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

ELAN Investigators

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

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- Additional file 2: ELAN collaborators

ABSTRACT

Rationale: Direct oral anticoagulants (DOAC) are highly effective in preventing ischaemic strokes in people with atrial fibrillation (AF). However, it is unclear how soon they should be started after acute ischaemic stroke (AIS). Early initiation may reduce early risk of recurrence but might increase the risk of haemorrhagic complications.

Aim: To estimate the safety and efficacy of early initiation of DOACs compared to late guideline-based initiation in people with AIS related to AF.

Methods and design: An international, multicentre, randomised (1:1) controlled, two-arm, open, assessor-blinded trial was conducted. Early treatment is defined as DOAC initiation within 48 hours of a minor or moderate stroke, or at day 6–7 following major stroke. Late treatment is defined as DOAC initiation after day 3–4 following minor stroke, after day 6–7 following moderate stroke, and after day 12–14 following major stroke. Severity of stroke is defined according to imaging assessment of infarct size

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Sample size: ELAN will randomise 2000 patients 1:1 to early versus late initiation of DOACs. This assumes a risk difference of 0.5% favouring the early arm, allowing an upper limit of the 95% confidence interval up to 1.5% based on the Miettinen & Nurminen formula.

Outcomes: The primary outcome is a composite of symptomatic intracranial haemorrhage, major extracranial bleeding, recurrent ischaemic stroke, systemic embolism or vascular death at 30±3 days after randomisation. Secondary outcomes include the individual components of the primary outcome at 30±3 and 90±7 days and functional status at 90±7 days.

Discussion: ELAN will estimate whether there is a clinically important difference in safety and efficacy outcomes following early anticoagulation with a DOAC compared to late guideline-based treatment in neuroimaging-selected people with an AIS due to AF.

Trial registration:

ClinicalTrials.gov Identifier: NCT03148457

INTRODUCTION AND RATIONALE

Anticoagulation therapy with direct oral anticoagulants (DOAC) is highly effective in preventing recurrent ischaemic events in people with strokes related to atrial fibrillation (AF).[1] However, it is unclear how soon DOACs should be started after acute ischaemic stroke (AIS). Randomised controlled trials comparing DOACs with vitamin K antagonists for prevention of AF-related ischaemic strokes excluded people with a recent AIS.[2] Early anticoagulation with DOACs may reduce the risk of early recurrent ischaemic events but might also increase the risk of haemorrhagic complications (particularly intracranial bleeding), thus outweighing any beneficial effect.

In the absence of randomised-trial evidence, the European Heart Rhythm Association (EHRA) and the European Society of Cardiology suggest following the "1-3-6-12 day rule" for initiation of anticoagulation following AF-related transient ischaemic attack (TIA), minor, moderate and severe AIS.[3] Thus, anticoagulation can be initiated on day one in patients with TIA, on day three in those with mild stroke, on day 5–7 in those with moderate stroke and on day 12–14 in those with major stroke.[3] This is based on the observation that larger infarcts are more likely than smaller ones to undergo haemorrhagic transformation.[4,5] Many countries, societies and expert opinions have now adopted this recommendation.[2,6,7] However, real-world data suggest that DOACs might be safely used earlier than recommended following AIS, although this evidence is limited by selection bias or small randomised controlled trials.[2,8,9] Furthermore, the risk of both recurrent ischaemic and haemorrhagic stroke is highest in the first 2 days following stroke onset, meaning that randomised trials are needed to establish whether it is safe and beneficial to start DOACs early after AIS.[10] Neuroimaging selection may help minimise the risk of intracranial haemorrhage.[4,5]

The **E**arly versus **L**ate initiation of direct oral **A**nticoagulants in post-ischaemic stroke patients with atrial fibrillatio**N** (ELAN) aims to estimate the safety and efficacy of early initiation of

DOACs compared to late guideline-based initiation in imaging-selected patients with AIS and AF.

METHODS

Study design

ELAN is an international, multicentre, randomised (1:1) controlled, two-arm, open, assessor-blinded trial comparing early versus late initiation of DOACs in people with AIS and AF. The trial is being conducted in more than 90 stroke units in Europe, India, the Middle East and Japan. The first patient was enrolled in November 2017.

Patient population

ELAN will randomise 2000 patients with an AIS and AF. Inclusion and exclusion criteria are listed in Table 1. ELAN has a gender policy aiming at an equal representation of sex.

Randomization and blinding

Based on the infarct size on CT and/or MRI prior to randomisation, participants are classified as having experienced minor, moderate or major ischaemic stroke (Figure 1 and Table 2).[11] Classification of infarct size is done by the treating team and in case of rapid clinical improvement after admission, especially after intravenous thrombolysis and thrombectomy, study teams are strongly encouraged to perform repeat imaging before randomisation. The qualifying imaging for stroke classification is the last imaging performed prior to randomisation. Participants are assigned in a 1:1 ratio to one of the two treatment arms using deterministic minimisation implemented via a web-based data management system (secuTrial) to ensure concealment of allocation. Randomisation is performed within 48 hours after symptom onset in participants with minor and moderate stroke and at day 6–7 in participants with major stroke (Figure 2). Allocation is stratified by trial site, age (<70 years versus ≥70 years), stroke severity (minor, moderate or major stroke) and NIHSS score (<10 versus ≥10).

Treatment

Any DOAC with marketing authorisation for the prevention of stroke and systemic embolism in the respective countries can be used. Early treatment means initiation of DOAC within 48 hours in participants with minor and moderate stroke, or on day 6–7 in those with major stroke. Late treatment means initiation of treatment in participants with minor stroke on day 3–4, those with moderate stroke on day 6–7 and with major stroke on day 12–14. The late treatment times were chosen to be consistent with the "1-3-6-12 day rule".[3]

Clinical and imaging evaluation

All trial procedures are summarised in supplemental Table 1. The primary outcome is assessed at 30±3 days after randomisation by a structured telephone interview conducted by trained medical personnel unaware of the treatment allocation. If the patient is unable to participate in the interview, the next of kin or treating physician is asked. For every reported outcome event (bleeding, stroke, embolism and/or death), corresponding source documents are collected. An independent clinical event committee (CEC) reviews these documents and adjudicates all outcome events. The CEC also reviews serious adverse events and unclassified events to identify potential unreported outcome events. A central imaging core lab evaluates all clinical imaging data prior to randomisation as well as imaging performed up to 90±7 days after randomisation.

Primary outcome

The primary outcome is a composite binary endpoint. The occurrence of at least one of the following up to 30±3 days after randomisation is considered as an outcome event: symptomatic intracranial haemorrhage, major extracranial bleeding, recurrent ischaemic stroke, systemic embolism or vascular death.

Symptomatic intracranial haemorrhage, including subdural, epidural, subarachnoid and intracerebral haemorrhage, is defined as a haemorrhage that leads to a clinical worsening and hospitalisation or prolongation of hospitalisation, and is assessed by the treating physician to

be the likely cause of the new neurological symptom or the death. Major extracranial bleeding (major bleeds are those that result in death or are life-threatening) is defined as clinically overt bleeding accompanied by one or more of the following: decrease in haemoglobin of ≥2g/dl over a 24-hour period; transfusion of ≥2 units of packed red blood cells; or bleeding occurring in a critical part of the body (intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal). For bleeding in a critical area (e.g. gastrointestinal) or organ to be classified as major extracranial bleeding it must be associated with a symptomatic clinical presentation.[12]

Secondary outcomes

Secondary outcomes are the individual components of the primary endpoint at 30±3 and 90±7 days after randomisation, favourable outcome at 90±7 days defined as mRS ≤2, mRS shift analysis at 30±3 and 90±7 days, individual components of major extracranial bleeding at 30±3 and 90±7 days, all-cause mortality at 30±3 and 90±7 days, drug compliance measured after 30±3 days and the difference between treatment randomised and treatment received. The main safety endpoints are symptomatic intracranial haemorrhage, major extracranial bleeding and vascular death. The main efficacy endpoints are prevention of recurrent ischaemic stroke and systemic embolism, as well as favourable outcome at 90±7 days.

Other outcomes of interest

Further relevant safety variables are myocardial infarction at 90±7 days, TIA and undetermined stroke at 30±3 and 90±7 days, major cardiovascular events at 90±7 days as a composite of stroke, myocardial infarct, heart failure or cardiovascular death, NIHSS at 90±7 days and silent brain lesions at 90±7 days.

Data safety monitoring board (DSMB)

An independent DSMB is monitoring the trial. The DSMB met after the first 250 patients reached data maturity and again after the first 500 patients. Thereafter it meets at least once a year.

Hypothesis and statistical analysis

The main aim of ELAN is to estimate the effect of early versus late initiation of DOACs in AIS patients. Therefore, no specific statistical hypothesis will be tested. The analysis plan will focus on estimating the treatment effect and its uncertainty by calculating 95% confidence intervals.

Sample size calculation

The sample size is estimated based on the precision of the estimation as reflected by the width of the confidence interval around the treatment effect estimate, i.e. the risk difference for the primary outcome. With 1,802 patients, an assumed event rate in the late treatment group of 5% at the trial end, and an assumed risk difference of −0.5% (i.e. an assumed event rate of 4.5% in the early treatment group), the upper limit of the 95% confidence interval will be up to 1.5% (based on Miettinen & Nurminen's formula) favouring the control group. This means that the resulting 95% CI will exclude values suggesting that early treatment increases the rate of the composite primary outcome by more than 1.5%. To account for possible missing outcome data, we plan to randomise 2,000 participants.

Statistical analysis

For the primary analysis, to avoid bias due to a small number of events, we will compare the event rate between late treatment and early treatment using a logistic regression model corrected for the bias via a penalised likelihood method.[13] The effect measure will be the odds ratio. Unadjusted analysis using Mantel-Haenszel risk difference will also be calculated along with the Miettinen & Nurminen confidence interval as sensitivity analyses. Details are provided in the statistical analysis plan. The variable mRS (scale with seven levels) will be analysed using mixed-effects ordered logistic regression. Continuous outcome data will be analysed

using linear regression. Time-to-event outcomes will be described using Kaplan-Meier curves and analysed using penalised survival methods.[14] The use of three stratification factors combined with over 90 recruiting sites may lead to imbalances in the randomization process. However, to overcome this problem the deterministic minimisation method has been implemented for allocation to reduce the impact of imbalances.

Interim analysis

Regular monitoring of outcome data, especially haemorrhage and ischaemic events, will be performed by the DSMB. The DSMB charter sets out thresholds for treatment effects and criteria based upon which it can recommend an early stopping of the trial or additional analysis. The thresholds are indicative of potential unacceptable harmful effects but are not binding.

Study organisation and funding

ELAN is an investigator-initiated clinical trial. The sponsor of the trial is the University Hospital Bern (Inselspital) and the trial is supported by grants from the Swiss National Science Foundation (32003B_197009; 32003B_169975), the Swiss Heart Foundation, the UK Stroke Association (2017/02) and the Intramural Research Fund (20-4-5) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Centre, Japan. The clinical trial is managed by the Neuro Clinical Trial Unit at the Department of Neurology, University Hospital Bern, Switzerland. The database, central data monitoring and statistical analyses are performed by the CTU Bern at the University of Bern, Switzerland.

Ethical approval

Ethical approval for the study was granted by the Cantonal Ethics Commission (KEK) in Bern, Switzerland and subsequently by all local authorities and/or, if applicable, by national lead ethics committees and competent regulatory authorities at all participating sites.

Trial status

On 30 March 2022, 1,649 patients had been randomised into the ELAN trial. Information of baseline characteristics of the first 1000 patients randomised are provided in supplemental table 2.

DISCUSSION

ELAN is a global pragmatic randomised controlled trial addressing an important unanswered clinical dilemma, whether it is safe and beneficial to start anticoagulation therapy with DOACs early on after an AF-related AIS. Observational studies suggest that the risk of recurrent stroke is seven times higher than the risk of haemorrhagic transformation early on after recent stroke, yet the fear of harming the patient by starting anticoagulation too early prevents many physicians from doing so.[15] In the absence of evidence, many physicians worldwide have adopted the "1-3-6-12 day rule".[3] This approach is supported by an expert opinion statement by the European Stroke Organisation.[4] However, it may be beneficial to start DOAC therapy earlier. The ELAN trial therefore compares an earlier treatment start (i.e. within 48 hours of a minor or moderate stroke and at day 6–7 after a major stroke) with this current standard of care.

Given that haemorrhagic transformation is dependent on lesion size, ELAN uses an imaging-based approach to exclude patients with early parenchymal haemorrhage, which can be easily detected on a CT scan prior to randomisation. Infarct size on imaging prior to randomisation is also used to classify participants according to whether they have minor, moderate or major stroke. This is in contrast to the EHRA guideline, which classifies stroke severity based on the NIHSS score.[3] We chose our approach because the NIHSS score is strongly influenced by infarct location as well as lesion size.[4,5] For example, patients with a deep or brainstem stroke can have a high NIHSS score but a low infarct volume, and patients with large cerebellar or non-dominant hemispheric infarction may have a relatively low NIHSS.

In the ELAN trial we will estimate the treatment effect and the degree of precision by calculating the odds ratio of the predefined outcomes and the corresponding 95% CI. The trial has not been designed to statistically test a specific statistical hypothesis, nor is it a non-inferiority trial. The rationale for this decision is twofold. First, when we designed the trial, there was a lack of high-quality data on event rates in this setting, making it difficult to identify an appropriate non-inferiority margin. Second, the assumed low event rate would require a very large trial to assess either superiority or non-inferiority and this would not necessarily provide greater clarity concerning patient management. ELAN is already one of the largest trials in this population with many participating sites that have been enrolling patients over several years. Although we propose a different analytic approach to that often seen in clinical trials, this should not hinder interpretation of trial data or their clinical utility. We also believe that the complexity of managing patients with AF early on after AIS precludes simplified dichotomous decision-making and necessitates some leeway for individual decision-making. This is best supported by estimation rather than statistical hypothesis-testing, and, where there is insufficient clinical information, this is an accepted approach.[16,17,18]

ELAN is one of several contemporaneous randomised controlled trials comparing early versus late anticoagulation with DOACs in people with AIS and AF (supplemental table 3). ELAN differs from the Swedish TIMING (NCT02961348) and the British OPTIMAS (NCT03759938) trials by randomising people with minor and moderate strokes within 48 hours, by its imaging-based approach and by comparing the ultra-early initiation with the 1-3-6-12 rule, which has become the standard of care for many physicians. In contrast to the American STAR (NCT03021928) trial, ELAN also includes patients with large infarct volumes. Furthermore, ELAN is a pragmatically designed global trial with sites in Europe, the Middle East and Asia, intending to provide easily applicable results for worldwide use. All four trials have their own strengths, and individual patient-data meta-analyses of all these trials are planned.

SUMMARY AND CONCLUSIONS

ELAN will establish whether there is a clinically important difference in efficacy and safety outcomes of early treatment with a DOAC compared to late guideline-based treatment, in neuroimaging-selected people with an AIS related to AF. The ELAN trial has the potential to resolve a major clinical dilemma for many stroke physicians, to change future stroke guidelines and to benefit patients.

References

1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet (London, England)* 2014; 383:955–962.
2. Seiffge DJ, Werring DJ, Paciaroni M, et al., for the ELAN, OPTIMAS, START and TIMING steering committees: Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. *Lancet Neurol* 2019; 18: 117–126.
3. Heidbuchel H, Verhamme P, Alings M, et al. EHRA Practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013; 34: 2094–2106.
4. Paciaroni M, Agnelli G, Ageno W, et al. Timing of anticoagulation therapy in patients with acute ischaemic stroke and atrial fibrillation. *Thromb Haemost*. 2016; 116:410–416.
5. Paciaroni M, Agnelli G, Falocci N, et al. Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) Study. *J Am Heart Assoc* 2017; 6.
6. Klijn CJ, Paciaroni M, Berge E, et al.. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J* 2019; 4):198–223. doi: 10.1177/2396987319841187. Epub 2019 Apr 9. PMID: 31984228
7. Jung S, Mattle H, Horvath T, et al. Stroke Guidelines of the Bern Stroke Network.2021. Available at: http://www.neurologie.insel.ch/fileadmin/Neurologie/Dokumente/Stroke_Center/Stroke_Guidelines_2021_English.pdf.
8. De Marchis GM, Seiffge DJ, Schaedelin S, et al. Early versus late start of direct oral

anticoagulants after acute ischaemic stroke linked to atrial fibrillation: an observational study and individual patient data pooled analysis. *J Neurol Neurosurg Psychiatr* 2022; 93:119–125.

9. Hong KS, Kwon SU, Lee SH, et al. Phase 2 Exploratory Clinical Study to Assess the Effects of Xarelto (Rivaroxaban) Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients With Non-valvular Atrial Fibrillation (Triple AXEL) Study Group. Rivaroxaban vs Warfarin Sodium in the Ultra-Early Period After Atrial Fibrillation-Related Mild Ischemic Stroke: A Randomized Clinical Trial. *JAMA Neurol* 2017; 74:1206–1215.
10. Abdul-Rahim AH, Fulton RL, Tatlisumak BFT, VISTA collaborators. Association of improved outcome in acute ischaemic stroke patients with atrial fibrillation who receive early antithrombotic therapy: analysis from VISTA. *Eur J Neurol*. 2015; 22:1048–1055.
11. Paciaroni M, Agnelli G, Falocci N, et al. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. *Stroke* 2015; 46:2175–2182
12. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3:692–694.

13. King G, Zeng L. Logistic Regression in Rare Events Data. *Polit Anal* 2001; 9:137–163.
14. Ambler G, Seaman S, Omar RZ. An evaluation of penalised survival methods for developing prognostic models with rare events. *Stat Med* 2012; 31:1150–1161.
15. Seiffge DJ, Traenka C, Polymeris A, et al. Early start of DOAC after ischemic stroke: Risk of intracranial hemorrhage and recurrent events. *Neurology* 2016; 87:1856–1862.
16. Sterne JAC, Smith GD. Sifting the evidence - what's wrong with significance tests? *BMJ* 2001; 322:226–231.
17. Greenland S et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* 2016; 31:337–350.
18. Szucs D, Ioannidis JPA. When null hypothesis significance testing is unsuitable for research: a reassessment. *Front Hum Neurosci* 2017; 11:390.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
• Written informed consent according to country-specific requirements
• Age ≥18 years
• Acute ischaemic stroke, either confirmed by MRI or CT scan (tissue-based definition) or by sudden focal neurological deficit of presumed ischaemic origin that persisted beyond 24 hours and otherwise normal non-contrast CT scan. Intravenous or endovascular treatment prior to randomisation is allowed.
• Permanent, persistent or paroxysmal spontaneous AF previously known or diagnosed during the index hospitalisation
• Agreement of treating physician to prescribe DOACs
Exclusion criteria
• AF due to reversible causes (e.g. thyrotoxicosis, pericarditis, recent surgery, myocardial infarct)
• Valvular disease requiring surgery
• Mechanical heart valve(s)
• Moderate or severe rheumatic mitral stenosis. Participants with other valvular diseases and biological valves are eligible
• Conditions other than AF that require anticoagulation, including therapeutic doses of low-molecular-weight heparin or heparin
• Anticoagulation above the relevant thresholds at ischaemic stroke onset or at hospital admission as follows: o vitamin K antagonist: International Normalized Ratio (INR) ≥ 1.7, or o anti-IIa: thrombin time ≥ 80 seconds and/or anti-IIa ≥ 100 ng/ml and/or aPTT value > 1.5× normal, or o anti-Xa: anti-Xa ≥ 100 ng/ml or ≥ 0.7 U/ml
• Contraindications to DOACs
• Females with a positive pregnancy test at time of randomisation, a suspicion of pregnancy, or lactating
• Patients with serious bleeding in the last 6 months or at high risk of bleeding (e.g. active peptic ulcer disease, platelet count < 100,000/mm^3 or haemoglobin < 10 g/dl or INR ≥ 1.7, documented haemorrhagic tendencies or blood dyscrasias)
• Subject currently uses or has a recent history of illicit use of drug(s) or abuses alcohol
• Severe comorbid condition with life expectancy < 6 months
• Severe renal impairment as described in the summary of medicinal product characteristics for the chosen DOAC (e.g. rivaroxaban, apixaban and edoxaban creatinine clearance <15 ml/min; dabigatran creatinine clearance <30 ml/min)
• Patient requires haemodialysis or peritoneal dialysis
• Patient with aortic dissection
• Current participation in another investigational trial

• Dual antiplatelet therapy (DAPT) at baseline or a strong likelihood of being treated with DAPT during the course of the trial. Transient DAPT is not an exclusion criterion if it is stopped prior to randomisation.
• CT or MRI evidence of haemorrhage classified as PH1 (defined as parenchymal haemorrhage = blood clots in < 30% of the infarcted area with or without slight space-occupying effect) and PH2 (defined as blood clots in > 30% of the infarcted area with a substantial space-occupying effect) independently of clinical deterioration. HI1 (defined as haemorrhagic infarct = small petechiae along the margins of the infarct) and HI2 (defined as confluent petechiae within the infarcted area but no space-occupying effect) are acceptable if not associated with clinical deterioration and if the treating physician feels comfortable about treating these patients with DOACs.
• CT or MRI evidence of mass effect or intracranial tumour (except small meningioma)
• CT or MRI evidence of cerebral vasculitis
• Endocarditis
• Evidence of severe cerebral amyloid angiopathy if MRI scan performed

AF: atrial fibrillation; aPTT: activated partial thromboplastin time; CT: computed tomography; INR: International Normalised Ratio; MRI: magnetic resonance imaging; DAPT: dual antiplatelet therapy; DOACs: direct oral anticoagulants; HI: haemorrhagic infarction; PH: parenchymatous haematoma.

Table 2. Ischaemic stroke size classification

Minor	**Moderate**	**Major**
Lesion is ≤ 1.5 cm in anterior or posterior circulation	Lesion is in a cortical superficial branch of the middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of the posterior cerebral artery, in a cortical superficial branch of the anterior cerebral artery	**Anterior:** lesion involves the complete territory of MCA, posterior cerebral artery, or anterior cerebral artery, in two cortical superficial branches of MCA, in a cortical superficial branch of MCA associated with the MCA deep branch or in > 1 artery territory (e.g. MCA associated with anterior cerebral artery territories) **Posterior:** lesion is ≥ 1.5 cm in the brainstem or cerebellum
Caveat: multiple minor tiny spots (embolic shower) = minor stroke	**Caveat**: two minor lesions = moderate lesion (the sum of the lesions)	**Caveat**: two moderate lesions = large lesion

Ischaemic stroke size classification is based on: Paciaroni M, Agnelli G, Falocci N, et al. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. *Stroke* 2015; 46(8): 2175–82.

Figure 1. Stroke size classification

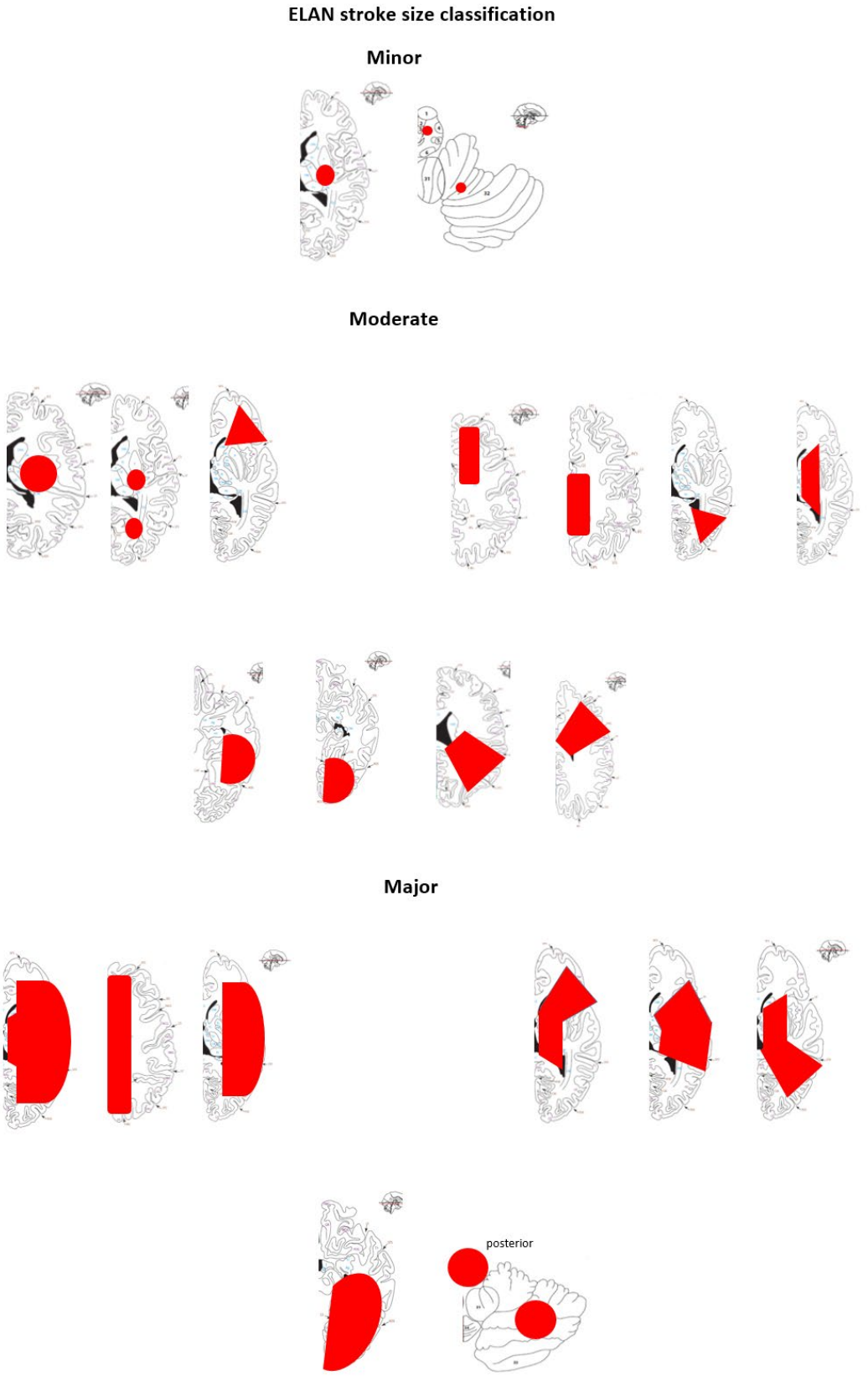
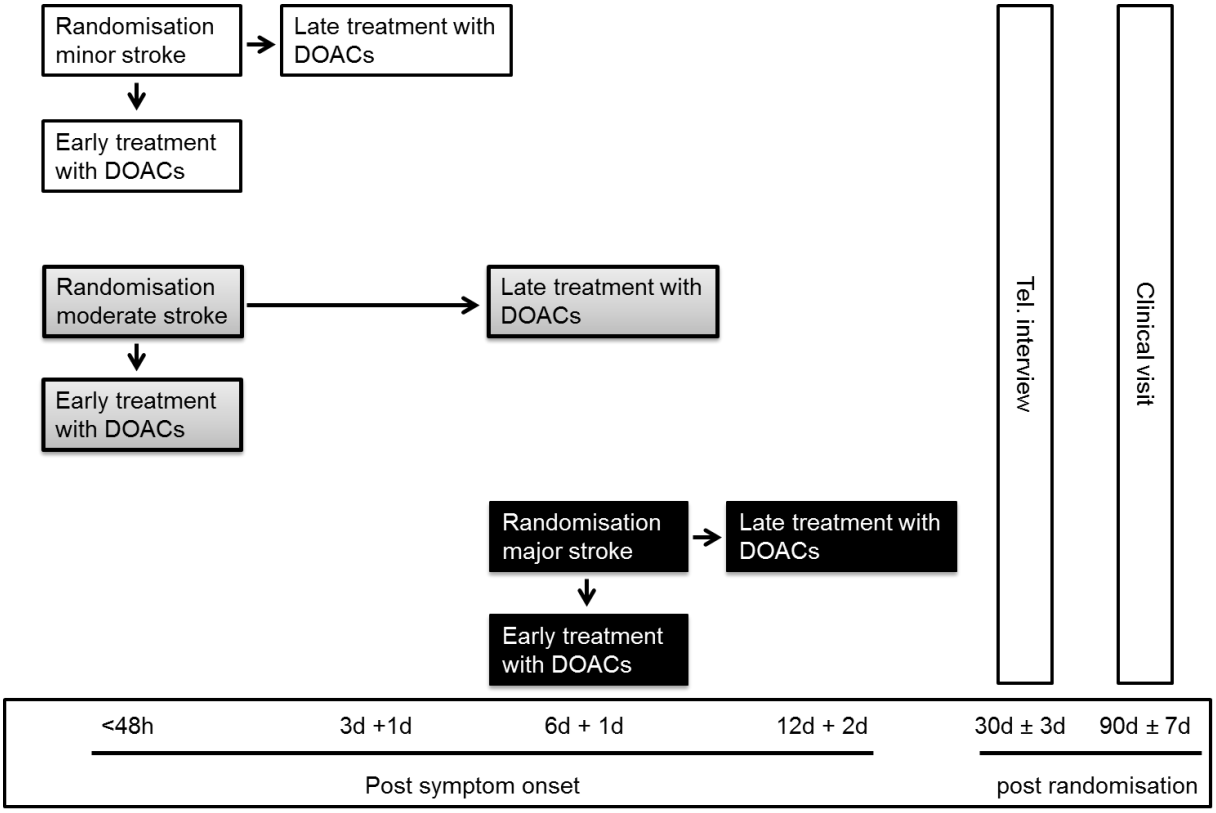


Figure 2. Trial schedule



DOAC, direct oral anticoagulants; Tel., telephone; h, hours; d, days

Author contributions

The following authors designed the ELAN trial protocol: UD, ST, MB, GS, MP, DS, GT, GN, LB, PM, KN, and JD. UF, MB and JD drafted the publication of the protocol and all other authors have revised the manuscript and made critical comments.

Appendix

Abbreviations

AF	atrial fibrillation
AIS	acute ischaemic stroke
CEC	Clinical Event Committee
DAPT	dual antiplatelet therapy
DSMB	Data Safety Monitoring Board
EHRA	European Heart Rhythm Association
INR	International Normalized Ratio
MCA	middle cerebral artery
SAE	serious adverse events

Supplemental Table 1: Table of trial procedures and assessments

Minor or Moderate Stroke	**Screening**	**Treatment, Intervention Period**						**Follow-up**
Visit	1	2	3	4	5	6	7	8
Time from symptom onset (visit 1 – 6)	<48h	<48h	<48h	3d + 1d	6d +1d	12d + 2d		
Time from randomisation (visit 7 – 8)							30d ± 3d	90d ± 7d
Patient information and informed consent	x							x*
Inclusion and exclusion criteria	x							
Demographics	x							
Pregnancy test	x							
CT / MRI scan	x							
Laboratory tests	x							
Medical history	x							
Vital signs	x							
NIHSS	x							x
mRS	x						x	x
Randomisation		x						
Minor stroke – early treatment: administration of DOAC			x					
Minor stroke – late treatment: administration of DOAC				x				
Moderate stroke – early treatment: administration of DOAC			x					
Moderate stroke – late treatment: administration of DOAC					x			
Minor stroke – early treatment: Concomitant medication or procedure including adverse events			x				x	x
Minor stroke – late treatment: Concomitant medication or procedure including adverse events				x			x	x
Moderate stroke – early treatment: Concomitant medication or procedure including adverse events			x				x	x
Moderate stroke – late treatment: Concomitant medication or procedure including adverse events					x		x	x
Telephone interview							x	(x)
Clinical visit								x

*: if informed consent was given by patient's next of kin/legally authorized representative and/or independent physician
NIHSS, National Institutes of Health Score Scale; mRS, modified Rankin Scale; DOACs, direct oral anticoagulants
(x) if patient is not able or willing to attend the clinical visit

Major stroke					**Screening**			**Follow-up**
					Treatment, Intervention Period			
Visit	1	2	3	4	5	6	7	8
Time from symptom onset (visit 1 – 6)	<48h	<48h	<48h	3d + 1d	6d +1d	12d + 2d		
Time from randomisation (visit 7 – 8)							30d ± 3d	90d ± 7d
Patient information and informed consent					x°			x*
Inclusion or exclusion criteria					x			
Demographics					x#			
Pregnancy test					x#			
CT / MRI scan					x#			
Laboratory tests					x#			
Medical history					x			
Vital signs					x			
NIHSS					x			x
mRS					x		x	x
Randomisation					x			
Major stroke – early treatment: administration of DOAC					x			
Major stroke – late treatment: administration of DOAC						x		
Major stroke – early treatment: Concomitant medication or procedure including adverse events					x		x	x
Major stroke – late treatment: Concomitant medication or procedure including adverse events						x	x	x
Telephone interview							x	(x)
Clinical visit								x

*: if informed consent was given by patient's next of kin/LAR and/or independent physician
#: These examinations may be performed between onset of symptoms and randomisation. The sponsor-investigator recommends performing these examinations on the day of randomisation.
NIHSS, National Institutes of Health Score Scale; mRS, modified Rankin Scale; DOACs, direct oral anticoagulants
(x) patient is not able or willing to attend the clinical visit

°: Informed consent must be obtained before any trial-related procedure is performed.

Supplemental Table 2

	Total (N = 1000)
Age at Informed Consent (years)	76 (±10)
NIHSS (before randomisation)	3.0 [1.0; 6.0]
NIHSS (dichotomized)	
NIHSS < 10	830 (83%)
NIHSS ≥ 10	170 (17%)
Classification of stroke	
Minor	363 (36%)
Moderate	392 (39%)
Major	245 (25%)
Sex	
Male	557 (56%)
Female	443 (44%)
Weight (kg)	78 (±17)
Blood pressure systolic (mmHg)	140 (±22)
Blood pressure diastolic (mmHg)	79 (±14)
Heart rate at reast (beat/min)	79 (±18)
Body temperature (°C)	37 (±0.6)

Premodified mRS (prior stroke)	
0	671 (67%)
1	151 (15%)
2	84 (8%)
3	59 (6%)
4	30 (3%)
5	5 (1%)

Descriptive baseline characteristics displayed with frequencies and percentage for categorical variables and mean with standard deviation or median with interquartile range for continuous variables.

Supplemental Table 3

Title	***ELAN*** *"Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients with Atrial fibrillation"*	***OPTIMAS*** *"OPtimal TIMing of Anticoagulation after AF-associated acute cardio-embolic ischaemic Stroke"*	***TIMING*** *"Timing of oral anticoagulant therapy in acute ischaemic stroke with atrial fibrillation"*	***START*** *"Optimal Delay Time to Initiate Anticoagulation After Ischaemic Stroke in Atrial Fibrillation"*
Planned sample size	2000 NCT03148457	3478 NCT03759938	3000 NCT02961348	1500 NCT03021928
Intervention: early start	<48 hours after onset (minor and moderate stroke) or at day 6 + 1 day after symptom onset (major stroke)	≤ day 4 after ischaemic stroke	≤ day 4 after ischaemic stroke	Adaptive trial design: time-to-treatment delay of 3, 6, 10 or 14 days in mild/moderate. 6,10,14 or 21 days in severe
Control: late start	Current recommend-dations (i.e. minor stroke after 3+1, moderate stroke after 6+1 and major stroke after 12 + 2 days).	between day 7 and day 14 after acute stroke	between day 5 and day 10 after acute stroke	
Follow-up period	30 days (secondary outcomes	90 days	90 days	30 days (secondary outcomes after

	after 90 days)			90 days)
Primary outcome	Composite outcome (major bleeding (i.e. symptomatic intracranial haemorrhage and major extracranial bleeding), recurrent ischaemic stroke, systemic embolism and/or vascular death)	Composite outcome (efficacy): recurrent ischaemic stroke, systemic embolism and/or vascular death. Principle safety outcome: major bleeding	Composite outcome (recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality)	Composite of any CNS haemorrhagic or other major haemorrhagic events and ischaemic events (stroke or systemic embolism) within 30 days
Patients with haemorrhagic transformation included	yes	yes	yes	yes
NIHSS exclusion criteria	No exclusion criteria	No exclusion criteria	No exclusion criteria	>3 and <23
Estimated end of study	10/2021	2021/22	12/2020	08/2021