Stroke

ORIGINAL CONTRIBUTION

Prior Reperfusion Strategy Does Not Modify Outcome in Early Versus Late Start of Anticoagulants in Patients With Ischemic Stroke: Prespecified Subanalysis of the Randomized Controlled ELAN Trial

Anke Wouters, MD, PhD; Jelle Demeestere, MD, PhD; Jean-Benoît Rossel, PhD; Annemie Devroye, BSc; Philippe Desfontaines, MD; Peter Vanacker, MD, PhD; Dimitri Hemelsoet, MD; Laetitia Yperzeele, MD, PhD; Matthieu Pierre Rutgers, MD; André Peeters, MD; Jan Vynckier, MD; Takeshi Yoshimoto, MD, PhD; Kanta Tanaka, MD, PhD; Jochen Vehoff, MD; Kosuke Matsuzono, MD, PhD; Caterina Kulyk, MD; Gerli Sibolt, MD, PhD; Peter Slade, MB, BCh; Alexander Salerno, MD; Takenobu Kunieda, MD, PhD; Arsany Hakim, MD; Roman Rohner, MD; Stefanie Abend, BSc; Martina Goeldlin, MD, PhD; Jesse Dawson, MD; Urs Fischer, MD, MSc*; Robin Lemmens, MD, PhD*; for the ELAN Investigators

BACKGROUND: Early initiation of direct oral anticoagulants (DOACs) in patients with nonvalvular atrial fibrillation and acute ischemic stroke is beneficial and safe. Whether prior acute reperfusion therapy modifies the treatment effect of early versus late DOAC initiation is unknown.

METHODS: For this post hoc analysis of the multicenter, randomized controlled ELAN trial (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients With Atrial Fibrillation), all participants with data concerning reperfusion treatment were included. The primary outcome was the composite outcome of recurrent ischemic stroke, symptomatic intracranial hemorrhage, major extracranial bleeding, systemic embolism, or vascular death within 30 days. Patients were divided into 4 groups based on prior reperfusion therapy: no treatment, intravenous thrombolysis (IVT), endovascular treatment (EVT), or IVT combined with EVT. We performed logistic regression adjusted for age, hypertension, infarct location/size, pre-modified Rankin Scale, NIHSS, and hemorrhagic transformation, including the interaction term between treatment groups (early versus late DOAC) and reperfusion strategy.

RESULTS: We included 1973 of 2013 (98%) patients of the ELAN trial population, with a median age of 77 (71–84) years and of whom 899 (46%) were female. Of them, 1015 (51%) underwent no prior reperfusion treatment, 519 (26%) IVT, 190 (10%) EVT, and 249 (13%) IVT+EVT. We did not identify an interaction for any of the outcome events between prior reperfusion therapy and timing of DOAC initiation. Rates were numerically lower in the early DOAC-initiated group for the following: no reperfusion therapy, 17 (3.3%) versus 24 (4.8%; adjusted odds ratio, 0.69 [95% CI, 0.36–1.28]); EVT, 1 (1.2%) versus 7 (6.4%; adjusted odds ratio, 0.25 [95% CI, 0.03–1.21]); and EVT+IVT, 3 (2.4%) versus 4 (3.3%; adjusted odds ratio, 0.76 [95% CI, 0.17–3.23]). In patients who had received IVT, the rates were 3% (n=8) in the early group versus 2% (n=5) in the late group (adjusted odds ratio, 1.52 [95% CI, 0.52–4.84]).

Correspondence to: Anke Wouters, MD, PhD, KU Leuven, Leuven Brain Institute, Herestraat 49, 3000 Leuven, Belgium, Email anke.wouters@kuleuven.be; or Urs Fischer, MD, MSc, Department of Neurology, University Hospital Bern, Rosenbühlgasse 25, 3010 Bern, Switzerland, Email urs.fischer@insel.ch
*U. Fischer and R. Lemmens contributed equally.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.125.050646.
For Sources of Funding and Disclosures, see page XXX.

Stroke is available at www.ahajournals.org/journal/str

ORIGINAL CONTRIBUTION

CONCLUSIONS: Prior reperfusion therapy does not modify the effect of early versus late DOAC initiation on clinical outcomes in patients with atrial fibrillation and acute ischemic stroke.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03148457.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ embolism ■ hypertension ■ infarction ■ ischemic stroke

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AIS	acute ischemic stroke
aOR	adjusted odds ratio
DOAC	direct oral anticoagulation
ECASS II	European Cooperative Acute Stroke Study II
ELAN	Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients With Atrial Fibrillation
EVT	endovascular treatment
HT	hemorrhagic transformation
IVT	intravenous thrombolysis
OPTIMAS	Optimal Timing of Anticoagulation After Acute Ischaemic Stroke: A Randomized Controlled Trial
START	Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation
TIMING	Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation

Patients with an acute ischemic stroke (AIS) and nonvalvular atrial fibrillation (AF) are given direct oral anticoagulants (DOACs) to prevent recurrent stroke and systemic embolism unless contraindicated.[1] For many years, the optimal timing of DOAC initiation was based on expert opinion and not on robust evidence from clinical trials.[1,2] Results of 3 randomized controlled trials—TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation), ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients With Atrial Fibrillation), and OPTIMAS (Optimal Timing of Anticoagulation After Acute Ischaemic Stroke: A Randomized Controlled Trial)—revealed early versus late DOAC initiation to result in similar rates of efficacy and safety outcomes.[3–5] A post hoc analysis of the ELAN trial even indicated that early DOAC initiation appeared safe in patients with hemorrhagic transformation (HT) before DOAC treatment.[6] However, it remains unclear whether prior reperfusion therapy modifies this treatment effect. Intravenous thrombolysis (IVT) and endovascular treatment (EVT) improve outcome in AIS but are also associated with increased risk of hemorrhagic complications.[7–10] DOAC initiation early thereafter could further increase risk. Current clinical guidelines recommend the suspension of antithrombotic therapy for a minimum of 24 hours following thrombolytic therapy, notwithstanding the brief plasma half-life of alteplase. Preclinical studies suggest that DOAC utilization may potentially confer neuroprotective effects, including preservation of the blood-brain barrier and a reduced likelihood of HT.[11] In addition, data from nonrandomized controlled trials suggest that early initiation of DOACs after acute reperfusion therapy might be safe,[12–14] but these analyses may be limited by confounding by indication or other factors. In comparison to these results, in ELAN, we were able to perform a post hoc analysis of a randomized controlled trial, thereby limiting potential confounding factors and bias in the results.

We aimed to investigate whether the treatment effect of early versus late DOAC initiation varied based on prior reperfusion therapy.

METHODS

Patient Population

This study is a post hoc analysis of the ELAN trial (https://www.clinicaltrials.gov; unique identifier: NCT03148457).[4] The ELAN trial was a multicenter randomized controlled trial assessing the optimal timing of starting DOACs for AF after AIS. Patients were assigned to early (<48 hours after the ischemic event for minor and moderate stroke, 6–7 days for major stroke) versus late (>48 hours for minor and moderate stroke, 12–14 days for major stroke) initiation of DOAC treatment. Patients without information on reperfusion treatment were excluded from this subanalysis. Prerandomization HT was defined according to the ECASS II (European Cooperative Acute Stroke Study II) criteria and assessed as described previously.[6] The study protocol received approval from all relevant ethical committees, and written informed consent was given either by participants, next of kin or other legal representatives, or an independent physician. Fully anonymized data may be made available after submitting a research and statistical analysis plan to the principal investigator of the ELAN trial (urs.fischer@insel.ch), subject to approval by the trial's leadership.

Outcome Events

The primary outcome in this analysis is the same as in the main ELAN trial; a composite of major extracranial bleeding, recurrent ischemic stroke, systemic embolism, symptomatic intracranial hemorrhage, and vascular death within 30 days after randomization.[4] Secondary outcomes were the composite outcome at 90 days, the individual elements of this outcome, and the functional outcome defined by the modified Rankin Scale score at 30 and 90 days after randomization.

Mortality was classified as vascular or nonvascular by a central adjudication committee. Vascular causes of death considered were sudden cardiac death, cardiac mechanical/pump failure, ischemic/hemorrhagic stroke, other major bleeding, clinically relevant nonmajor bleeding, systemic embolism, and myocardial infarction.

Statistical Analysis

All statistical analyses were done with Stata, version 17.0, and R, version 4.3.1. For the statistical analysis in ELAN, no hypothesis was tested, but rates of outcome events and CIs were reported for both the early and late initiation of DOACs. Here, for the primary analysis, patients were grouped according to the acute reperfusion therapy (none versus IVT versus EVT versus IVT+EVT) and treatment allocation (early versus late anticoagulation). Treatment allocation was based on a modified intention-to-treat strategy, as described previously.[4] A descriptive analysis of baseline clinical variables was performed within all 8 groups. To investigate the differences between the groups, a χ^2 test for categorical variables and an ANOVA and Kruskal-Wallis test for continuous variables were done. To avoid bias due to the small number of events, we compared the event rate for the binary outcome events between the late (control) treatment and the early (interventional) treatment arm using Firth penalized univariable and multivariable logistic regression.[15,16] For the total modified Rankin Scale as outcome, an ordinal logistic regression model was applied. The multivariable regressions were adjusted for age, hypertension, infarct location (anterior versus posterior circulation), infarct size, prestroke modified Rankin Scale, NIHSS, and HT using the inverse probability weighting method. Risk differences from the adjusted logistic regression analyses were estimated and presented in Table S1 and Figure S1. Missing baseline data were handled with a simple (single) imputation. Further analyses were performed using complete cases (ie, available outcomes) as done in the main analysis of the ELAN trial. The STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) was followed (Supplemental Material).

RESULTS

For 40 (2%) of the 2013 patients included in the ELAN trial, no data on reperfusion therapy were available. We, therefore, included 1973 patients for this post hoc analysis, of whom 519 (26%) received IVT, 190 (10%) EVT, and 249 (13%) both (Figure 1). Median age was 77 (71–84) years, and 899 (46%) patients were female.

Baseline Characteristics

When comparing early and late DOAC treatment, baseline characteristics were well-balanced across all reperfusion strategies (Table 1). Table 2 presents the baseline characteristics of patients who received IVT, EVT, or IVT+EVT compared with those who did not undergo prior reperfusion therapy. Patients who had received any reperfusion therapy had lower rates of previous ischemic stroke. The NIHSS score before randomization was higher in patients who had undergone EVT, compared with patients without any acute reperfusion treatment. HT on imaging before randomization was more frequent in patients with EVT (n=49; 25.8%) or EVT+IVT (n=49; 19.7%) compared with patients without reperfusion therapy (n=88; 8.7%; Table 2). Also, the distribution of the various DOACs initiated exhibited slight differences between patients who received reperfusion therapy and those who did not (Table 2).

Primary Outcome

For the primary outcome analysis, we had to exclude another 38 participants, as their primary outcome was unknown (Figure 1). The composite outcome at 30 days did not statistically differ between those in the early or late group in any reperfusion group. In those patients treated with no reperfusion therapy, there were 17 (3.3%) events in the early group versus 24 (4.8%) events in the late group (adjusted odds ratio [aOR], 0.69 [95% CI, 0.36–1.28]), in patients treated with EVT, 1 (1.2%) versus 7 (6.4%; aOR, 0.25 [95% CI, 0.03–1.21]), in patients who received IVT, 8 (3%) events happened in the early group versus 5 (2%) in the late group (aOR, 1.52 [95% CI, 0.52–4.84]), and in patients who received EVT+IVT, 3 (2.4%) versus 4 (3.3%; aOR, 0.76 [95% CI, 0.17–3.23]; Tables 3 and 4; Figure 2). No interaction was found between the type of reperfusion therapy and the treatment effect of early versus late DOAC initiation (P=0.25; Table 4).

Additionally, in the subgroup of patients with only minor and moderate stroke, for whom early initiation of DOAC occurred within 48 hours, no interaction was observed (P=0.27). Figure S2 illustrates the forest plot of the 30-day outcome in this subgroup.

Functional Outcome

In patients without prior reperfusion therapy, poor functional outcome (modified Rankin Scale score 3–6) at day 30 was observed in 37.9% (n=197) with early DOAC initiation versus 38.1% (n=191) with late DOAC initiation (aOR, 0.98 [95% CI, 0.76–1.27]). The rates for patients treated with IVT were 33.2% (n=88) versus 30.7% (n=78; aOR, 1.14 [95% CI, 0.79–1.65]), for patients treated with EVT were 54.3% (n=44) versus 46.8% (n=51; aOR, 1.35 [95% CI, 0.76–2.40]); and in patients with combined acute treatment were 31.7% (n=40) versus 36.6% (n=45; aOR, 0.82 [95% CI, 0.48–1.38]; Tables 3 and 4; Figure 2). Similar results were observed for poor functional outcome at 90 days

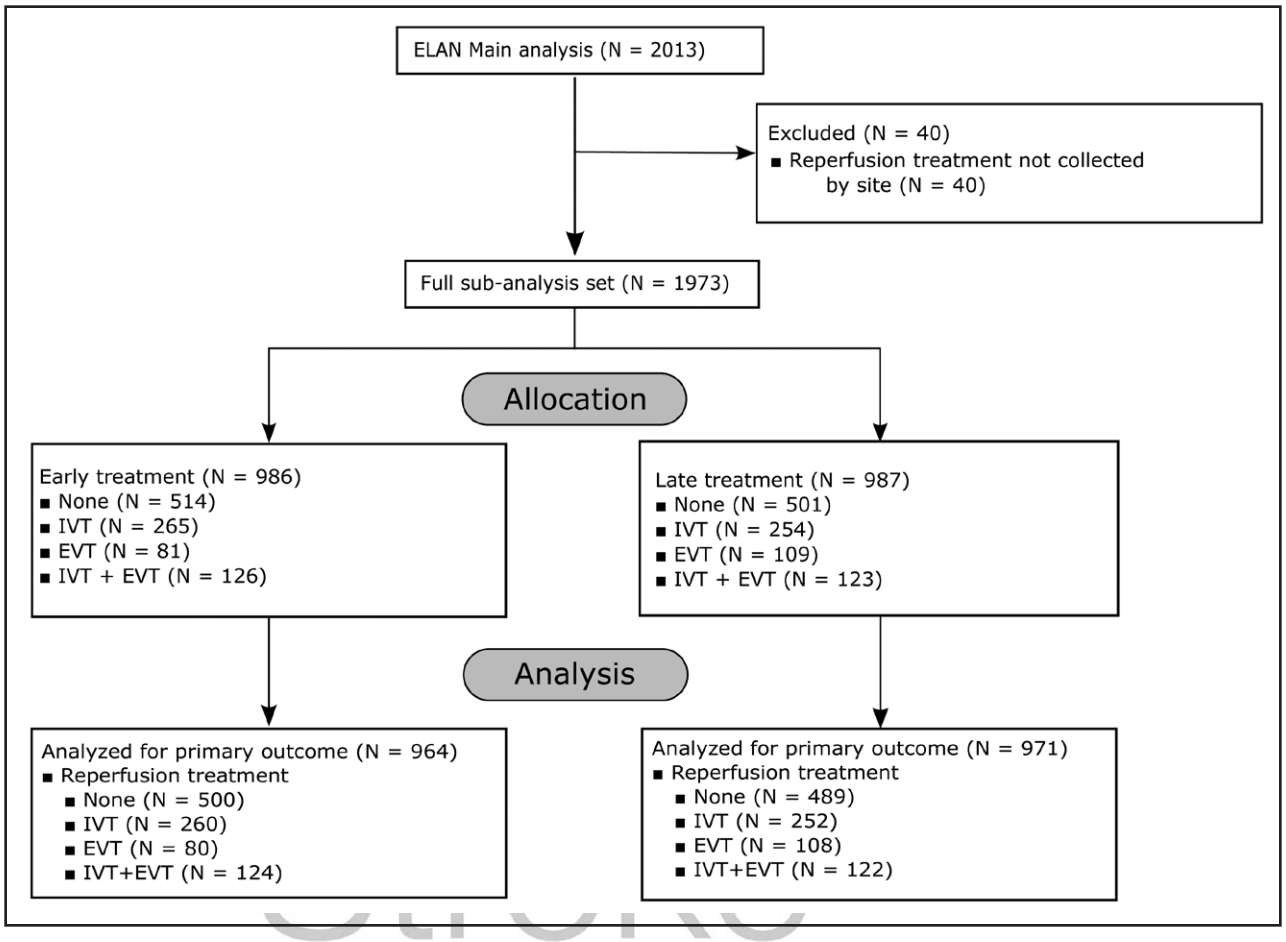

Figure 1. Inclusion flowchart.
ELAN indicates Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients With Atrial Fibrillation; EVT, endovascular treatment; and IVT, intravenous thrombolysis.

(Tables 3 and 4). Across all the reperfusion treatment groups, there was no difference in the effect of early versus late DOAC initiation on poor functional outcome (adjusted *P* values for interaction: for day 30, *P*=0.57; for day 90, *P*=0.21).

Secondary Outcomes

The comparison of rates for the composite outcome at 90 days was similar to that at 30 days, with numerically less events occurring in the early than in the late group with the exception of patients treated with IVT (Tables 3 and 4). There was no interaction between acute reperfusion therapy and the timing of DOAC initiation (*P*=0.35) for the composite outcome (Table 4). The other secondary outcome events were generally rare across the different reperfusion treatment groups (Tables 3 and 4; Figure 2). Only 1 symptomatic intracranial hemorrhage occurred over the 90-day follow-up period in the total group of patients who received prior reperfusion therapy. There was no interaction between the type of acute reperfusion therapy and the effect of DOAC timing on any of the secondary outcome events.

DISCUSSION

In this post hoc analysis of the randomized controlled ELAN trial, prior reperfusion therapy did not modify the treatment effect of early DOAC initiation in patients with AIS with nonvalvular AF. Similar to the overall trial results, regardless of acute reperfusion therapy, we did not observe safety concerns in patients with early initiation of DOACs. The percentage of recurrent stroke at 30 days ranged between 0.8% to 3.7% for patients with late initiation versus 1.2% to 1.6% for those with an early start. The safety end point of symptomatic intracranial hemorrhage at 30 days was rare overall, ranging between 0% to 0.4% for late and 0% to 1.2% for early start.

Historically, clinicians are rather cautious with starting antiplatelet or anticoagulant treatment early after IVT or EVT, due to the increased risk of hemorrhagic complications.[8,10] Initiating antiplatelet therapy is recommended only after 24 hours following IVT.[17–19] Additionally, a recent trial demonstrated an increased risk of hemorrhagic complications in patients receiving periprocedural aspirin or heparin during EVT.[20] So far, the optimal timing of starting DOAC therapy for stroke prevention in

 Stroke. 2025;56:00–00. DOI: 10.1161/STROKEAHA.125.050646

Table 1. Baseline Characteristics of Early Versus Late DOACs

	Early No RT (n=514)	Late No RT (n=501)	Early IVT (n=265)	Late IVT (n=254)	Early EVT (n=81)	Late EVT (n=109)	Early IVT+EVT (n=126)	Late IVT+EVT (n=123)
Age, y; median [lq, uq]	77 [71, 84]	78 [72, 84]	76 [70, 84]	77 [69, 84]	78 [72, 86]	79 [74, 84]	76 [68, 82]	76 [69, 83]
Female, n (%)	216 (42.0%)	228 (45.5%)	129 (48.7%)	110 (43.3%)	43 (53.1%)	57 (52.3%)	64 (50.8%)	52 (42.3%)
Prestroke mRS score 0–2, n (%)	452 (87.9%)	444 (88.6%)	234 (88.3%)	225 (88.6%)	67 (82.7%)	96 (88.1%)	117 (92.9%)	115 (93.5%)
Hypertension, n (%)	355 (69.1%)	326 (65.1%)	185 (69.8%)	177 (69.7%)	52 (64.2%)	77 (70.6%)	89 (70.6%)	85 (69.1%)
Diabetes, n (%)	106 (20.6%)	92 (18.4%)	38 (14.3%)	40 (15.7%)	15 (18.5%)	15 (13.8%)	22 (17.5%)	12 (9.8%)
Prior ischemic stroke, n (%)	79 (15.4%)	90 (18.0%)	27 (10.2%)	24 (9.4%)	7 (8.6%)	11 (10.1%)	13 (10.3%)	13 (10.6%)
Prior systemic embolism, n (%)	10 (1.9%)	15 (3.0%)	5 (1.9%)	9 (3.5%)	1 (1.2%)	4 (3.7%)	3 (2.4%)	2 (1.6%)
Prior myocardial infarction, n (%)	44 (8.6%)	44 (8.8%)	16 (6.0%)	21 (8.3%)	9 (11.1%)	9 (8.3%)	10 (7.9%)	11 (8.9%)
NIHSS before randomization, median [lq, uq]	3.0 [1.0, 6.0]	3.0 [1.0, 6.0]	2.0 [1.0, 5.0]	3.0 [1.0, 6.0]	5.0 [2.0, 14.0]	5.0 [2.0, 11.0]	3.0 [1.0, 8.0]	3.0 [1.0, 8.0]
Stroke size, n (%)								
Minor	213 (41.4%)	200 (39.9%)	101 (38.1%)	103 (40.6%)	14 (17.3%)	27 (24.8%)	38 (30.2%)	36 (29.3%)
Moderate	170 (33.1%)	177 (35.3%)	121 (45.7%)	108 (42.5%)	41 (50.6%)	50 (45.9%)	63 (50.0%)	53 (43.1%)
Major	131 (25.5%)	124 (24.8%)	43 (16.2%)	43 (16.9%)	26 (32.1%)	32 (29.4%)	25 (19.8%)	34 (27.6%)
HT before randomization, n (%)	48 (9.3%)	40 (8.0%)	32 (12.1%)	27 (10.6%)	25 (30.9%)	24 (22.0%)	25 (19.8%)	24 (19.5%)

Baseline clinical and neuroimaging characteristics according to reperfusion therapy and treatment group. No significant differences were found between the early and late DOAC-treated groups for all different reperfusion strategies. DOAC indicates direct oral anticoagulant; EVT, endovascular treatment; HT, hemorrhagic transformation; IVT, intravenous thrombolysis; lq, lower quartile; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RT, reperfusion therapy; and uq, upper quartile.

patients with AF after acute reperfusion therapy is not known. However, our study suggests that an early start—in ELAN within 48 hours for minor or moderate stroke or on day 6 to 7 for major stroke—appears to be safe. This aligns with the findings of a review of 3 small observational studies, which reported a median DOAC initiation

Table 2. Baseline Characteristics According to Reperfusion Therapy

	No RT (n=1015)	IVT (n=519)	*P* value	EVT (n=190)	*P* value	IVT+EVT (n=249)	*P* value
Age, y; median [lq, uq]	77 [71, 84]	77 [69, 84]	0.14	79 [73, 84]	0.33	76 [69, 82]	0.01
Female, n (%)	444 (43.7%)	239 (46.1%)	0.39	100 (52.6%)	0.02	116 (46.6%)	0.42
Prestroke mRS score 0–2, n (%)	896 (88.3%)	459 (88.4%)	0.99	163 (85.8%)	0.30	232 (93.2%)	0.03
Hypertension, n (%)	681 (67.1%)	362 (69.7%)	0.40	129 (67.9%)	0.67	174 (69.9%)	0.37
Diabetes, n (%)	198 (19.5%)	78 (15.0%)	0.09	30 (15.8%)	0.46	34 (13.7%)	0.09
Prior ischemic stroke, n (%)	169 (16.7%)	51 (9.8%)	0.001	18 (9.5%)	0.02	26 (10.4%)	0.03
Prior systemic embolism, n (%)	25 (2.5%)	14 (2.7%)	0.21	5 (2.6%)	0.76	5 (2.0%)	0.88
Prior myocardial infarction, n (%)	88 (8.7%)	37 (7.1%)	0.34	18 (9.5%)	0.53	21 (8.4%)	0.99
NIHSS before randomization, median [lq, uq]	3.0 [1.0, 6.0]	3.0 [1.0, 6.0]	0.25	5.0 [2.0, 13.0]	<0.001	3.0 [1.0, 8.0]	0.39
Stroke size, n (%)			<0.001		<0.001		<0.001
Minor	413 (40.7%)	204 (39.3%)		41 (21.6%)		74 (29.7%)	
Moderate	347 (34.2%)	229 (44.1%)		91 (47.9%)		116 (46.6%)	
Major	255 (25.1%)	86 (16.6%)		58 (30.5%)		59 (23.7%)	
HT before randomization, n (%)	88 (8.7%)	59 (11.4%)	0.11	49 (25.8%)	<0.001	49 (19.7%)	<0.001
Type of DOAC started, n (%)			0.02		0.01		<0.001
Apixaban	624 (62.4%)	338 (65.8%)		113 (60.1%)		164 (66.4%)	
Dabigatran	158 (15.8%)	90 (17.5%)		40 (21.3%)		53 (21.5%)	
Edoxaban	173 (17.3%)	58 (11.3%)		20 (10.6%)		18 (7.3%)	
Rivaroxaban	45 (4.5%)	28 (5.4%)		15 (8.0%)		12 (4.9%)	
Missing	15 (1.5%)	5 (1.0%)		2 (1.0%)		2 (1.0%)	

Baseline clinical and neuroimaging characteristics according to reperfusion therapy. *P* values are for the comparison between each reperfusion treatment and no reperfusion therapy. DOAC indicates direct oral anticoagulant; EVT, endovascular treatment; HT, hemorrhagic transformation; IVT, intravenous thrombolysis; lq, lower quartile; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RT, reperfusion therapy; and uq, upper quartile.

Table 3. Outcomes at 30 and 90 Days; Descriptive Analysis

	Early No RT (n=514)	Late No RT (n=501)	Early IVT (n=265)	Late IVT (n=254)	Early EVT (n=81)	Late EVT (n=109)	Early IVT+EVT (n=126)	Late IVT+EVT (n=123)
Outcomes at 30 d								
Composite outcome	17 (3.3%)	24 (4.8%)	8 (3.0%)	5 (2.0%)	1 (1.2%)	7 (6.4%)	3 (2.4%)	4 (3.3%)
mRS score 3–6	195 (37.9%)	191 (38.1%)	88 (33.2%)	78 (30.7%)	44 (54.3%)	51 (46.8%)	40 (31.7%)	45 (36.6%)
Recurrent ischemic stroke	7 (1.4%)	14 (2.8%)	4 (1.5%)	5 (2.0%)	1 (1.2%)	4 (3.7%)	2 (1.6%)	1 (0.8%)
Systemic embolism	2 (0.4%)	6 (1.2%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.6%)
Bleeding events	2 (0.4%)	4 (0.8%)	1 (0.4%)	0 (0.0%)	1 (1.2%)	2 (1.8%)	1 (0.8%)	1 (0.8%)
Major extracranial bleeding	1 (0.2%)	2 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (0.8%)	1 (0.8%)
sICH	1 (0.2%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular death	8 (1.6%)	5 (1.0%)	2 (0.8%)	1 (0.4%)	1 (1.2%)	2 (1.8%)	0 (0.0%)	1 (0.8%)
Outcomes at 90 d								
Composite outcome	20 (3.9%)	33 (6.6%)	10 (3.8%)	8 (3.1%)	2 (2.5%)	8 (7.3%)	4 (3.2%)	4 (3.3%)
mRS score 3–6	176 (34.2%)	174 (34.7%)	74 (27.9%)	71 (28.0%)	44 (54.3%)	48 (44.0%)	30 (23.8%)	41 (33.3%)
Recurrent ischemic stroke	10 (1.9%)	18 (3.6%)	4 (1.5%)	6 (2.4%)	2 (2.5%)	4 (3.7%)	2 (1.6%)	1 (0.8%)
Systemic embolism	2 (0.4%)	7 (1.4%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (1.6%)
Bleeding events	2 (0.4%)	6 (1.2%)	1 (0.4%)	1 (0.4%)	1 (1.2%)	2 (1.8%)	1 (0.8%)	1 (0.8%)
Major extracranial bleeding	1 (0.2%)	4 (0.8%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	2 (1.8%)	1 (0.8%)	1 (0.8%)
sICH	1 (0.2%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular death	9 (1.8%)	9 (1.8%)	6 (2.3%)	2 (0.8%)	1 (1.2%)	3 (2.8%)	1 (0.8%)	1 (0.8%)

Descriptive statistics (n with percentage) of different outcomes within/at 30 and 90 days divided by reperfusion therapy group and timing of DOAC initiation. DOAC indicates direct oral anticoagulant; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; RT, reperfusion therapy; and sICH, symptomatic intracranial hemorrhage.

time of 2 to 6 days after AIS.[13] This study was limited by a small sample size (106 patients) and low number of patients who underwent EVT (2.8%) or IVT+EVT (3.9%). Similarly, a large observational study of 2159 patients with AIS, with a median DOAC initiation time of 7 days after the index event, found no differences in 90-day outcomes between patients who received prior reperfusion therapy and those who did not.[12] Finally, the TIMING trial, which compared early (≤4 days) and delayed (5–10 days) DOAC initiation, and the recently published OPTIMAS trial, which defined early as ≤4 days and delayed as 7 to 14 days, found no interaction with prior reperfusion therapy.[3,5] The key strengths of our analysis are the separate evaluation of different types of reperfusion therapies (IVT, EVT, and IVT+EVT), information about an early start within 48 hours, and the inclusion of detailed information on prior HT.

The number of patients with HT on scans before DOAC initiation was higher in those who received acute reperfusion therapy compared with those who did not. While up to 30% of patients in the EVT group experienced HT (hemorrhagic infarction type 1 or 2), this was not reflected in a different effect of early DOAC initiation on clinical outcomes compared with patients in whom DOAC treatment was started later. The safety of early DOAC treatment in the presence of HT has been reported on previously.[6] These findings and the rates presented here in patients with prior reperfusion therapy are reassuring for the early start of DOACs regardless of acute stroke treatment and the presence of hemorrhagic infarction type 1 and 2. However, the same data also show that early start of DOACs should be avoided in patients with parenchymal hematoma type 1 and 2. Patients with parenchymal hematoma 1 and 2 on prerandomization imaging were to be excluded from participating in ELAN according to the trial protocol; however, the final decision was at the discretion of the local site investigators. We have no information on screen failures based on the presence of parenchymal hematoma 1 and 2. Potentially, the proportion of patients with these more severe forms of HT was larger in the patients with prior reperfusion therapy. Therefore, it is possible that the number of patients qualifying for early DOAC initiation may be smaller after prior reperfusion therapy compared with those without. Hence, we recommend performing postreperfusion brain imaging before DOAC initiation to exclude patients with parenchymal hematoma 1 and 2.

The absolute number of bleeding events at 30 days was low, limiting the power of reporting on these events in the subgroups based on acute reperfusion strategy. The planned meta-analysis of individual patient data from the 4 randomized controlled trials (ELAN, TIMING, OPTIMAS, and START [Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation])[3–5,21,22] will hopefully provide more evidence regarding these subgroups of patients.

Table 4. Outcomes at 30 and 90 Days; Results of Multivariable Regression Analysis

	No RT	IVT	EVT	IVT+EVT	
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	*P* value
Outcomes at 30 d					
Composite outcome	0.69 (0.36–1.28)	1.52 (0.52–4.84)	0.25 (0.03–1.21)	0.76 (0.17–3.23)	0.25
mRS score	0.89 (0.71–1.11)	1.03 (0.76–1.40)	1.24 (0.75–2.05)	0.70 (0.45–1.09)	…
mRS score 3–6	0.98 (0.76–1.27)	1.14 (0.79–1.65)	1.35 (0.76–2.40)	0.82 (0.48–1.38)	0.57
Recurrent ischemic stroke	0.48 (0.18–1.14)	0.79 (0.21–2.84)	0.43 (0.04–2.38)	1.64 (0.22–17.54)	0.62
Systemic embolism	0.40 (0.08–1.53)	4.73 (0.37–655.24)	0.45 (0.00–8.55)	0.20 (0.00–2.54)	0.09
Bleeding events	0.55 (0.09–2.56)	3.06 (0.17–444.75)	0.83 (0.07–6.68)	0.96 (0.07–12.39)	0.57
Major extracranial bleeding	0.59 (0.05–4.64)	3.06 (0.17–444.75)	0.28 (0.00–3.62)	0.96 (0.07–12.39)	0.31
sICH	0.61 (0.06–4.64)	0.98 (0.01–180.21)	4.05 (0.21–595.45)	0.99 (0.01–183.56)	0.58
Vascular death	1.55 (0.54–4.91)	1.68 (0.21–19.69)	0.78 (0.07–5.97)	0.34 (0.00–6.57)	0.53
Outcomes at 90 d					
Composite outcome	0.57 (0.32–1.00)	1.20 (0.48–3.12)	0.36 (0.06–1.37)	1.00 (0.25–3.96)	0.35
mRS score	0.95 (0.77–1.19)	1.00 (0.73–1.36)	1.19 (0.71–1.98)	0.65 (0.41–1.02)	…
mRS score 3–6	0.98 (0.75–1.27)	1.02 (0.70–1.50)	1.53 (0.86–2.73)	0.65 (0.37–1.13)	0.21
Recurrent ischemic stroke	0.53 (0.23–1.12)	0.66 (0.18–2.20)	0.69 (0.11–3.22)	1.62 (0.21–17.28)	0.77
Systemic embolism	0.34 (0.07–1.26)	4.66 (0.37–646.87)	0.44 (0.00–8.34)	0.20 (0.00–2.50)	0.08
Bleeding events	0.37 (0.07–1.46)	1.00 (0.09–12.28)	0.81 (0.07–6.52)	0.95 (0.07–12.21)	0.85
Major extracranial bleeding	0.31 (0.03–1.70)	1.00 (0.09–12.28)	0.27 (0.00–3.54)	0.95 (0.07–12.21)	0.57
sICH	0.60 (0.06–4.62)	0.96 (0.01–177.88)	3.95 (0.20–581.49)	0.98 (0.01–180.81)	0.58
Vascular death	0.97 (0.39–2.43)	2.67 (0.66–15.26)	0.55 (0.05–3.44)	1.06 (0.09–13.43)	0.46

Results of the multivariable logistic regression analysis represented as ORs. For the ORs, the reference is late treatment, and the OR interpretation is based on the early treatment. Adjustment was performed including the following variables in the model: age, arterial hypertension, infarct location (anterior vs posterior circulation), prestroke mRS, NIHSS, and HT applying IPW weights. *P* value is given for the interaction between DOAC initiation (early vs late) and the different types of acute reperfusion treatment (none, IVT, EVT, and IVT+EVT). aOR indicates adjusted odds ratio; DOAC, direct oral anticoagulant; EVT, endovascular treatment; HT, hemorrhagic transformation; IPW, inverse probability weighting; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RT, reperfusion therapy; and sICH, symptomatic intracranial hemorrhage.

The main limitation in interpreting our findings is that they stem from a post hoc analysis, and the main trial was not designed for this specific subgroup analysis. The number of individual outcome events, especially those related to bleeding complications, were generally low. Nevertheless, the absence of any treatment effect

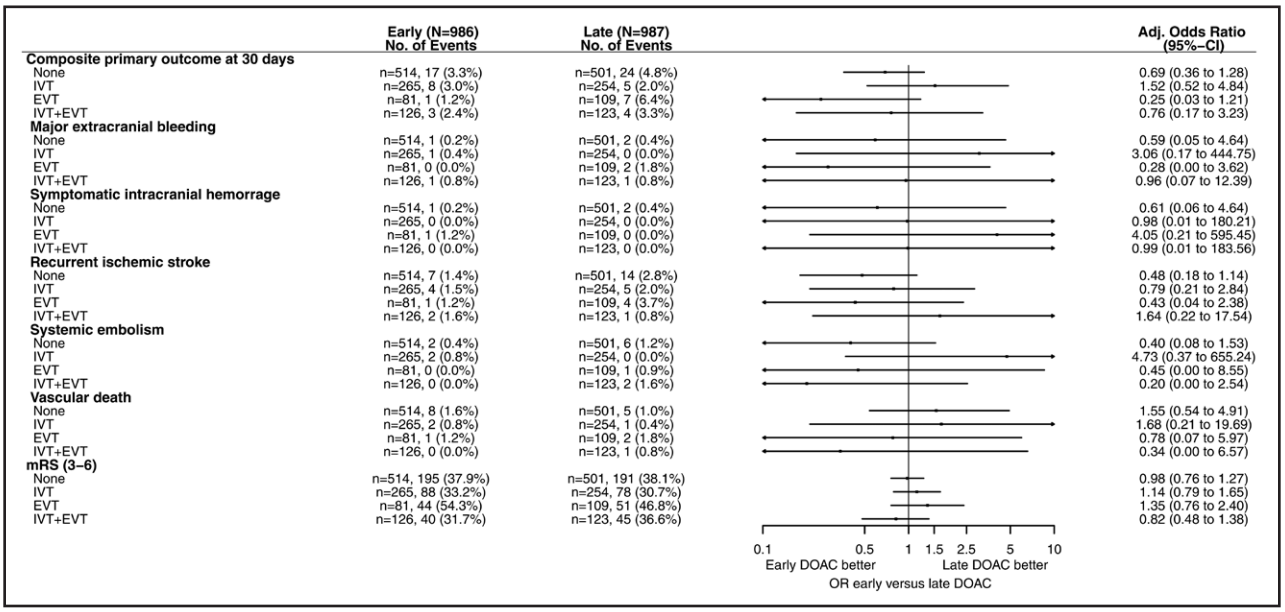

Figure 2. Outcome at 30 days.
Forest plot representing the adjusted odds ratios of the main outcomes of interest by different reperfusion treatment groups. DOAC indicates direct oral anticoagulant; EVT, endovascular treatment; IVT, intravenous thrombolysis; and mRS, modified Rankin Scale.

heterogeneity based on the type of prior reperfusion therapy is novel supportive evidence for early initiation of DOAC treatment across all patient subgroups.

CONCLUSIONS

In this post hoc analysis of the randomized controlled ELAN trial results, prior acute reperfusion therapy did not modify the treatment effect and bleeding risk associated with early DOAC initiation in patients with AF and AIS. These results might reassure clinicians to start DOACs early, also after IVT or EVT.

ARTICLE INFORMATION

Received January 09, 2025; final revision received April 1, 2025; accepted April 3, 2025.

Presented in part at the European Stroke Organisation Conference, Helsinki, Finland, May 21–23, 2025.

Affiliations

Department of Neurosciences, Experimental Neurology, KU Leuven, Leuven Brain Institute, Belgium (A.W., J. Demeestere, R.L.). Department of Neurology, University Hospitals Leuven, Belgium (J. Demeestere, A.D., R.L.). Department of Clinical Research (J.-B.R.), Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital (A.H., R.R.), Graduate School for Health Sciences (R.R.), and Department of Neurology, University Hospital Bern, Inselspital (S.A., M.G., U.F.), University of Bern, Switzerland. Department of Neurology, Stroke Unit, CHC Montlégia Hospital, Liège, Belgium (P.D.), Department of Neurology, Algemeen Ziekenhuis Groeninge Kortrijk, Belgium (P.V.). Department of Neurology, Ghent University Hospital, Belgium (D.H.). Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium (L.Y.). Stroke Unit and Neurovascular Center, Department of Neurology, Antwerp University Hospital, Edegem, Belgium (L.Y.). Neurology Department, Europe Hospitals (M.P.R.) and Neurology Department, Cliniques Universitaires Saint Luc (A.P.), H.uni - UCLouvain, Brussels, Belgium. Department of Neurology, Onze-Lieve-Vrouwziekenhuis Aalst, Belgium (J. Vynckier). Departments of Neurology (T.Y.) and Cerebrovascular Medicine (K.T.), National Cerebral and Cardiovascular Center, Osaka, Japan. Department of Neurology University Teaching and Research Hospital St. Gallen, Switzerland (J. Vehoff). Division of Neurology, Department of Medicine, Jichi Medical University, Tochigi, Japan (K.M.). Department of Neurology, Kepler University Hospital GmbH, Johannes Kepler University, Linz, Austria (C.K.). Neurology and Clinical Neurosciences, University of Helsinki and Helsinki University Hospital, Finland (G.S.). Morriston Hospital, Swansea Hospital, Wales, United Kingdom (P.S.). Stroke Center, Neurology Service, Lausanne University Hospital and University of Lausanne, Switzerland (A.S.). Department of Neurology, Kansai Medical University, Hirakata (T.K.). School of Cardiovascular and Metabolic Health, Queen Elizabeth University Hospital, University of Glasgow, United Kingdom (J. Dawson). Department of Neurology, University and University Hospital Basel, Switzerland (U.F.).

Sources of Funding

This study was supported by grants from the Swiss National Science Foundation (32003B_197009 and 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.

Disclosures

Dr Rossel is affiliated with CTU Bern, Department of Clinical Research, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in the design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest, see https://dcr.unibe.ch/services/terms__conditions/index_eng.html. Dr Yperzeele has received speaker and consultancy fees from Bayer, Bristol Myers Squibb/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, PPD Global, and Janssen Research & Development (payment to organization, not to personal account). Dr Rutgers has received fees as a consultant from Daiichi Sankyo, Teva Pharmaceuticals, and Novartis and as Data Monitoring Committee Member for Medpace, Inc. Dr Yoshimoto reports compensation from Daiichi Sankyo for other services and compensation from Stryker for other services. Dr Hakim received a grant from Schweizerische Herzstiftung. Dr Rohner received grants from Schweizerische Herzstiftung and the Department of Teaching and Research, Insel Group AG, and Gottfried und Julia Bangerter-Rhyner-Stiftung (outside the submitted work). Dr Goeldlin received a travel grant of the European Academy of Neurology, grant from the European Stroke Organisation, the Gottfried und Julia Bangerter-Rhyner-Stiftung, Inselspital Bern University Hospital, Mittelbauvereinigung Universitaet Bern, Swiss Heart Foundation, Swiss Neurological Society, and the Swiss Stroke Society. Dr Dawson reports speaker fees from AstraZeneca, Pfizer, Bristol Myers Squibb, Bayer, and Daiichi Sankyo and a grant from the Stroke Association. Dr Fischer reports research support from the Swiss National Science Foundation and the Swiss Heart Foundation. He is a principal investigator of the ELAN trial (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischaemic Stroke Patients With Atrial Fibrillation) and a co-principal investigator of the DISTAL (Endovascular Therapy Plus Best Medical Treatment [BMT] Versus BMT Alone for Medium Vessel Occlusion Stroke), TECNO (Safety and Efficacy of Intra-Arterial Tenecteplase for Non-Complete Reperfusion of Intracranial Occlusions), SWIFT DIRECT (Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke), SWITCH (Decompressive Hemicraniectomy in Intracerebral Hemorrhage), ELAPSE (Early Closure of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic Stroke Despite Anticoagulation Therapy), and ICARUS (Colorectal Cohort Analysis From the Intraperitoneal Chemotherapy After Cytoreductive Surgery for Peritoneal Metastasis) trials. He also reports research grants from Medtronic (BEYOND SWIFT [Bernese-European Registry for Ischemic Stroke Patients Treated Outside Current Guidelines With Neurothrombectomy Devices Using the SOLITAIRE FR With the Intention for Thrombectomy] and SWIFT DIRECT) and from Stryker, Rapid Medical, Penumbra, Medtronic and Phenox (DISTAL), and Boehringer Ingelheim (TECNO); support from the Horton Foundation for the DO IT trial (The DOAC International Thrombolysis); consultancies for Medtronic (fees paid to institution); and participation in an advisory board for AstraZeneca (former Alexion/Portola), Bayer, Boehringer Ingelheim, Biogen, AbbVie, and Siemens (fees paid to institution). He is the member of a clinical event committee of the COATING study (Coating to Optimize Aneurysm Treatment in the New Flow Diverter Generation; Phenox); member of the data and safety monitoring committee of the TITAN (A Study of Apalutamide [JNJ-56021927, ARN-509] Plus Androgen Deprivation Therapy [ADT] Versus ADT in Participants With mHSPC), LATE_MT, IN EXTREMIS (Large Stroke Therapy Evaluation), and RapidPulse trials; and president of the Swiss Neurological Society and president-elect of the European Stroke Organisation. Dr Lemmens has no personal disclosures but reports institutional fees for consultancy from Boehringer Ingelheim and Pfizer. The other authors report no conflicts.

Supplemental Material

Table S1
Figures S1–S2
List of ELAN Investigators
STROBE Checklist

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