RESEARCH ARTICLE

Early vs Late Anticoagulation After Ischemic Stroke in Patients With Atrial Fibrillation and Covert Brain Infarcts

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Neurology® 2025;104:e210157. doi:10.1212/WNL.0000000000210157

Abstract

Background and Objectives

Covert brain infarcts (CBIs) in patients with first-ever ischemic stroke (IS) and atrial fibrillation (AF) are associated with an increased risk of stroke recurrence. We aimed to assess whether CBIs modify the treatment effect of early vs late initiation of direct oral anticoagulants (DOACs) in patients with IS and AF.

Methods

We conducted a post hoc analysis of the international, multicenter, randomized-controlled ELAN trial, which compared early (<48 hours after ischemic stroke for minor and moderate stroke, 6–7 days for major stroke) vs late (>48 hours for minor, 3–4 days for moderate, 12–14 days for major stroke) initiation of DOACs in patients with IS and AF. The primary outcome was a composite of recurrent IS, symptomatic intracranial hemorrhage (sICH), major extracranial bleeding, systemic embolism, or vascular death within 30 days after stroke; secondary outcomes were the individual components. We estimated outcomes based on the presence of CBIs (any CBI vs no CBI) on prerandomization imaging (core-lab rating) using adjusted risk differences (aRDs) between treatment arms. Point estimates and 95% CIs are presented without reporting *p* values.

Results

Of the 1,694 participants with first-ever IS included (median age: 77 years, 45.9% female), 678 (40.0%) had CBI. The imaging core-lab interrater reliability for the presence of CBI was 0.87 (0.81–0.94). The primary outcome occurred in 8 (2.3%; recurrent IS: 3/342) of 342 participants with CBI assigned to the early treatment arm vs 20 (6.0%; recurrent IS: 12/336) of 336 assigned to the late treatment arm (aRD: −3.6%, 95% CI −6.6 to −0.6) (*p* for interaction: 0.063). With early DOAC treatment, IS recurrence risk was lower in participants with CBI (aRD: −2.7%, 95% CI −5.0 to −0.4), but not in participants without CBI (aRD: −0.4, 95% CI −2.1 to 1.2). No sICH was observed in the early treatment group.

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Coinvestigators are listed in the supplemental digital content available online Neurology.org/N.

Glossary

AF = atrial fibrillation; **aORs** = adjusted odds ratios; **aRDs** = adjusted risk differences; **CBIs** = covert brain infarcts; **DOAC** = direct oral anticoagulant; **ICEMAN** = Instrument to assess the Credibility of Effect Modification Analyses; **IQR** = interquartile range; **IS** = ischemic stroke; **lq** = lower quartile; **mRS** = modified Rankin Scale; **NIHSS** = National Institutes of Health Stroke Scale; **RCT** = randomized-controlled trial; **sICH** = intracranial hemorrhage; **uq** = upper quartile.

Discussion

The presence of CBI may indicate a subgroup of patients with first-ever IS and AF who particularly benefits from early DOAC initiation to prevent ischemic event recurrence, without increasing harm. Our findings should be considered in clinical decision making regarding timely DOAC treatment in patients with stroke and AF.

Classification of Evidence

This study provides Class II evidence that in patients with covert brain infarcts, atrial fibrillation, and first-ever ischemic stroke, early (vs late) initiation of DOACs is associated with lower risk of recurrent stroke with no increase in harm.

Trial Registration Information

URL: clinicaltrials.gov/study/NCT03148457; Unique identifier: NCT03148457; *submitted*: April 7, 2017; *first patient enrolled*: November 6, 2017.

Introduction

Effective prevention of secondary stroke in patients with acute ischemic stroke and atrial fibrillation (AF) relies on targeted use of direct oral anticoagulants (DOACs).[1,2] Recent research has focused on determining the optimal timing for initiating DOACs, in view of the increased risk of stroke recurrence during the early poststroke phase.[3,4] This period, however, is also associated with an elevated risk of bleeding complications, which may potentially counteract the anticipated benefits of early anticoagulation therapy.[5,6] Observational studies, together with data from 3 randomized-controlled trials (RCTs), have shown that an early treatment start is noninferior to a late treatment start and may be beneficial.[3,4,7-10] It is important to note that no increase in symptomatic intracranial bleeding events was observed.[8-10]

However, whether the likely benefit and absence of harm from early DOAC initiation are similar in all patients is unclear because a considerable proportion of the real-world stroke population does not meet the inclusion and exclusion criteria of the RCTs.[8-10] For such individuals, additional risk stratification tools are desirable to assist clinicians in determining the optimal timing for initiating DOACs. In this context, covert brain infarcts (CBIs) emerge as a promising target because they have been linked to a twofold increase in recurrent event risk in patients with AF-related stroke.[11,12] Furthermore, CBIs have been identified in approximately one-third of all patients experiencing their first-ever ischemic stroke, representing a substantial vulnerable subgroup within the stroke population.[13]

In this post hoc analysis using data from the Early versus Late initiation of direct oral Anticoagulants in post-ischemic stroke patients with atrial fibrillatioN (ELAN) trial, the primary research question was to assess whether the presence of CBI on prerandomization imaging modifies the estimated treatment effect for safety and efficacy of early vs late DOAC initiation in patients with acute ischemic stroke and AF.

Methods

This study is a post hoc analysis of the international, multicenter, randomized-controlled ELAN trial,[9] which randomized participants with acute ischemic stroke and AF to early (<48 hours after ischemic stroke for minor and moderate stroke, 6–7 days for major stroke) or late (>48 hours for minor, 3–4 days for moderate, 12–14 days for major stroke) DOAC initiation. The ELAN trial was a global trial conducted from November 6, 2017 (start of enrollment), to September 12, 2022 (end of enrollment), which included more than 2,000 participants at 103 stroke units and 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.[9,14,15]

In brief, patients with an acute ischemic stroke and AF (history or newly diagnosed during the index hospitalization) were eligible. Participants with transient ischemic attacks, with severe hemorrhagic transformation of the infarction, or with a particularly high risk of intracranial bleeding (e.g., multiple cerebral microbleeds, therapeutic anticoagulation at stroke onset, or expected before randomization) 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). For this study, we included all participants from the ELAN trial with available prerandomization brain imaging

(either MRI or CT). Participants with imaging of insufficient quality for CBI assessment were excluded, as were those who did not meet the criteria for CBI because of a history of a stroke.

All study data were gathered by local investigators and collected in a secuTrial database hosted by the Clinical Trials Unit Bern, Switzerland.

Neuroimaging Assessment

Local site investigators transferred all neuroimaging studies obtained during the study period to the imaging core-lab at the Support Center for Advanced Neuroimaging (SCAN, Inselspital Bern, Switzerland). Prerandomization imaging studies were assessed for the presence and location of CBIs using either plain CT scans or MR-based images (1.5 or 3 Tesla) that included T2 or FLAIR sequences. If both modalities were available, MR-based images were analyzed because of their higher sensitivity for small CBIs.[13]

Ratings were conducted by a board-certified neuroradiologist (S.F.) who was supported by a neurologist with considerable experience in neuroimaging (M.K., MR-based ratings) and a neuroradiology resident proficient in neuroimaging diagnostics (R.R., CT-based ratings). In case of discrepancies between 2 raters, a senior, board-certified neuroradiologist with special expertise in neurovascular imaging (A.H.) reviewed the images and had the casting vote. All raters were blinded to clinical data.

CBIs were identified based on recently published studies and categorized into those of presumed embolic origin (i.e., isolated cortical gray matter lesion [either supratentorial or cerebellar]; combined cortical and subcortical lesions; nonlacunar subcortical lesions >15 mm in diameter) vs CBIs of presumed nonembolic origin (i.e., covert lacunar infarcts).[11-13] Participants with a covert lacunar infarct and ≥1 additional CBI of presumed embolic origin were categorized in the emboli CBI group (eFigure 1).

Outcomes

The primary outcome used in this study was the same as in the main ELAN trial analysis. It comprised the composite of recurrent ischemic stroke, symptomatic intracranial hemorrhage (sICH), major extracranial bleeding, systemic embolism, or vascular death within 30 days after stroke. Secondary outcomes included the same composite end point at 90 days and functional outcome according to the modified Rankin Scale (mRS) score at 30 and 90 days after stroke.[14]

Statistical Analysis

M.B. performed the statistical analyses using Stata version 17.0 (2021) and R version 4.3.1 (2023). Analyses were based on a statistical analysis plan written by M.K., A.H., M.B., R.R., S.A., J.D., and U.F. For the primary analysis, participants were categorized based on the presence of CBIs on prerandomization imaging (any CBI vs no CBI) as assessed by the imaging core-lab. Treatment allocation (early vs late initiation of anticoagulation) was determined according to a modified intention-to-treat strategy.[9] Descriptive statistics were used to analyze and compare baseline clinical characteristics. We used number and percentage to present categorical variables. Continuous variables are described using mean and standard deviation or median and upper/lower quartile (lq/uq).

To account for the small number of outcome events, univariable and multivariable Firth penalized logistic regressions were performed for binary outcomes. Ordinally scaled outcomes were assessed with ordinal logistic regression. Based on previous studies and pathophysiologic considerations,[11-13] multivariable regressions were adjusted for age (per year), hypertension (binary), infarct size (minor vs moderate vs major), infarct location (anterior vs posterior circulation), prestroke mRS score, admission National Institutes of Health Stroke Scale (NIHSS) score, and acute treatment (intravenous thrombolysis and/or endovascular treatment) using the inverse probability weighting method. The credibility of the interaction being investigated was evaluated according to the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) guidelines.[16]

Sensitivity Analysis

In the sensitivity analyses, participants with CBI were categorized into 2 groups: CBI of presumed embolic origin and CBI of presumed nonembolic origin.

Adjusted odds ratios (aORs) and adjusted risk differences (aRDs) were used to present effectiveness and safety of early vs late DOAC initiation in participants with ischemic stroke and AF. Owing to the small number of outcome events and, consequently, limited statistical power, this study is intended to offer hypothesis-generating evidence without any binary statements (significant vs nonsignificant). Point estimates and 95% CIs are presented without reporting *p* values.

Interrater Reliabilities and Procedures for Handling Missing Data

Interrater reliabilities for detecting the presence of CBI on prerandomization neuroimaging were assessed among different raters in the imaging core-lab using Gwet's AC1.

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

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol received approval from all relevant authorities and ethics committees. Written informed consent was given either by participants, next of kin or other legal representatives, or an independent physician. The ELAN

trial was registered at ClinicalTrials.gov (unique identifier: NCT03148457).

Data Availability

Deidentified study data will be accessible on reasonable request and after approval by the ELAN trial steering committee. Data can be requested through urs.fischer@insel.ch.

Results

For this post hoc analysis of the ELAN trial, 22 (2.1%) of 2013 participants had to be excluded because of insufficient quality of brain imaging and 267 participants (13.3%) who had experienced a previous stroke were excluded. Additional 37 participants were excluded from the primary analysis because their primary outcome was missing (24 participants died from a nonvascular cause during follow-up, 12 withdrew consent, and one was lost to follow-up) (eTable 1). Thus, the final study cohort consisted of 1,694 participants with first-ever ischemic stroke and AF (median age: 77 years, 45.9% female) (Figure 1). Overall, 678 (40.0%) of the included participants showed CBI on prerandomization imaging (eTables 2 and 3). The imaging core-lab interrater reliability for the presence of CBI was 0.87 (0.81–0.94). Among the participants with CBI (n = 678), most had at least one embolic CBI phenotype (n = 582, 85.8%). Within this group, most frequent embolic CBI phenotypes were cortical lesions (supratentorial: n = 30; cerebellar: n = 343), combined cortical and subcortical lesions (n = 248), and large nonlacunar subcortical lesions (n = 16). Isolated CBIs of presumed nonembolic origin (i.e., covert lacunar infarcts) were observed in 96 participants (14.2%) (eFigure 1).

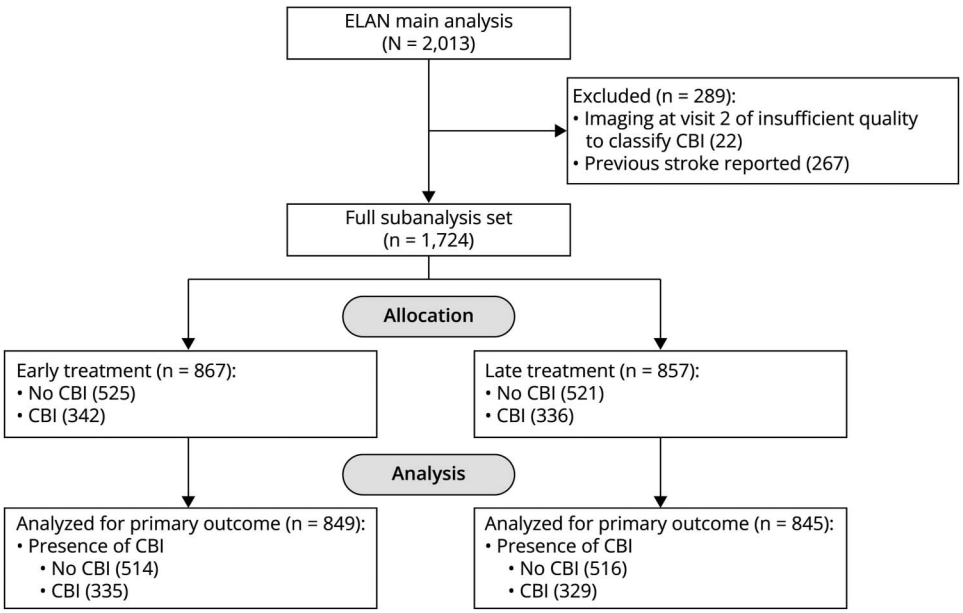
Characteristics of Study Participants

Age, sex, prestroke disability, and comorbidities were well balanced between the subgroups. The median CHA2DS2-VASc score was 5 points in all groups. Numbers of participants who underwent acute recanalization therapies were similar in all subgroups as were infarct size categories on post-treatment brain imaging. Stroke severity, as indicated by the median NIHSS score before randomization, was 3 (interquartile range [IQR] 1–6) in both the early and late CBI subgroups. In participants without CBI undergoing early treatment, the median NIHSS score was 2 (IQR 1–7) while for those who underwent late treatment, it was 3 (IQR 1–6). At the screening visit, single antiplatelet therapy (mostly aspirin) was used by 165 participants with CBI (48.2%) in the early and 193 (57.4%) in the late treatment arm. In the non-CBI group, 239 participants (45.5%) in the early and 282 (54.1%) in the late treatment group were treated with single antiplatelet therapy. No participant was given dual antiplatelet therapy, and no left atrial appendage closures were observed (details in Table 1).

Primary Outcome

In participants with CBI, the primary composite outcome at 30 days was observed in 8 participants (2.3%) in the early vs 20 (6.0%) in the late treatment group (aOR: 0.39, 95% CI 0.16–0.87). In the non-CBI groups, primary outcome events occurred in 16 participants (3.1%) in the early vs 15 (2.9%) in the late treatment arm (aOR: 1.06, 95% CI 0.52–2.15). This resulted in an estimated aRD between the early and late groups of −3.59% (95% CI −6.63 to −0.56%) in participants with CBI and 0.16% (95% CI −1.94%–2.27%) in those without CBI (p for interaction within the treatment groups: 0.063) (Table 2, Figure 2, and eTable 4). When applying the

Figure 1 Trial Flowchart



CBIs = covert brain infarcts

Table 1 Baseline Characteristics According to the Presence of CBI and Treatment Arm

	Early—No CBI (N = 525)	Late—No CBI (N = 521)	Early—CBI (N = 342)	Late—CBI (N = 336)
Demographics				
Age, median [lq, uq]	77 [69, 83]	76 [69, 83]	77 [72, 85]	79 [73, 85]
Female, n (%)	248 (47.2)	240 (46.1)	157 (45.9)	146 (43.5)
Prestroke mRS scores, n (%)				
mRS scores 0–2	479 (91.2)	478 (91.7)	300 (87.7)	299 (89.0)
mRS scores 3–5	45 (8.6)	42 (8.1)	42 (12.3)	37 (11.0)
Comorbidities				
Previous systemic embolism, n (%)	4 (0.8)	12 (2.3)	10 (2.9)	12 (3.6)
Previous myocardial infarction, n (%)	34 (6.5)	32 (6.1)	31 (9.1)	32 (9.5)
Hypertension, n (%)	338 (64.4)	330 (63.3)	248 (72.5)	226 (67.3)
Diabetes, n (%)	84 (16.0)	68 (13.1)	68 (19.9)	60 (17.9)
Dyslipidemia, n (%)	207 (39.4)	204 (39.2)	156 (45.6)	144 (42.9)
Smoking (current), n (%)	53 (10.1)	51 (9.8)	39 (11.4)	21 (6.3)
CHA2DS2-VASc score, median [lq, uq]	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]
Stroke severity				
NIHSS score at admission, median [lq, uq]	5.0 [2.0, 12]	6.0 [2.0, 12]	5.0 [2.0, 10]	5.0 [2.0, 11]
NIHSS score before randomization, median [lq, uq]	2.0 [1.0, 7.0]	3.0 [1.0, 6.0]	3.0 [1.0, 6.0]	3.0 [1.0, 6.0]
Acute recanalization therapy, n (%)				
Thrombolysis	215 (41.0)	222 (42.6)	134 (39.2)	115 (34.2)
Thrombectomy	125 (23.8)	134 (25.7)	61 (17.8)	72 (21.4)
Stroke size, n (%)				
Minor	195 (37.1)	193 (37.0)	126 (36.8)	118 (35.1)
Moderate	212 (40.4)	219 (42.0)	137 (40.1)	128 (38.1)
Major	118 (22.5)	109 (20.9)	79 (23.1)	90 (26.8)
Antiplatelet prerandomization, n (%)				
Aspirin	239 (45.5)	282 (54.1)	165 (48.2)	193 (57.4)
Other	24 (4.6)	25 (4.8)	23 (6.7)	19 (5.7)
Imaging prerandomization, n (%)				
MRI	179 (34.1)	182 (34.9)	185 (54.1)	179 (53.3)
CT	346 (65.9)	339 (65.1)	157 (45.9)	157 (46.7)
Competing stroke etiology, n (%)				
Large artery atherosclerosis ≥50%	18 (3.4)	18 (3.5)	10 (2.9)	21 (6.3)
Small vessel disease	38 (7.2)	38 (7.3)	48 (14.0)	35 (10.4)
Other determined etiologies	1 (0.2)	4 (0.8)	0 (0.0)	4 (1.2)

Abbreviations: CBIs = covert brain infarcts; lq = lower quartile; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; uq = upper quartile.

Table 2 Multivariable Regression Model Comparing Early vs Late Initiation of Direct Oral Anticoagulation According to the Presence of CBI

	No CBI-adjusted OR (95% CI)	CBI-adjusted OR (95% CI)	P for interaction[a]
Outcomes at 30 d			
Composite outcome	1.06 (0.52–2.15)	0.39 (0.16–0.87)	0.063
mRS score (ordinal)	0.85 (0.69–1.06)	0.85 (0.65–1.11)	0.976
mRS score (3–6)	0.91 (0.70–1.17)	1.04 (0.76–1.41)	0.520
Recurrent ischemic stroke	0.79 (0.31–1.97)	0.26 (0.07–0.80)	0.126
Systemic embolism	0.79 (0.18–3.21)	0.41 (0.04–2.61)	0.517
Major extracranial bleeding	1.04 (0.16–6.74)	0.21 (0.00–2.65)	0.149
sICH	0.33 (0.00–5.94)	0.34 (0.00–6.50)	>0.999
Vascular death	4.20 (0.88–39.38)	0.53 (0.15–1.63)	0.025
Nonmajor bleeding	1.13 (0.59–2.20)	1.09 (0.43–2.85)	0.957
Outcomes at 90 d			
Composite outcome	1.08 (0.57–2.05)	0.35 (0.16–0.70)	0.018
mRS score (ordinal)	0.93 (0.75–1.16)	0.86 (0.66–1.12)	0.640
mRS score (3–6)	0.97 (0.74–1.26)	0.93 (0.68–1.28)	0.860
Recurrent ischemic stroke	0.97 (0.42–2.23)	0.22 (0.06–0.66)	0.029
Systemic embolism	0.64 (0.15–2.37)	0.40 (0.04–2.57)	0.623
Major extracranial bleeding	1.03 (0.16–6.69)	0.11 (0.00–1.00)	0.056
sICH	0.32 (0.00–5.90)	0.33 (0.00–6.41)	>0.999
Vascular death	2.28 (0.71–8.99)	0.66 (0.26–1.59)	0.086
All-cause death	1.38 (0.73–2.64)	0.62 (0.32–1.16)	0.077
Nonmajor bleeding	1.06 (0.62–1.82)	0.79 (0.32–1.89)	0.572

Abbreviations: CBIs = covert brain infarcts; mRS = modified Rankin Scale; OR = odds ratio; sICH = symptomatic intracranial hemorrhage.
[a] The *p* for interaction represents the interaction between the presence and absence of CBI within the treatment groups (early and late).

ICEMAN criteria, a moderate level of credibility was observed regarding the effect of CBI on the primary outcome (eAppendix 1).

Secondary Outcomes

The most frequently observed primary outcome component in all treatment groups was recurrent ischemic stroke: In the CBI group, it occurred in 3 participants (0.9%) in the early and 12 (3.6%) in the late treatment group (aOR: 0.26, 95% CI 0.07–0.80), resulting in an estimated aRD of −2.7% (95% CI −5.00 to −0.43%). Of the participants without CBI, 8 (1.5%) in the early and 10 (1.9%) in the late treatment arm (aOR: 0.79, 95% CI 0.31–1.97) experienced recurrent ischemic strokes, leading to an estimated aRD of −0.42% (95% CI −2.05% to 1.21%).

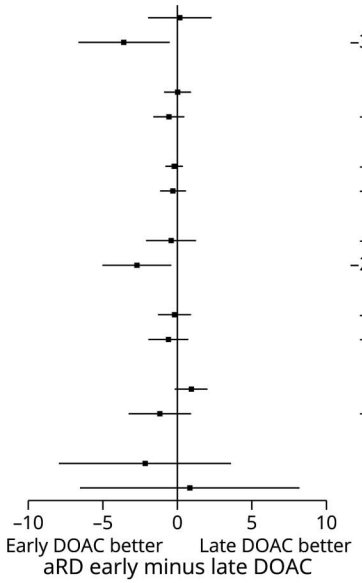
In the late treatment group, sICH occurred in 1 (0.2%) of 336 participants with CBI and in 1 (0.1%) of 521 participants without CBI. No sICH was observed in participants in the early DOAC treatment groups (Figure 2, eFigure 2, and eTable 5). The functional outcome at 90 days was similar in the CBI and non-CBI groups, with a tendency toward better outcomes in the early treatment arm (Figure 3).

Sensitivity Analysis

In participants with embolic CBI, the composite outcome at 30 days occurred in 8 participants (2.8%) in the early and 17 (6.0%) in the late treatment group, resulting in an estimated aRD of −3.16% (95% CI −6.51% to 0.18%). In the group with nonembolic CBI, the number of outcome events was low (early: 0 [0.0%], late: 3 [6.7%]) with an estimated aRD of −6.14 (95% CI −14.05% to 1.76%). Of the participants with embolic CBI, recurrent ischemic stroke occurred in 3 (1.0%) in the early and 11 (3.9%) in the late treatment arm (aRD: −2.81%, 95% CI −5.39 to −0.24%) while only one occurrence of recurrent stroke was observed in the nonembolic CBI group (early: 0 [0.0%], late: 1 [2.2%]) (aRD: −2.07%, 95% CI −7.79% to 3.64%) (eTables 6–8 and eFigure 3).

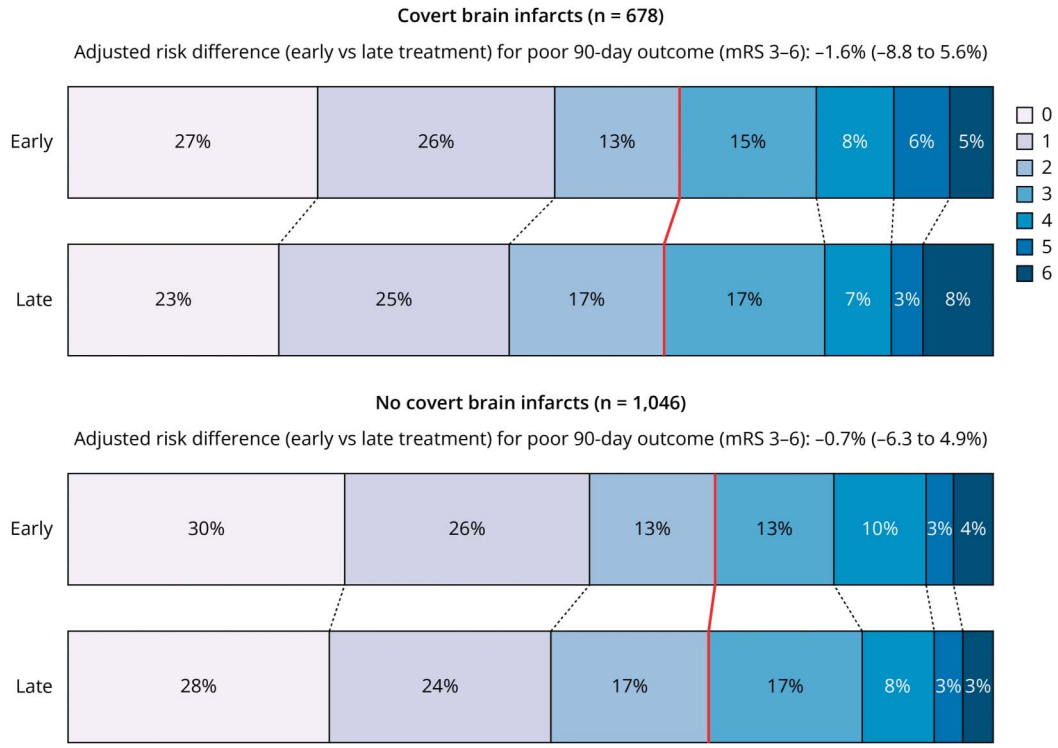
Figure 2 Forest Plots

	Early (n = 867) Number of events	Late (n = 857) Number of events	Adjusted risk difference (95% CI)
Composite primary outcome at 30 days			
No CBI	n = 525; 16 (3.0%)	n = 521; 15 (2.9%)	0.16% (–1.94 to 2.27%)
CBI	n = 342; 8 (2.3%)	n = 336; 20 (6.0%)	–3.59% (–6.63 to –0.56%)
Major extracranial bleeding			
No CBI	n = 525; 2 (0.4%)	n = 521; 2 (0.4%)	0.02% (–0.83 to 0.87%)
CBI	n = 342; 0 (0.0%)	n = 336; 2 (0.6%)	–0.57% (–1.56 to 0.42%)
Symptomatic intracranial hemorrage			
No CBI	n = 525; 0 (0.0%)	n = 521; 1 (0.2%)	–0.20% (–0.74 to 0.34%)
CBI	n = 342; 0 (0.0%)	n = 336; 1 (0.3%)	–0.29% (–1.11 to 0.53%)
Recurrent ischemic stroke			
No CBI	n = 525; 8 (1.5%)	n = 521; 10 (1.9%)	–0.42% (–2.05 to 1.21%)
CBI	n = 342; 3 (0.9%)	n = 336; 12 (3.6%)	–2.71% (–5.00 to –0.43%)
Systemic embolism			
No CBI	n = 525; 3 (0.6%)	n = 521; 4 (0.8%)	–0.19% (–1.26 to 0.88%)
CBI	n = 342; 1 (0.3%)	n = 336; 3 (0.9%)	–0.60% (–1.88 to 0.68%)
Vascular death			
No CBI	n = 525; 6 (1.1%)	n = 521; 1 (0.2%)	0.94% (–0.12 to 1.99%)
CBI	n = 342; 4 (1.2%)	n = 336; 8 (2.4%)	–1.17% (–3.22 to 0.89%)
mRS (3–6)			
No CBI	n = 525; 173 (33.0%)	n = 521; 183 (35.1%)	–2.19% (–7.93 to 3.56%
CBI	n = 342; 130 (38.0%)	n = 336; 124 (36.9%)	0.83% (–6.48 to 8.14%)



Adjusted risk differences (early vs late anticoagulation) of the composite outcome, its components, and the functional outcome at 30 days for participants with (A) covert brain infarcts and (B) no covert brain infarcts. aRD = adjusted risk difference; CBIs = covert brain infarcts; DOAC = direct oral anticoagulant; mRS = modified Rankin Scale.

Figure 3 Grotta Bars



Distribution of mRS categories according to treatment arm at 90 days in participants with (A) covert brain infarcts and (B) no covert brain infarcts. mRS = modified Rankin Scale.

Classification of Evidence

This study provides Class II evidence that in patients with covert brain infarcts, atrial fibrillation, and first-ever ischemic stroke, early (vs late) initiation of DOACs is associated with lower risk of recurrent stroke with no increase in harm.

Discussion

This subgroup analysis of data from the ELAN trial included patients with first-ever ischemic stroke with AF and CBI. The primary outcome occurred less often in participants randomized to early vs late anticoagulation whereas the numbers were similar in participants without CBI. The presence of CBI may indicate a subgroup of patients with ischemic stroke and AF who would particularly benefit from early DOAC initiation to prevent ischemic event recurrence, without increasing harm.

A recently published meta-analysis including data from observational studies and data from the randomized-controlled Swedish TIMING trial and the global ELAN trial identified a reduced risk of event recurrence in patients with ischemic stroke and AF who underwent early compared with late DOAC initiation.[17] It is important to note that no safety concerns were reported, suggesting noninferiority, or even a beneficial effect of early DOAC treatment in this stroke population.[8,9] In a real-world setting, a considerable number of patients with ischemic stroke and AF do not meet the inclusion and exclusion criteria of the RCTs. To balance the benefits and risks in such cases, features indicative of ischemic event recurrence, such as CBIs, could potentially serve as valuable tools for identifying high-risk populations that would benefit from earlier treatment initiation.[11,12]

This subgroup analysis of the ELAN trial data corroborates previous studies that have observed a link between the presence of CBIs and an increased risk of early stroke recurrence in patients with first-ever ischemic stroke and AF.[12] Following standard, late, guideline-based DOAC initiation, the incidence of the composite outcome at 30 days was more than twofold higher in the CBI group than in the non-CBI group (6.0% vs 2.3%). The main contributor to these findings was recurrent stroke, with a 30-day stroke recurrence rate of 3.6% compared with 1.9%. It is important to note that in participants with CBI, the risk of early stroke recurrence within 30 days was lower with early compared with a late treatment start (aRD: −2.7%, 95% CI −5.0 to −0.4%) and this effect was maintained until the 90-day follow-up (aRD: −3.5%, 95% CI −5.9 to −1.0%). Although there is some imprecision due to the small number of events, the absolute risk reduction for stroke recurrence at 90 days in participants with CBI suggests an estimated number needed to treat of 29 (95% CI 16 to 100) for an intervention that adds minimal cost and shows no signal of harm.

Therefore, our findings emphasize the importance of timely DOAC initiation in the high-risk group of patients with first-ever ischemic stroke and CBI and could help clinicians to balance the risks and benefits of early DOAC treatment in routine clinical practice. Moreover, because recently published data encourage researchers to investigate whether starting anticoagulation even earlier might be beneficial in certain vulnerable subgroups (e.g., patients with major strokes), the presence of CBI should be noted as an important cofactor in such patients.[18]

It is important to note that our results are based on a comparable number of MRI-detected and CT-detected CBIs (53.7 vs 46.3%). Moreover, we did not observe marked differences in outcome measures between the CT and MRI subgroups based on the time of treatment initiation (eTable 9). Therefore, we are confident that our findings are applicable to both MRI-based and CT-based imaging, which increases feasibility and facilitates the translation of our results into daily clinical practice.

It must be noted that our findings predominantly stem from individuals who have CBIs of presumed embolic origin (85% of all participants with CBI), highlighting the importance of stratifying CBIs according to infarct pattern (embolic vs nonembolic).[19] Sensitivity analysis also showed a lower risk of stroke recurrence within 30 days among participants with embolic CBI receiving early treatment compared with those in whom DOAC initiation was delayed (aRD: −2.8%, 95% CI −5.4 to −0.2%). However, the limited number of outcome events and the lack of information on the presumed etiology of these events (embolic vs nonembolic) preclude drawing substantial conclusions regarding the impact of nonembolic infarcts (i.e., covert lacunar infarcts) on the recurrence of ischemic events in patients with early vs late treatment start.

Further limitations may have influenced our results: First, this study is a secondary analysis of a trial[9] that was not originally designed to assess the impact of CBI on early vs late anticoagulation in patients with ischemic stroke and AF. Although local site investigators had to state whether a patient had had a previous stroke, we cannot exclude the possibility that some participants were incorrectly labeled as having had a CBI. However, because all such patients share the same pathophysiologic mechanisms, this should not have influenced the interpretation of our study.[20] Second, only a moderate level of credibility was observed regarding the effect of CBI on the primary outcome. This emphasizes the importance of including CBI in individual participant data meta-analysis on trials investigating the optimal timing of DOAC initiation in patients with IS with AF (i.e., TIMING, ELAN, OPTIMAS, and START).[8-10,21] Third, we did not analyze CBI volumes. Although these measurements might offer additional insights into the presumed origin of CBI, we chose a pragmatic study design to ensure easy translation into clinical practice. Fourth, median baseline NIHSS values were rather low (≤5 points), which could possibly limit our results for individuals with large strokes.

In conclusion, this study estimated the effects of early vs later anticoagulation in patients with first-ever ischemic stroke and AF according to the presence of CBI. Although the primary outcome was comparable in patients without CBI and early vs late DOAC treatment, the CBI group showed a decrease in the primary outcome if treated early after stroke. This effect was mainly attributable to a reduction of recurrent ischemic events in the early poststroke phase. Patients with first-ever ischemic stroke with AF and CBI might, therefore, indicate a high-risk group for stroke recurrence who may particularly benefit from early initiation of anticoagulation. These aspects should be considered in routine clinical practice and in future research endeavors aiming to optimize secondary stroke prevention in patients with ischemic stroke and AF.

Author Contributions

M. Kneihsl: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A. Hakim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.B. Goeldlin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T.R. Meinel: drafting/revision of the manuscript for content, including medical writing for content. M. Branca: analysis or interpretation of data. R. Rohner: major role in the acquisition of data. S. Fenzl: major role in the acquisition of data. S. Abend: major role in the acquisition of data. G.C. Shim: drafting/revision of the manuscript for content, including medical writing for content. C. Gumbinger: drafting/revision of the manuscript for content, including medical writing for content. L. Zhang: drafting/revision of the manuscript for content, including medical writing for content. E.S. Kristoffersen: drafting/revision of the manuscript for content, including medical writing for content. P. Desfontaines: drafting/revision of the manuscript for content, including medical writing for content. P. Vanacker: drafting/revision of the manuscript for content, including medical writing for content. A. Alonso: drafting/revision of the manuscript for content, including medical writing for content. S. Poli: drafting/revision of the manuscript for content, including medical writing for content. A.P. Nunes: drafting/revision of the manuscript for content, including medical writing for content. N.G. Caracciolo: drafting/revision of the manuscript for content, including medical writing for content. T. Gattringer: drafting/revision of the manuscript for content, including medical writing for content. T. Kahles: drafting/revision of the manuscript for content, including medical writing for content. D. Giudici: drafting/revision of the manuscript for content, including medical writing for content. J. Demeestere: drafting/revision of the manuscript for content, including medical writing for content. J. Dawson: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. U. Fischer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Acknowledgment

The ELAN trial was supported by grants from the Swiss National Science Foundation (32003B_197009; 32003B_169975), the Swiss Heart Foundation, the Stroke Association in the United Kingdom (2017/02), and the Intramural Research Fund (20-4-5) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center, Japan.

Study Funding

M.B. Goeldlin received a protected research time grant from the Swiss Academy of Medical Sciences/Bangerter-Rhyner Foundation for the present study (YTCR_13/18).

Disclosure

M. Kneihsl and A. Hakim report no disclosures relevant to the manuscript. M.B. Goeldlin reports a congress grant from Pfizer/Bristol Meyer Squibb. T.R. Meinel, M. Branca, R. Rohner, S. Fenzl, S. Abend, G.C. Shim, C. Gumbinger, L. Zhang, E.S. Kristoffersen, P. Desfontaines, P. Vanacker, and A. Alonso report no disclosures relevant to the manuscript. S. Poli reports speaker fees and grants from Pfizer/Bristol Meyer Squibb, Boehringer Ingelheim, Bayer, and Daiichi Sankyo. A.P. Nunes reports consultant fees from Boehringer Ingelheim and travel support from Daiichi Sankyo. N.G. Caracciolo reports no disclosures relevant to the manuscript. T. Gattringer reports advisory board and speakers' honoraria from Pfizer/Bristol Meyer Squibb, Boehringer Ingelheim, and Bayer. T. Kahles and D. Giudici report no disclosures relevant to the manuscript. J. Dawson reports speaker fees from Pfizer/Bristol Meyer Squibb, Boehringer Ingelheim, Bayer, and Daiichi Sankyo. U. Fischer reports advisory board fees from Boehringer Ingelheim. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 1, 2024. Accepted in final form October 23, 2024. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

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