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

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ABSTRACT

Background: There is uncertainty regarding the optimal timing for initiation of oral anticoagulant treatment (OAC) in patients with recent ischaemic stroke and atrial fibrillation (AF). We surveyed the current UK practice and assessed clinician's opinions of when to use OAC in recent stroke patients with AF.

Methods: An online survey was sent to stroke physicians within the United Kingdom via their national societies.

Results: One hundred and twenty-one clinicians responded to the survey. Ninety-five percent of responders agreed there was uncertainty regarding timing of OAC initiation after AF-related ischaemic stroke. Thirty-six percent of responders followed the '1-3-6-12' European Society of Cardiology (ESC) guidelines recommendation. Uncertainty was greater in cases of moderate stroke than in cases of TIA, mild or severe stroke. Eighty-eight percent of responders would be willing to participate in a clinical trial of early vs. later initiation of OAC after stroke. Direct-acting oral anticoagulant (DOAC) were the preferred OAC of choice.

Conclusion: There is a lack of consensus amongst stroke physicians for when to initiate OAC to prevent recurrence in stroke patients with AF. There is little uncertainty regarding TIA. A clinical trial assessing use of early vs. later initiation of DOAC in patients with recent ischaemic stroke and AF would be beneficial.

INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disturbance in the UK¹ and confers a near 5-fold risk of stroke.^{2,3,4} The risk of stroke recurrence following AF-related stroke is also especially high during the first fourteen days.^{5,6,7} Oral anticoagulants (OAC) reduce recurrence risk by two-thirds.⁸ Given the high early recurrence risk, use of OAC as early as possible seems desirable, but OAC use is associated with increased risk of intracerebral haemorrhage (ICH), including symptomatic ICH (sICH) after ischaemic stroke. Balancing these possible benefits and risks is challenging.

The European Society of Cardiology (ESC) guidelines recommend that OAC should be initiated between one and twelve days in patients with AF and recent acute ischaemic stroke depending on the stroke severity.⁹ This ‘1-3-6-12’ day rule states OAC would be started on day 1 following a TIA, day 3 following a mild stroke, day 6 following a moderate stroke and on day 12 following severe stroke.¹⁰ This pragmatic guidance is based on “expert opinion” and such practice evolved during a time where only vitamin K antagonists (VKA) and heparins were available. Direct-acting oral anticoagulants (DOACs) are at least as effective as VKAs in preventing recurrent stroke in patients with ischaemic stroke and AF. DOACs have a rapid onset of action (0.5-4 hours) along with lower rates of ICH.⁹ It may therefore be safer to use these drugs very early after stroke compared to VKA, but exactly when, and in whom, the balance of risk and benefit is in favour is unclear.

Whilst there is considerable uncertainty on the optimal latency after acute stroke at which OACs should commence, the magnitude of this uncertainty, and the minimum and maximum delays that are acceptable to stroke physicians are unclear. Clarity in this regard would help inform the need and design of clinical trials in this area. We conducted a survey aimed to

establish specialist opinion and current practice on the timing of OAC initiation in patients with recent ischaemic stroke and AF within the United Kingdom.

METHODS

The study was discussed with the West of Scotland Research Ethics Service and formal review was not required under the Governance Arrangements for Research Ethics Committees. A survey was created online using www.onlinesurveys.ac.uk. An online format was used to maximise response return and ease of dissemination. Questions aimed to assess what clinicians do in practice, rather than assess knowledge of guidelines. The survey consisted of 22 questions (see Online-only Supplemental Data). The first four explored demographic data of responders. Further questions explored whether clinicians followed the '1-3-6-12' day rule, whether they were uncertain regarding when to initiate OAC, and whether clinicians would be willing to participate in related clinical trials. Finally, the survey included four clinical vignettes of people with TIA and different severities of stroke. In each scenario, the patient had AF, no contraindications for anticoagulation, and scenarios were consistent regarding age, sex and cardiovascular risk factors (only severity of stroke differed), (see Online-only Supplemental Data for the clinical vignettes) Responders were asked to give their view on the optimal time to start OAC, and the earliest and latest times they would be willing to start OAC in a clinical trial for each scenario. A free text section at the end of the survey was included.

The survey was piloted, reviewed and then circulated to members of the British Association of Stroke Physicians (BASP), Association of British Neurologists (ABN), Scottish Association of Neurological Science (SANS), British Cardiovascular Society (BCS), Scottish Cardiac Society (SCS) and Society of Acute Medicine (SAM) along with a cover letter

detailing the background of the project. It was also disseminated via the UK Clinical Research Networks. The survey was distributed via email with a hyperlink embedded allowing access to the survey. Responders were provided six weeks to complete the survey, with reminders sent 2 weeks prior to the closing date. Descriptive statistics were produced to describe responses.

RESULTS

Demographics:

A total of 121 clinicians completed the survey. Responders were distributed throughout the UK with 54% from England, 31% from Scotland, 11% from Wales and 4% from Northern Ireland. The commonest speciality of responders was Geriatric Medicine (n=88, 73%) followed by Neurology (n=18, 15%) and Acute Internal Medicine (n= 5, 4%). Three responders selected “other” but stated a special interest in stroke medicine. In the UK, acute stroke management is undertaken by either neurologists, geriatricians or internists with specialist interest in stroke medicine. Free text comments regarding timing of initiation of OAC are shown in Online-only Supplemental Table I.

Use of OAC after stroke:

One hundred and fifteen (95%) responders answered that there was uncertainty regarding when to administer OAC after AF-related ischaemic stroke. One hundred and four (86%) of the responders replied that they would be willing to participate in a clinical trial of early vs. later initiation of OAC. Forty-three (36%) responders used the 1-3-6-12 guidelines outlined by the ESC. Sixty (50%) responders reported using DOACs early after ischaemic stroke in patients with AF, 60 (50%) reported that their drug choice differed between patients but none reported a preference for VKA.

TIA scenario: All responders reported that they currently initiate OAC within three days of a TIA (78% on the same day, median day 0, IQR day 0 to day 0) (Figure 1). The earliest and the latest acceptable times to start OAC in a clinical trial for patients with TIA are shown in Figure 2 (panel a and b).

Mild stroke scenario: All responders reported that they currently initiate OAC within 15 days of a mild stroke (10% on the same day and 71% within 7 days) (Figure 1). The earliest and the latest acceptable times to start OAC in a clinical trial for patients with mild stroke are shown in Figure 2 (panel c and d). The median response regarding the earliest acceptable time to start OAC in a clinical trial was day 2 (IQR: day 0 -3). The median response regarding the latest time was day 7 (IQR: day 6 -14).

Moderate stroke scenario: All responders reported that they currently initiate OAC within 15 days of a moderate stroke (3% on the same day and 34% within 7 days) (Figure 1). The earliest and the latest acceptable times to start OAC in a clinical trial for patients with moderate stroke are shown in Figure 3 (panel a and b). The median for the earliest acceptable time to start OAC in a clinical trial setting was day 5 (IQR: day 2 -day 7). Meanwhile, the median for the latest time of such was day 14 (IQR: day 10 -14).

Severe stroke scenario: All responders reported that they currently initiate OAC within 20 days of a severe stroke (0% on the same day and 2% within 7 days) (Figure 1). The earliest and the latest acceptable times to start OAC in a clinical trial for patients with moderate stroke are shown in Figure 3 (panel c and d). The median for the earliest acceptable time to

start OAC in a clinical trial was day 10 (IQR: day 7 -14). Meanwhile, the median for the latest time of such was day 14 (IQR: day 14 -20).

In the feedback section whilst a clinical trial measuring use of early vs. later initiation of DOACs in ischaemic stroke in patients with AF would be welcomed, opinions were mixed regarding the structure and intricacies of such a trial. The free text comments are shown in the Online-only Supplemental Table II.

DISCUSSION

The results of this UK-wide online survey amongst stroke physicians indicated that there was a lack of consensus regarding when to administer OAC after a stroke in patients with AF. It was clear from the survey that physicians felt that a clinical trial to answer this clinical conundrum would be beneficial.

Current clinical practice was shaped during an era where warfarin was the only available oral drug. Warfarin, compared to acetylsalicylic acid, increases the risk of bleeding by two-thirds (2.2 vs. 1.3 events per 100 patient years).¹¹ DOACs are at least as effective as warfarin for stroke prevention in AF and cause lower rates of intracranial haemorrhage. In the ARISTOTLE trial, the rate of intracranial haemorrhage was half with apixaban vs. warfarin (HR 0.51, 95% CI 0.35 to 0.70), and in the AVERROES trial it was similar to aspirin.^{12,13} Similar data in comparison to warfarin have been shown for other DOACs.^{14,15,16} DOACs may therefore offer a better risk benefit ratio early after stroke but this cannot be concluded at present. Most trials of DOACs excluded patients who had suffered recent stroke, defined as within the last seven days after stroke onset, and in some trials much later.

Interestingly the survey found that only 36% of clinicians used the '1-3-6-12' day outlined in ESC guidelines. However, from the responses, it is clear that most followed the basic principle of delaying OAC initiation in proportion to stroke severity. For those who did not use the '1-3-6-12' rule, our free text comments suggest their decisions were based in a pragmatic way using their clinical judgement to assess for factors such as; swallow status, haemorrhagic transformation, likelihood of falls and size of infarct. The survey found little uncertainty regarding timing of OAC initiation after TIA. There was little disagreement in severe stroke but more uncertainty in cases of moderate stroke. Clinicians were also asked their opinions regarding the earliest/latest time for OAC intervention in the context of a clinical trial. Answers regarding the earliest and latest acceptable time points were more varied for severe and mild stroke, respectively. The nature of the uncertainty therefore differs with severity of stroke but exists nonetheless. It is clear that there is support from clinicians for a clinical trial in this area.

We used an online survey and case vignettes. Each scenario was carefully selected, and all external risk factors were kept constant. This was to ensure the survey was easy to complete, and that we could identify clear patterns of practice that could inform trial design. There were no contraindications for OAC in each case although this oversimplification would not apply to real life clinical practice where many contraindications make the decision-making process more complex. To differentiate between the stroke severity in each of the cases provided, the definitions from the ELAN clinical protocol¹¹ were used along with a National Institute of Health Stroke Scale (NIHSS) score. We felt, given the patient in each vignette had suffered TIA or stroke and had AF, that they were already of high risk of recurrence and had a CHA₂DS₂VASc score of at least 2 and that ABCD₂ score may not alter decision to

anticoagulate. Our data do not allow us to explore how hyperacute thrombectomy therapy would influence decision-making.

Limitations: The design of this survey had several limitations. There is a risk of selection bias, where clinicians with a more active interest in this subject, or perhaps with more uncertainty, were more likely to answer. Social-desirability bias was another potential limitation, where responders would answer in a way they thought they should answer rather than what they would actually do. The survey was anonymised to try to reduce bias. This was a UK survey so results may not be generalisable to other European and non-European countries. This may be particularly relevant given that most responders were trained in geriatric medicine. The multiple-choice options were kept short and the list was not exhaustive which may have caused some responders to answer too quickly or in an over simplistic manner. The survey was distributed via email with a hyperlink embedded allowing access to the survey. Thus, we were also unable to provide the proportion of active clinicians from each organisation who completed the survey.

Future Directions: It is clear that randomised, controlled trials are needed to address this uncertainty. Four randomised, controlled clinical trials investigating early vs. late initiation of DOACs in patients with AF-related ischemic stroke have been initiated: Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillation (ELAN, NCT03148457, Switzerland); OPTimal TIMing of Anticoagulation after AF-associated acute ischaemic Stroke (OPTIMAS, British Heart Foundation, UK); Timing of Oral Anticoagulant Therapy in Acute Ischaemic Stroke with Atrial Fibrillation (TIMING, NCT02961348, Sweden) and Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation (START, NCT03021928, USA). Results are expected in 2021.

CONCLUSION

This on-line survey of UK stroke physicians showed a lack of consensus for when to initiate OAC for patients with an acute stroke and AF, and clinical trials are needed.

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Declaration of conflicting interests

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Informed consent

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Ethical approval

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Guarantor

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Contributorship

JD and AHAR jointly supervised the project. DM, AHAR and JD designed the survey. DM collected and analysed the responses. DM drafted the initial article. DM, AHAR and JD were involved in reviewing and reporting of the work. All authors provided critical revision of the article for important intellectual content and approved the final version.

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FIGURES LEGENDS

Figure 1: Response analysis of current initiation of OAC after TIA and stroke.

Figure 2: The earliest and latest acceptable OAC initiation timings after TIA (a and b, respectively) and mild stroke (c and d, respectively) in patients with AF for a potential clinical trial.

Figure 3: The earliest and latest acceptable OAC initiation timings after a moderate stroke (a and b, respectively) and severe stroke (c and d, respectively) in patients with AF for a potential clinical trial.