



Clinical trial results:

Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillation (ELAN): an international, multicentre, randomised-controlled, two-arm, assessor-blinded trial

Summary

EudraCT number	2017-000236-34
Trial protocol	AT FI BE DE SK PT IT
Global end of trial date	21 December 2022

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024
Summary attachment (see zip file)	NEJM_ELAN (NEJMoa2303048.pdf) NEJM_ELAN_Supplementary material (ELAN_NEJM_Supplement_revised_R2_15May23.pdf)

Trial information

Trial identification

Sponsor protocol code	ELAN
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03148457
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inselspital (University Hospital) Bern
Sponsor organisation address	Freiburgstrasse 10, Bern, Switzerland, 3010
Public contact	Neuroclinical Trial Coordination , Inselspital (University Hospital) Bern, nctu@insel.ch
Scientific contact	Neuroclinical Trial Coordination , Inselspital (University Hospital) Bern, nctu@insel.ch

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2022
Global end of trial reached?	Yes
Global end of trial date	21 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to determine the net benefit of early versus late initiation of DOACs in patients with acute ischaemic stroke related to AF. Net benefit is estimated by a composite outcome that combines the outcomes of interest (recurrent ischaemic stroke and systemic embolism) to estimate efficacy and the bleeding outcomes of interest (intracerebral and extracranial major bleeding) as well as vascular death to estimate safety.

Protection of trial subjects:

Safety evaluations were conducted in regular intervals, in order to monitor patient safety and to assess the risk/benefit. Based on this, the IDMC gave recommendations on the continuation/stop of the trial. Furthermore, both investigators and the sponsor-investigators made a causality assessment of the serious adverse events to the trial drug based on the latest ICH guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 81
Country: Number of subjects enrolled	Portugal: 28
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Austria: 97
Country: Number of subjects enrolled	Belgium: 183
Country: Number of subjects enrolled	Finland: 83
Country: Number of subjects enrolled	Germany: 195
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Switzerland: 505
Country: Number of subjects enrolled	United Kingdom: 482
Country: Number of subjects enrolled	Japan: 192
Country: Number of subjects enrolled	India: 55
Country: Number of subjects enrolled	Israel: 34
Country: Number of subjects enrolled	Ireland: 17
Country: Number of subjects enrolled	Greece: 25
Worldwide total number of subjects	2013
EEA total number of subjects	745

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	257
From 65 to 84 years	1307
85 years and over	449

Subject disposition

Recruitment

Recruitment details:

2032 participants were enrolled at 103 sites in 15 countries between November 6, 2017, and September 12, 2022.

Pre-assignment

Screening details:

All patients of 18 years or older with an acute ischaemic stroke related to AF were screened for this trial. Primary responsibility for recruitment of patients will lie with the PI at each site. A total of 36,643 participants were screened.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

All data for the primary endpoint was collected with a telephone interview by an assessor, who was not aware of treatment allocation, if possible. All events deemed potentially primary outcomes for the trial by the local investigators were reviewed by the independent CEC, who was not aware of treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Early DOAC treatment

Arm description:

Early treatment was defined as initiation of a DOAC within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke.

Arm type	Early treatment start
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use

Dosage and administration details:

5 mg 2x/d or 2.5 mg 2x/d

Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use

Dosage and administration details:

20 mg 1xd or 15 mg 1x/d

Investigational medicinal product name	Dabigatran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use

Dosage and administration details:

150 mg 2x/d or 110 mg 2x/d

Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use
Dosage and administration details: 60 mg 1x/d or 30 mg 1x/d	
Arm title	Late DOAC treatment

Arm description:

Later treatment was defined as initiation of a DOAC in participants with a minor stroke on day 3 or 4 after stroke onset, in participants with a moderate stroke on day 6 or 7, and in participants with a major stroke on day 12, 13, or 14.

Arm type	Late treatment start
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use

Dosage and administration details:

5 mg 2x/d or 2.5 mg 2x/d

Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use

Dosage and administration details:

20 mg 1xd or 15 mg 1x/d

Investigational medicinal product name	Dabigatran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use

Dosage and administration details:

150 mg 2x/d or 110 mg 2x/d

Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Oral use

Dosage and administration details:

60 mg 1x/d or 30 mg 1x/d

Number of subjects in period 1	Early DOAC treatment	Late DOAC treatment
Started	1006	1007
Completed	949	946
Not completed	57	61
Adverse event, serious fatal	45	49

Consent withdrawn by subject	9	10
Lost to follow-up	3	2

Baseline characteristics

Reporting groups

Reporting group title	Early DOAC treatment
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Reporting group description:

Early treatment was defined as initiation of a DOAC within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke.

Reporting group title	Late DOAC treatment
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Reporting group description:

Later treatment was defined as initiation of a DOAC in participants with a minor stroke on day 3 or 4 after stroke onset, in participants with a moderate stroke on day 6 or 7, and in participants with a major stroke on day 12, 13, or 14.

Reporting group values	Early DOAC treatment	Late DOAC treatment	Total
Number of subjects	1006	1007	2013
Age categorical			
Units: Subjects			
Adults (18-64 years)	133	124	257
From 65-84 years	645	662	1307
85 years and over	228	221	449
Gender categorical			
Units: Subjects			
Female	459	456	915
Male	547	551	1098

End points

End points reporting groups

Reporting group title	Early DOAC treatment
Reporting group description: Early treatment was defined as initiation of a DOAC within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke.	
Reporting group title	Late DOAC treatment
Reporting group description: Later treatment was defined as initiation of a DOAC in participants with a minor stroke on day 3 or 4 after stroke onset, in participants with a moderate stroke on day 6 or 7, and in participants with a major stroke on day 12, 13, or 14.	

Primary: Primary endpoint

End point title	Primary endpoint
End point description: The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization.	
End point type	Primary
End point timeframe: 30 days	

End point values	Early DOAC treatment	Late DOAC treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	984	991		
Units: integers				
Major extracranial bleeding	3	5		
Symptomatic intracranial hemorrhage	2	2		
Recurrent ischemic stroke	14	25		
Systemic embolism	4	9		
Death from vascular cause	11	10		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description: The primary composite outcome was analyzed with the use of a penalized logistic-regression model to account for low event rates. The risk difference with 95% confidence intervals was derived from the estimated odds ratio and its standard error.	
Comparison groups	Early DOAC treatment v Late DOAC treatment

Number of subjects included in analysis	1975
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.14

Notes:

[1] - The main aim of the trial was to estimate the effect of early initiation as compared with later initiation of anticoagulation and to estimate the degree of precision of these estimates. Therefore, no statistical hypotheses as to superiority, inferiority, or noninferiority were tested.

Secondary: Secondary endpoint

End point title	Secondary endpoint
End point description:	
Secondary outcomes assessed at 30 and 90 days were: recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, vascular death, nonmajor bleeding, death from any cause, a binary outcome of a score of 0 to 2 versus 3 to 6 on the modified Rankin scale (a 7-point scale with a range from 0 to 6; scores of 0, 1, and 2 indicate slight or no disability and a score of 6 indicates death), and an ordinal shift in the distribution of scores.	
End point type	Secondary
End point timeframe:	
30 and 90 days	

End point values	Early DOAC treatment	Late DOAC treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1006	1007		
Units: integers				
Major extracranial bleeding	3	8		
Symptomatic intracranial hemorrhage	2	2		
Recurrent ischemic stroke	18	30		
Systemic embolism	4	10		
Vascular death	17	16		
Death from any cause	45	48		
Non-major bleeding	39	41		
Modified Rankin scale score ≤ 2	659	654		
Any serious adverse event	132	157		

Statistical analyses

Statistical analysis title	Secondary endpoint
Statistical analysis description:	
Secondary binary outcomes were analyzed with the use of penalized logistic regression (dichotomized scores on the modified Rankin scale). Ordinal scores on the modified Rankin scale were analyzed with the use of ordinal logistic regression. Binary outcomes were also analyzed as time-to-event outcomes with the use of penalized survival models to estimate cause-specific hazard ratios and nonparametric	

cumulative incidence, from which risk differences and odds ratio.

Comparison groups	Early DOAC treatment v Late DOAC treatment
Number of subjects included in analysis	2013
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.99

Notes:

[2] - The main aim of the trial was to estimate the effect of early initiation as compared with later initiation of anticoagulation and to estimate the degree of precision of these estimates. Therefore, no statistical hypotheses as to superiority, inferiority, or noninferiority were tested.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse events and serious adverse events were recorded throughout the entire duration of the trial, from November 2017 to December 2022.

Adverse event reporting additional description:

The adverse event reporting period for each patient encompassed the time from when the participant signed the consent form until the last protocol-specific procedure has been completed, including a safety follow-up period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Details on all serious and non-serious adverse events can be found in the supplementary material.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2017	Version 1.1: Modification of background and rationale to include ethical considerations; specification of assumed event rate; introduction of post-hoc consent; addition of TIA and undetermined stroke as secondary outcomes; clarification of anonymisation procedures; update of preventive measures for female participants of childbearing potential; clarification of follow-up procedures; listing of relevant AEs; administrative changes.
27 October 2017	Version 1.3: Administrative changes
02 August 2018	Version 1.2: Clarification of trial schedule; modification of consenting procedure to include LAR; specification of major bleeding; clarification of stroke classification; update of safety monitoring strategy; administrative changes
07 February 2019	Version 1.5: Addition of separate appendices for country-specific information; addition of information on the future use of data; administrative changes.
03 October 2019	Version 1.4: Update of trial schedule; administrative changes
15 January 2021	Version 2.0: Deletion of IMP brand names; clarification of the primary outcome to emphasize the two main components of "major bleeding" (i.e. "extracranial major bleeding" and "symptomatic intracranial haemorrhage"); specification of the components of "major bleeding" (i.e. symptomatic intracranial haemorrhage and individual components of major extracranial bleeding) as secondary outcomes; modification of eligibility criteria to expand inclusion (1) to those with moderate renal impairment / (2) after transient DAPT; specification of criteria for IMP discontinuation; update of criteria for IMP dose reduction; administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37222476>