OPTIMAS Scientific Update: Equipoise

Equipoise and enrolling into OPTIMAS

Like all randomised controlled trials, OPTIMAS aims to enrol participants for whom there is equipoise regarding the best treatment. In OPTIMAS, this means that participants can be enrolled if the treating clinician thinks that the optimal timing to begin anticoagulation is uncertain. Recently, we have had requests from sites for guidance on the patients for whom equipoise, or uncertainty, should exist.

What does the trial protocol say?

An international group of stroke physicians and neurologists, haematologists, and clinical trials specialists contributed to our trial protocol. Based on their expert opinion, we decided to specifically exclude only participants with the most severe form of haemorrhagic transformation – that is, parenchymal haematoma type 2 by the ECASS classification (a confluent haematoma occupying at least one-third of the infect volume, exerting mass effect beyond it). However, we considered that there was insufficient evidence to exclude participants based on infarct size alone, or the presence of less severe haemorrhagic transformation.

What do international guidelines say?

Numerous guidelines exist covering the timing of anticoagulation initiation after ischaemic stroke in patients with atrial fibrillation. Older guidelines have sometimes referenced the '1-3-6-12' rule – the guidance (based on expert opinion) that anticoagulation should be initiated on day 3 in mild stroke, day 6 for moderate stroke, and day 12 for severe stroke (1). Several newer guidelines recognise that a lack of evidence in this area precludes specific recommendations and encourage recruitment into randomised controlled trials instead (2–4). The European Society of Cardiology's guidelines no longer suggests using infarct size or severity to guide anticoagulation timing, recognising evidence that larger infarct size is a risk factor for recurrent ischaemic stroke as well as haemorrhagic transformation (5).

Guideline	**Date**	**Summary of recommendations**
CHEST	2018	Oral anticoagulation should usually be started within two weeks. The optimal timing within this period is not known. Infarct size is predictive of early recurrence, haemorrhagic transformation, and poor outcome, so might not be helpful in determining the net benefit of early treatment.

European Stroke Organisation	2019	No recommendation based on randomised trials possible. Inclusion of patients in ongoing randomised trials of early anticoagulation encouraged.
European Society of Cardiology and EACTS	2020	Robust data to inform optimal timing are lacking. Initiate as soon as considered possible from neurological perspective. Whereas infarct size/stroke severity is used clinically to guide timing of OAC initiation, the usefulness of such an approach in estimating the net benefit of early treatment may be limited.

Is there any evidence from randomised controlled trials?

Only one randomised controlled trial has reported results addressing a similar research question to OPTIMAS – the TIMING study, which was presented at the European Stroke Organisation Conference this year (6). Based on a study sample of approximately 900 participants (out of a target of 3000), the study found that early anticoagulation (defined as 0 – 5 days; actual median initiation time 3 days) with a DOAC was of similar efficacy to delayed anticoagulation (defined as 0 – 5 days; actual median initiation time 5 days) in patients who mainly had minor stroke (median NIHSS 3). It was unable to show which strategy was superior, and the implications of its result for patients with moderate or severe stroke are uncertain.

What do observational studies show?

We summarised the evidence available at the start of the OPTIMAS trial in a review in the Lancet Neurology (7). Two additional observational studies of particular interest that have reported since are the ABC and SAMURAI-NVAF studies (8,9). Overall, the observational data suggest that early anticoagulation (usually within 5 days of stroke onset) with a DOAC is associated with a very low rate of symptomatic intracranial haemorrhage or clinically significant haemorrhagic transformation in patients with milder stroke (usually NIHSS <5), and this rate is consistently lower than the rate of recurrent ischaemic stroke. However, observational studies cannot tell us the best time to begin anticoagulation, and are inherently limited by selection bias and unmeasured confounding.

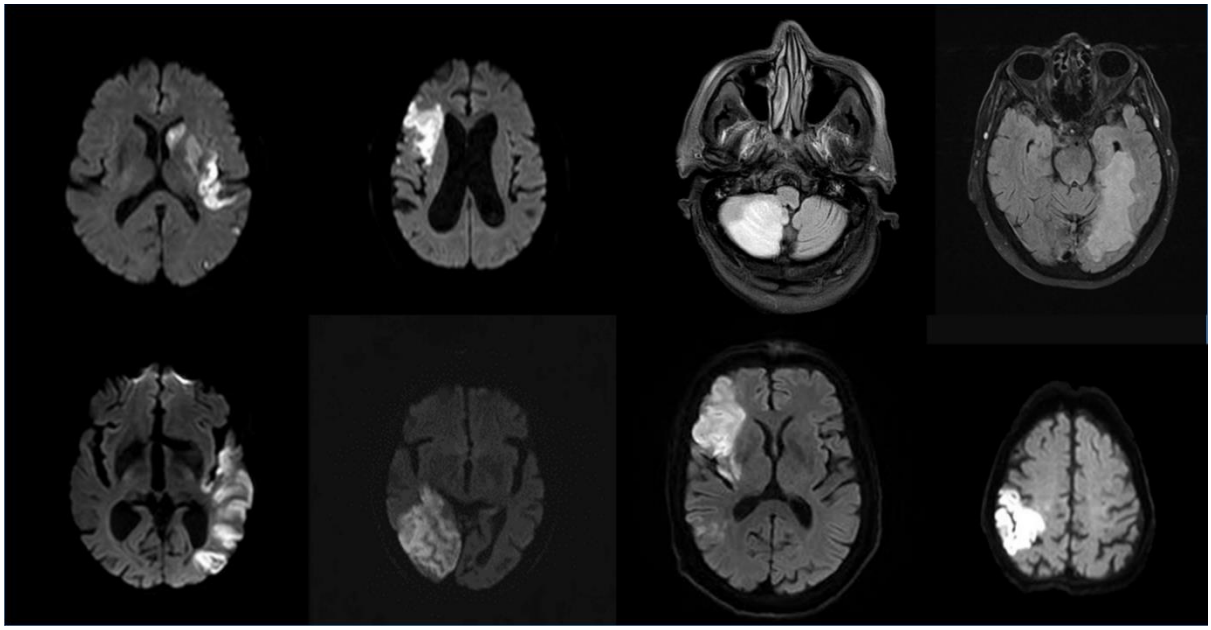
What sort of patients are currently being enrolled into OPTIMAS?

We recently reviewed data on the NIHSS scores of the first 1200 participants enrolled into OPTIMAS. Over half of participants had an NIHSS of 5 or more at randomisation, and around one-quarter had an NIHSS of 11 or more. This is similar to the overall distribution of NIHSS scores for unselected ischaemic

stroke patients nationally, based on SSNAP data, meaning that results obtained in the OPTIMAS population should be generalisable to the national population of patients with stroke.

NIHSS	OPTIMAS	SSNAP
0 - 4	40.4%	53.9%
5 - 10	34.0%	32.7%
11 - 15	11.6%	
16 - 20	9.2%	5.6%
21+	4.8%	7.8%

The participant imaging received to date also shows that patients with larger strokes (such as large cerebellar or PCA infarcts, and MCA branch infarcts) are being enrolled into OPTIMAS. Examples are shown below. Importantly, an Independent Data Monitoring Committee meets regularly to review interim data from the trial, and has not raised concerns regarding participant safety.



So which patients should we enrol into OPTIMAS?

Given the lack of high-quality data in this area, and in accordance with international guidelines, we encourage investigators to consider randomising any patient meeting our eligibility criteria. For patients with milder strokes, we still need to definitively know whether early or later anticoagulation is superior. For patients with moderate or severe strokes, there remains very limited evidence to guide

treatment, and we think that the finding from TIMING that early anticoagulation appears safe in patients with minor stroke is encouraging regarding the recruitment of more severely affected patients. The more representative the patients enrolled into OPTIMAS are of the patients we see in day-to-day clinical practice, the better the results of OPTIMAS will be able to guide clinical practice and improve patient care in the future.

References:

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