SUPPLEMENTAL MATERIAL

Online Supplement for manuscript entitled:

A survey of opinion: When to start oral anticoagulants in patients with acute ischaemic stroke and atrial fibrillation?

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Supplemental Data

Supplemental Tables: I - II

Supplemental Data : Survey Questions, Case Scenarios and Answers

Question 1. Do you work in a hyperacute or acute stroke unit caring for patients within the first few days of a stroke?

Rank value	Option	Count
1	Yes	117
2	No	4

Question 2. What is your parent speciality?

Rank value	Option	Count
1	Acute internal medicine	5
2	Cardiology	0
3	Clinical pharmacology and therapeutics	4
4	Emergency medicine	0
5	General internal medicine	2
6	Geriatric medicine	88
7	Neurology	18
8	Rehabilitation medicine	1
9	Other	3

Question 3. Have you completed the speciality training year in stroke medicine?

Rank value	Option	Count
1	Yes	42
2	No	79

Question 4. Which country are you based?

Rank value	Option	Count
1	England	65
2	Northern Ireland	5
3	Scotland	37
4	Wales	13

Question 5. Would you be willing to randomise patients with non-valvular atrial fibrillation (AF) and recent stroke to a clinical trial of early (within first few days) vs. later initiation of oral anticoagulant (OAC) drugs?

Rank value	Option	Count
1	Yes	104
2	No	14

Question 6. Which OAC drug class do you currently use early after ischaemic stroke in patients with AF?

Rank value	Option	Count
1	Vitamin K Antagonists	0
2	NOACs (novel oral anticoagulants)	60
3	It varies in different patients	60
4	Heparinoids	1

Question 7. Would you be more comfortable randomsing patients to a trial of early OAC use after stroke if the drugs used were:

Rank value	Option	Count
1	Vitamin K Antagonists	0
2	NOACs	51
3	No preference	29
4	Allowed to vary in different patients	39

Question 8. Do you think there is uncertainty regarding the optimal time to initiate OAC drugs after stroke?

Rank value	Option	Count
1	Yes	115
2	No	6

Question 9. Do you use the 1-3-6-12 rule outlined in the European Society of Cardiology (ESC) AF guidelines when deciding when to start OAC drugs after stroke or tranisent ischaemic attack (TIA)?

Rank value	Option	Count
1	Yes	43
2	No	78

Question 10. If you do not use the 1-3-6-12 rule, how do you decide when to start OAC? (See Supplemental Table 1, below)

Case 1: TIA

A 76 year old male presents with a left hemisphere TIA lasting for 30 minutes. Plain CT brain shows no obvious abnormality. Cardiovascular risk factors include hypertension and ischaemic heart disease. His ECG shows shows AF. Assume there are no contraindications to long term anticoagulation in your answers.

Question 11. When do you currently start OAC drugs after a TIA in patients with AF? (Day of TIA is considered as Day 0)

Rank value	Option	Count
1	Day 0	94
2	Day 1	25
3	Day 2	1
4	Day 3	1
5	Day 4	0
6	Day 5	0
7	Day 6	0
8	Day 7	0
9	Day 8	0
10	Day 9	0
11	Day 10	0
12	Day 11	0
13	Day 12	0
14	Day 13	0
15	Day14	0
16	Day 15	0
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	0

Question 12. When would be the earliest time (acceptable to you) to start OAC drugs in a trial after TIA in patients with AF? (Day of TIA is considered as Day 0)

Rank value	Option	Count
1	Day 0	104
2	Day 1	16
3	Day 2	1
4	Day 3	0
5	Day 4	0
6	Day 5	0
7	Day 6	0
8	Day 7	0
9	Day 8	0
10	Day 9	0
11	Day 10	0
12	Day 11	0
13	Day 12	0
14	Day 13	0
15	Day 14	0
16	Day 15	0
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	0

Question 13. When would be the latest time (acceptable to you) to start OAC drugs in a trial after TIA in patients with AF? (Day of TIA is considered as Day 0)

Rank value	Option	Count
1	Day 0	37
2	Day 1	32
3	Day 2	12
4	Day 3	15
5	Day 4	2
6	Day 5	2
7	Day 6	0
8	Day 7	13
9	Day 8	0
10	Day 9	0
11	Day 10	2
12	Day 11	0
13	Day 12	0
14	Day 13	1
15	Day14	3
16	Day 15	0
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	2

Case 2: Mild Stroke

A 76 year old male presents with right sided weakness. He has a NIHSS score of 4. A CT scan of the brain reveals a cortical lesion of <1.5 cm in the left middle cerebral artery territory. Cardiovascular risk factors include hypertension and ischaemic heart disease. BP and bloods are unremarkable. ECG shows AF. Assume there are no contraindications to long term anticoagulation in your answers.

Question 14. When do you currently start OAC drugs after a mild stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	12
2	Day 1	9
3	Day 2	6
4	Day 3	36
5	Day 4	11
6	Day 5	4
7	Day 6	8
8	Day 7	24
9	Day 8	0
10	Day 9	1
11	Day 10	1
12	Day 11	0
13	Day 12	0
14	Day 13	0
15	Day14	8
16	Day 15	1
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	0

Question 15. When would be the earliest time (acceptable to you) to start OAC drugs in a trial after a mild stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	40
2	Day 1	19
3	Day 2	7
4	Day 3	32
5	Day 4	7
6	Day 5	3
7	Day 6	1
8	Day 7	8
9	Day 8	0
10	Day 9	0
11	Day 10	0
12	Day 11	0
13	Day 12	0
14	Day 13	0
15	Day 14	2
16	Day 15	1
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	0

Question 16. When would be the latest time (acceptable to you) to start OAC drugs in a trial after a mild stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	2
2	Day 1	1
3	Day 2	2
4	Day 3	13
5	Day 4	3
6	Day 5	9
7	Day 6	5
8	Day 7	35
9	Day 8	0
10	Day 9	1
11	Day 10	6
12	Day 11	1
13	Day 12	1
14	Day 13	1
15	Day14	37
16	Day 15	2
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	2

Case 3: Moderate Stroke

A 76 year-old male presents with right sided weakness and dysarthria. He has a NIHSS score of 8. CT brain reveals a lesion in a cortical superficial branch of the middle cerebral artery in the left hemisphere. Cardiovascular risk factors include hypertension and ischaemic heart disease. ECG shows AF. Assume there are no contraindications to long term anticoagulation in your answers.

Question 17. When do you currently start OAC drugs after a moderate stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	4
2	Day 1	0
3	Day 2	3
4	Day 3	7
5	Day 4	3
6	Day 5	9
7	Day 6	15
8	Day 7	43
9	Day 8	2
10	Day 9	1
11	Day 10	7
12	Day 11	1
13	Day 12	3
14	Day 13	0
15	Day14	21
16	Day 15	1
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	0

Question 18. When would be the earliest time (acceptable to you) to start OAC drugs in a trial after a moderate stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	20
2	Day 1	5
3	Day 2	7
4	Day 3	21
5	Day 4	3
6	Day 5	14
7	Day 6	7
8	Day 7	27
9	Day 8	0
10	Day 9	1
11	Day 10	5
12	Day 11	0
13	Day 12	0
14	Day 13	0
15	Day 14	7
16	Day 15	1
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	0

Question 19. When would be the latest time (acceptable to you) to start OAC drugs in a trial after a moderate stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	1
2	Day 1	0
3	Day 2	0
4	Day 3	1
5	Day 4	0
6	Day 5	1
7	Day 6	3
8	Day 7	17
9	Day 8	0
10	Day 9	5
11	Day 10	15
12	Day 11	1
13	Day 12	3
14	Day 13	1
15	Day14	61
16	Day 15	6
17	Day 16	1
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	4

Case 4: Severe Stroke

A 76 year old male presents with right sided weakness, hemianopia and dysphasia. He has a NIHSS score of 18. Brain CT shows hypodensity changes in most of the left middle cerebral artery territory, consistent with acute infarction. Cardiovascular risk factors include hypertension and ischaemic heart disease. ECG shows AF. Assume there are no contraindications to long term anticoagulation in your answers.

Question 20. When do you think is the ideal time to start OAC drugs after severe stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	0
2	Day 1	0
3	Day 2	1
4	Day 3	0
5	Day 4	1
6	Day 5	0
7	Day 6	0
8	Day 7	9
9	Day 8	1
10	Day 9	1
11	Day 10	13
12	Day 11	1
13	Day 12	8
14	Day 13	1
15	Day14	73
16	Day 15	7
17	Day 16	1
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	4

Question 21. When would be the earliest time (acceptable to you) to start OAC drugs in a trial after severe stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	7
2	Day 1	2
3	Day 2	1
4	Day 3	7
5	Day 4	1
6	Day 5	3
7	Day 6	1
8	Day 7	31
9	Day 8	1
10	Day 9	1
11	Day 10	11
12	Day 11	0
13	Day 12	7
14	Day 13	0
15	Day 14	43
16	Day 15	3
17	Day 16	0
18	Day 17	0
19	Day 18	0
20	Day 19	0
21	Day 20	2

Question 22. When would be the latest time (acceptable to you) to start OAC drugs in a trial after severe stroke in patients with AF? (Day of stroke is considered as Day 0)

Rank value	Option	Count
1	Day 0	0
2	Day 1	0
3	Day 2	0
4	Day 3	0
5	Day 4	0
6	Day 5	0
7	Day 6	0
8	Day 7	0
9	Day 8	0
10	Day 9	0
11	Day 10	2
12	Day 11	1
13	Day 12	4
14	Day 13	0
15	Day14	65
16	Day 15	9
17	Day 16	1
18	Day 17	1
19	Day 18	1
20	Day 19	0
21	Day 20	36

Supplemental Table I: Free text comments regarding how clinicians decide when to initiate OAC.

Size of infarct, HT, ischaemic stroke risk, Echo, etc.
I base timing on an individual assessment taking account of size of infarct/severity HTI likelihood of cardiac embolism swallow status timing of discharge likelihood of falls patient/family views
Similar to 1-3-6-12 rule; based on infarct size etc but more flexible with timings
Depends on the size of the lesion. For bigger strokes I tend to wait for two weeks, for TIAs with normal MR, I tend to start immediately.
Traditional view of small and large stroke severity
Extent of infarction
Clinical judgement
Stroke severity
I make the decision based on the size of ischemic lesion in the imaging .
depending on the size of infarct
I usually follow 1-3-6-12 rule.Alternatively I intend to start OAC 2 weeks after Stroke if there is a large area of infarction but I start as soon as possible if there is minor disability stroke or mild ischemic changes in brain imaging.
usually 2 weeks after stroke or as soon as symptoms resolved
Minor stoke with low NIHSS <5) and no or smallinforact on CT: immediately, Severe stroke wait two weeks. In between minor and severe: varialbe, spendds on patient details.
Roughly similar, depending on infarct size and patient factors
Based on a more nuanced judgement of risk versus benefit
On a patient by patient basis, taking account of blood pressure, bleeding diathesis, infarct size, etc
Swallowing status, absence of PH2 haemorrhagic transformation
Based on combination of patient factors and imaging
clinical judgement
Clinical judgement by patient
I use a variation of this - if large infarct on NIHSS or scan I delay up to 14 days
size of the acute infarct and clinical deficit
Individualised, largely relating to stroke severity/ underlying extent of infarction, and other factors e.g. preceding TIA etc
Depends upon stroke severity
Depending on infarct size
Day 1 for TIA Day 7 for mild /moderate stroke Day 14 for severe stroke
size of the infarct on CT Brain. clinically improvement.
TIA/very minor stroke - start early More major stroke- wait for 2 week
Infarct size and patient clinical condition.
Use RCP guidelines

I am not familiar with this rule. If I find a large infarct on scan I wait 14 days before starting a NOAC. If CT is normal or shows a small infarct I usually anticoagulate at 7 days.
UK RCP/NICE stroke guidance and MDT discussion
Depends on stroke severity and other factors? NBM ? Other patient risk factors
Usually either immediately, day 3, 5, 7, 10 or 14 - entirely pragmatic numbers.
On a case by case basis depending on the volume of ischemic tissue from the infarct
size of infarct, white matter disease burden, any CAA features on MRI, patient's past history..all factored in. In reality what I do is something akin to the 1 3 6 12 rule.
Size of infarct, other factors such as oral route availability and cardio-embolic risk
I wait 2 weeks if big stroke with significant lesion on scan and I tend to start immediately if TIA or small stroke with minimal scan lesion
Immediately after TIA, 1 week after small infarct, 2 weeks after large infarct
Never heard of the rule! In TIA if ICH is excluded and patient has AF I start NOAC straight away. In a 'minor stroke' e.g. NIHSS 1 to 3 and no ICH or large volume infarct on scan and patient is high risk with AF I often continue or start NOAC very early e.g. 1-2 days
Individual decision based on size of infarction and Chadsvasc
Individual case basis, depending on BP and infarct appearance
default is 2 weeks otherwise depending on the patient
Based on clinical deficit from stroke or based on volume of infarct on MRI usually, sometimes CT. Also risk of further stroke (metal mitral valve or other such pressing indication)
size of infarct, current disability and medical conditions of patient
Occasionally not strictly as per above rules depending on size of infarction and risk of haemorrhage
depending on patient clinical history, co morbidities, clinical signs etc
TIA - straight away Minor stroke - one week to 10 days Major stroke - 14 days (or more if haem transformation)
tia or smallish stroke straight away. big stroke 2 weeks, others inbetween but varies
Immediate for TIA, either at 14 days or on discharge from hospital (whichever comes first) after ischaemic stroke.
Generally, start anticoagulants as soon as possible if infarct size judged small, or no new MRI infarct findings in TIA pt
Severity/size of stroke leading to delay in restarting at least a week Presumption of aetiology to be embolic more likely to continue inside same week if TIA (I have subsequently reviewed the 1-3-6-12 and find it to be largely in keeping with these thoughts as a handy guide)
Acute infarct - wait for 2 weeks
normally wait until the 14 days of high dose aspirin has completed before changing to secondary prevention with either clopidogrel in non-AF and OAC in AF I am not aware of the 1-3-6-12 rule!
It depends on the size of the infarct, and if there is any imaging evidence of haemorrhagic transformation

Supplemental Table II: Survey general free text comments

The initiation of OAC depends on following factors:Severity of the Stroke clinically and in NIHSS score, Area of ischemic involvement in the imaging and haemorrhagic transformation in ischemic area.It is usually 2weeks after moderate to large stroke.In minor disability stroke you can start ASAP safely.
If patient has AF and minor stroke / TIA then we know there's a clot in the atrium at risk of large embolus. Thus need to anticoagulated immediately.
difficult to answer questions as my clinical decision is based on symptom resolution. NIHSS scores quoted are on admission and have assumed resolved on 2 milder strokes
deciding between mild and moderate stroke can be difficult - clinical experience/judgement has to come into it rather than wholly protocol
Indefinite delay could be considered for last case depending on progress, patient/family wishes, swallowing status etc.
We clearly need a trial to provide evidence for best practise.
If asked a couple of years ago I would have considered this trial. Now I think we have reached and equilibrium where we have a reasonable clinical logic as to when to start. It get earlier and earlier. A trial with forced delay wouldn't be comfortable to me.
Consideration of time for patients to consider consent options when early anticoagulation is indicated. Should not delay treatment but informed consent will need time.
Very important to answer the dilemma soon. The trail design should include various times of OAC as well as heparinoids left to the clinicians' discretion
The decision to start anticoagulants also depends on co-morbidities and other patient related factors and also CT/MRI findings after the acute event.
I think the question on the latest time to start an anticoagulant is difficult to answer particularly in large stroke and depends on the functional recovery/risk of falls which may not be know for some time
DOAC preferable due to reduced risk of ICH as revealed in clinical trials
Consistency of oral route, renal function may influence choices. A study of early(<7 days) vs late(>/14 days OAC would be very helpful-to achieve consistency of OAC would probably have to use a NOAC only (Preferable) or LMWH/Wafarin as an option to ensure consistent anticoagulation.
I think in general the safest time to start NOACs after a stroke is after 2 weeks. After TIA it is ASAP.
Starting OACs is very variable and multiple factors are usually taken into consideration. In general we are probably too reticent. It is a particularly nervous interval after successful thrombectomy in patients with AF as so much effort has gone into treating the acute stroke that to have another while waiting for the ''haemorrhage risk window'' to pass, is a disheartening failure of nerve. What is also not clear is if patients should or should not be on antiplatelets while waiting the appropriate time interval for OACs
For the more severe stroke, you may not be starting OAC but dalteparin which would need to be factored into the equation and might also be an option for more moderate strokes
The trial should answer whether a second CT scan should be performed especially in severe stroke before commencing OAC early
Clarification on optimal timing would be helpful
Very content to randomise. There is sufficient uncertainty and presumably this survey will show a wide range of responses- we need a trial rather than our 'expert' opinion.

this is an excellent area for study - it is common, there is (to me at least) clinical equipoise and I think that there is considerable variation in clinician approach there is a balance to be struck between reversibility and the irreversible nature of anticoagulation with low molecular weight heparins and the direct anti-Xa DOACs versus warfarin and the predictable anticoagulation provided; there is also a risk/benefit in terms of both risk of haemorrhage, risk of further thrombotic stroke and in the more disabled/severe stroke patients VTE risk which would also be treated by anticoagulation but are currently not protected by the antiplatelet regime
I'd also be interested in when one might start/restart post intracerebral haemorrhage