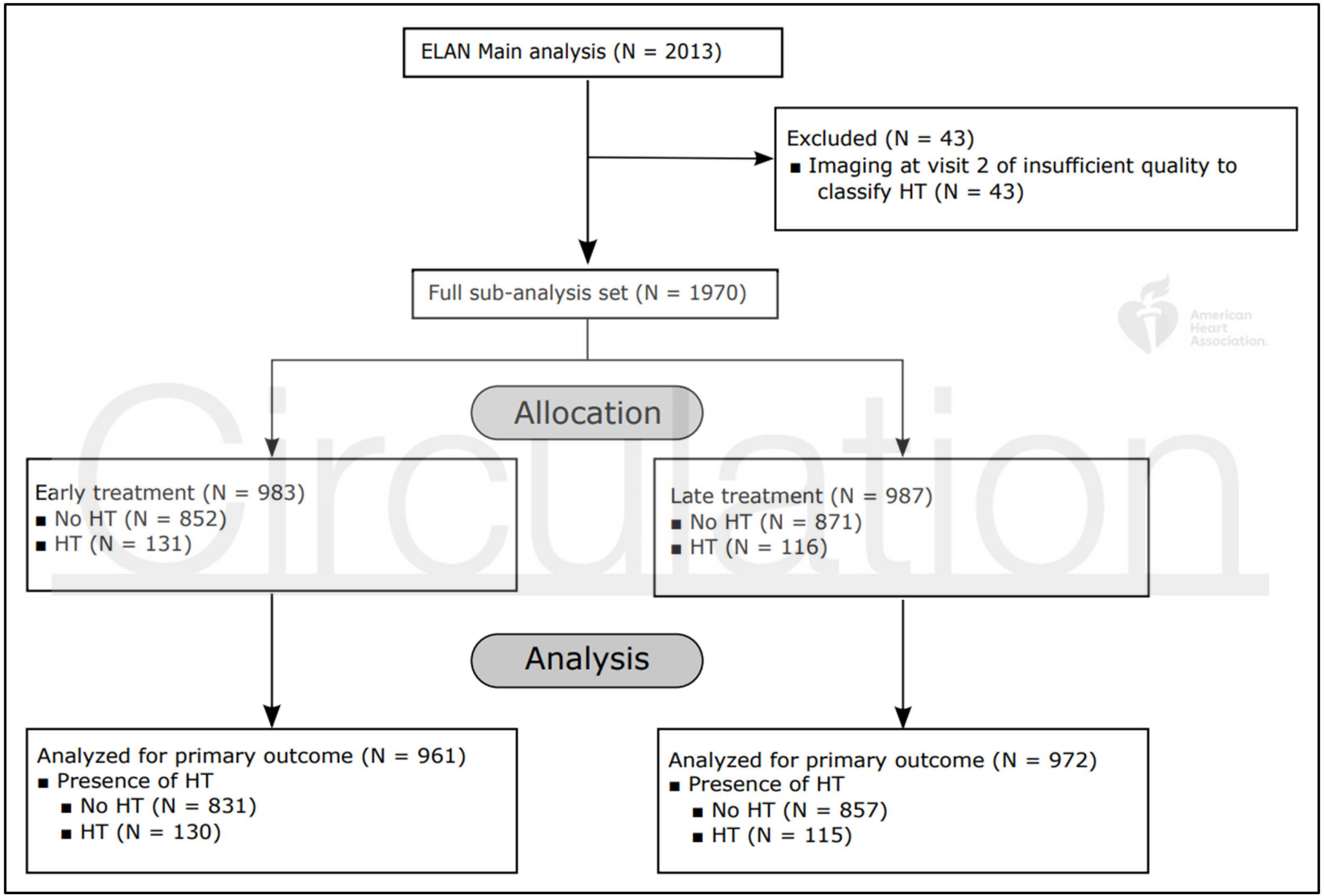
Figure 1: Trial flowchart

Figure 2: Primary and secondary outcomes: Forest plots representing the adjusted risk differences (early versus late anticoagulation) of the composite outcome, its components and functional outcome at 30 days for participants with A) hemorrhagic transformation (HT) and B) no hemorrhagic transformation.

DOAC, direct oral anticoagulation; mRS, modified Rankin scale; aRD, adjusted risk difference

Figure 3: 90-day functional outcome using Grotta bars: Distribution of mRS categories according to treatment arm at 90 days in participants with A) no hemorrhagic transformation, B) hemorrhagic infarction and C) parenchymal hemorrhage/remote hemorrhage.

mRS, modified Rankin scale



	Early (N=983) No. of Events	Late (N=987) No. of Events	Adj. Risk Difference (95%−CI)
Composite primary outcome at 30 days			
No HT	n=852, 24 (2.8%)	n=871, 33 (3.8%)	−0.92% (−2.63 to 0.78%)
HT	n=131, 5 (3.8%)	n=116, 7 (6.0%)	−2.15% (−7.78 to 3.48%)
Major extracranial bleeding			
No HT	n=852, 2 (0.2%)	n=871, 5 (0.6%)	−0.31% (−0.94 to 0.32%)
HT	n=131, 1 (0.8%)	n=116, 0 (0.0%)	0.74% (−1.46 to 2.95%)
Symptomatic intracranial hemorrhage			
No HT	n=852, 2 (0.2%)	n=871, 2 (0.2%)	0.02% (−0.49 to 0.54%)
HT	n=131, 0 (0.0%)	n=116, 0 (0.0%)	−0.06% (−1.66 to 1.53%)
Recurrent ischemic stroke			
No HT	n=852, 12 (1.4%)	n=871, 18 (2.1%)	−0.68% (−1.94 to 0.58%)
HT	n=131, 2 (1.5%)	n=116, 6 (5.2%)	−3.57% (−8.35 to 1.20%)
Systemic embolism			
No HT	n=852, 4 (0.5%)	n=871, 7 (0.8%)	−0.30% (−1.09 to 0.48%)
HT	n=131, 0 (0.0%)	n=116, 2 (1.7%)	−1.82% (−4.68 to 1.04%)
Vascular death			
No HT	n=852, 9 (1.1%)	n=871, 8 (0.9%)	0.19% (−0.78 to 1.15%)
HT	n=131, 2 (1.5%)	n=116, 2 (1.7%)	−0.26% (−3.76 to 3.25%)
mRS (3−6)			
No HT	n=852, 296 (34.7%)	n=871, 319 (36.6%)	−1.88% (−6.41 to 2.65%)
HT	n=131, 70 (53.4%)	n=116, 51 (44.0%)	10.71% (−1.71 to 23.13%)