OPTIMAS scientific update: five key messages following the publication of the ELAN clinical trial

The results of the Early versus Later ANticoagulation for stroke with atrial fibrillation (ELAN) were announced during the recent European Stroke Congress in Munich and published in the New England Journal of Medicine[1] on the 23rd of May.

Summary of ELAN

Methods: ELAN was a partially blinded randomised controlled trial, where patients with acute ischaemic stroke secondary to AF were randomised 1:1 into early versus later initiation of anticoagulation with a direct oral anticoagulant (DOAC). Participants were divided into three groups depending on infarct size, and the definitions of early and later initiation varied according to size:

Stroke severity (infarct size)	***Early group***	***Later group***
Minor (infarct < 1.5 cm)	<48 hours	Day 3 or 4
Moderate (branch ACA, MCA, or PCA infarct)	<48 hours	Day 6 or 7
Severe (full territory cerebral artery infarct, brainstem or cerebellar infarct >1.5 cm)	Day 6 or 7	Day 12-14

The primary outcome was the incidence of a composite of recurrent ischaemic stroke, systemic arterial embolism, symptomatic intracranial haemorrhage, major extracranial bleeding and vascular death.

Results: 2013 participants enrolled, 1006 assigned to early anticoagulation and 1007 to later anticoagulation. There was a lower primary outcome event in the early group compared to the later group, 29 events (2.9%) vs 41 (4.1%), risk difference -1.2%, 95% CI -2.84 to 0.47. The direction of effect of the intervention favours early anticoagulation, but the results were not statistically significant.

Since the clinical question in ELAN is similar to that of OPTIMAS, we have prepared this brief summary of five key messages emerging from the results to explain what they mean for ongoing recruitment into OPTIMAS.

1. *Early anticoagulation was found to be safe in the trial population*

There was a very low incidence of symptomatic intracranial haemorrhage in both arms of the trial (just 2 in each arm). However, on average the stroke severity in ELAN was less than in OPTIMAS (median (IQR) 3 (1 to 6), vs 4 (2 to 7)), and, unlike OPTIMAS, ELAN excluded people with mild bulk haemorrhage within the infarct (PH type 1). Therefore, we need to continue to enrol into OPTIMAS to confirm this important safety question for more severe strokes.

2. *The results support the main hypothesis of OPTIMAS but are inconclusive*

ELAN found a lower incidence of the primary outcome (a composite of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, systemic embolism, major extracranial bleeding or vascular death), and a lower incidence of recurrent ischaemic stroke in the early group (2.9%) compared to the late group (4.1%). This is encouraging, as it supports our hypothesis that early anticoagulation will be at least as effective as late anticoagulation. However, their results were not statistically significant at the 5% level (adjusted odds ratio 0.70, 95% CI 0.44 to 1.14), and could not demonstrate superiority, so the research question of OPTIMAS has not been definitively answered. The results of ELAN therefore strongly encourage ongoing recruitment into OPTIMAS, especially for people with moderate to severe strokes.

3. *ELAN did not enrol participants already anticoagulated at the time of stroke*

Therefore, there is no data on this group of patients. So far, about 25% of participants enrolled into OPTIMAS were already anticoagulated, so if we demonstrate non-inferiority or superiority of early anticoagulation, our results will also apply to this important group who may be at especially high recurrence risk. These patients should be prioritised for enrolment into OPTIMAS.

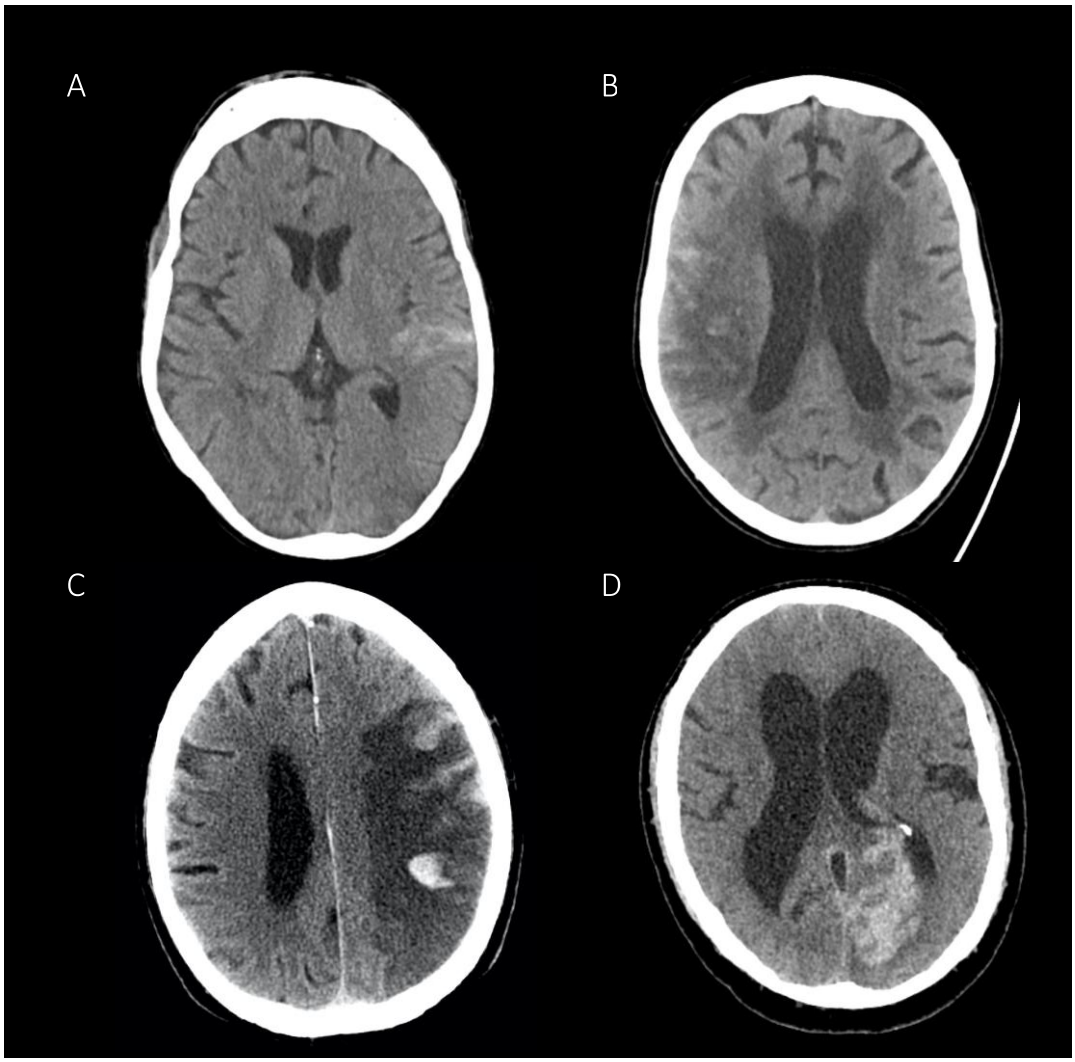
4. *We need more data on people with moderate to severe stroke*

ELAN enrolled a relatively low number of patients with severe stroke (17% with NIHSS ≥ 10, 23% with large infarcts). Interestingly, they found a statistically significant lower outcome rate of the composite primary outcome for those randomised to early anticoagulation in this group (risk difference -3.04%, 95% CI -5.57 to -0.51 for NIHSS ≥ 10). These results have to be interpreted with caution since the numbers in this group were relatively small, but it means that this group (i.e., NIHSS ≥5) should be prioritised for ongoing enrolment into OPTIMAS so we can hopefully validate this important finding.

5. ELAN excluded those with significant haemorrhagic transformation at baseline

Although ELAN permitted enrolment for petechial haemorrhage (HI1 or HI2 according to the Heidelburg classification[2]), more significant haemorrhagic transformation (PH type 1) was an exclusion criterion. The eligibility criteria for OPTIMAS additionally permit enrolment of parenchymal haemorrhage 1 (space-occupying haemorrhage involving <30% of the infarct volume, please see the figure below for more details). If we can demonstrate non-inferiority or superiority of early anticoagulation overall, our results will be more broadly generalisable to include those with haemorrhagic transformation.

Fig. 1: Heidelberg classification of haemorrhagic transformation[2]



A) HI1; scattered small petechiae, no mass effect
B) HI2; confluent petechiae, no mass effect
C) PH1; haematoma within infarcted tissue, occupying <30%, no substantive mass effect3, excluded from ELAN but not OPTIMAS
D) PH2; haematoma occupying 30% or more of the infarcted tissue, with obvious mass effect, excluded from OPTIMAS

References

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2. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, Treurniet KM, Majoie CB, Marquering HA, Mazya MV, San Román L, Saver JL, Strbian D, Whiteley W, Hacke W. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. Stroke. 2015 Oct;46(10):2981-6. doi: 10.1161/STROKEAHA.115.010049. Epub 2015 Sep 1. PMID: 26330447.
3. Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 23422