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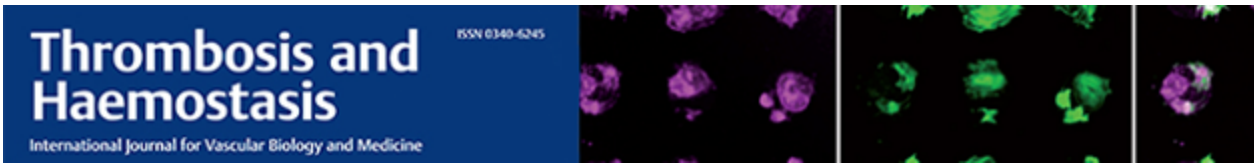

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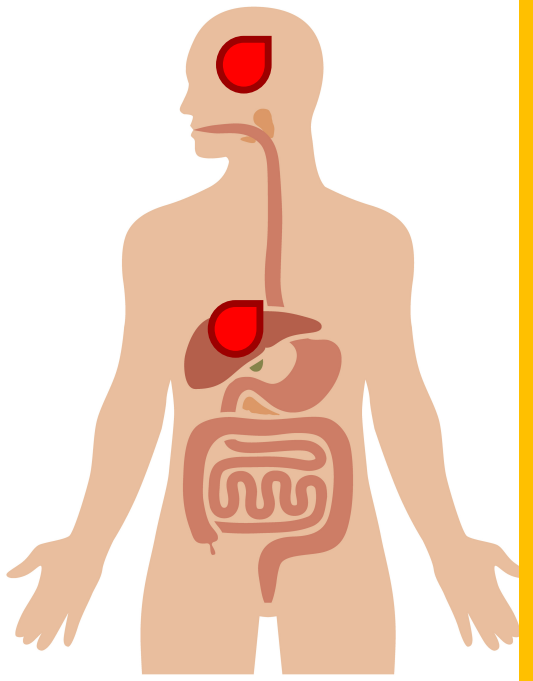
352 ANNEXA-4 patients



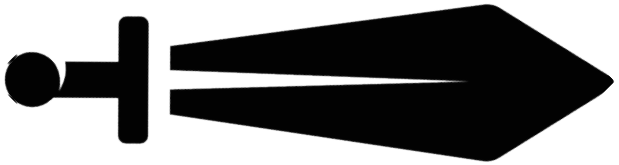
Major bleed whilst on a DOAC

DOAC reversal

30-day event rate

3.7% thrombotic stroke
3.7% DVT

9.7% thrombotic events



4.3% bleeding events (after 3 days)

14% died

Day 14 Landmark Analysis

Excluded patients with an event before day 14

Restarted OAC by day 14 (n = 67)	NOT restarted OAC by day 14 (n = 234)
0 thrombotic events	12 thrombotic events (5%)
3 bleeding events (4.5%)	2 bleeding events (0.9%)

Time-dependent Cox model restarting OAC associated with;

Reduced composite of thrombosis + bleeding + death
HR 0.384 (C.I 0.16-0.91)

Editorial

Balancing risks and benefits when recommencing oral anticoagulants after major bleeding

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A significant growth in the prescribing of oral anticoagulants (OAC) has occurred over the last decade, largely due to their increasing role in stroke prevention, especially in the aging patient diagnosed with AF [1]. Indeed, there has been a move away from traditional OACs (ie. vitamin K antagonists), towards the more contemporary Direct Oral Anti-Coagulants (DOACs) [2, 3], which have been shown to be at least as effective as warfarin in stroke prevention, and have a lower rate of associated intracranial haemorrhage (ICH) and mortality in clinical trials [4] and real world studies [5-7].

An inevitable double-edged sword exists with the prescribing of any anticoagulant, with an elevated thrombotic risk in patients not treated, but an increased haemorrhage risk in those that are. Safe, effective and rapid-onset NOAC-reversal agents are required should major haemorrhage occur, and new drugs have been developed specifically for this purpose [8-10].

However, studies assessing NOAC reversal fail to address what happens after the NOAC is reversed and the bleeding is under control. What new and growing risks exist in relation to having stopped NOAC therapy, which was designed to prevent thrombosis in the first instance? Underlying thrombotic risk factors have not resolved, and in some cases may be

elevated in view of a new critical illness. Clinicians are forced to make decisions about timely but safe recommencement of the very drug which has contributed to the recent bleeding event. The most common major bleeding events that concern physicians in relation to OACs are gastrointestinal (GI) bleeding and ICH, with evidence in both cases that subsequent anti-coagulation resumption is beneficial for reducing thrombotic events and mortality in the longer term [11-14]. However, there is a lack of high-quality published data and evidence-based guidelines on how early resumption should occur, meaning that clinical practice is varied and outcomes poorly understood.

In this issue of *Thrombosis and Haemostasis,* Milling *et al* aims to provide data around this challenging topic by performing a post-hoc analysis on the DOAC reversal study, ANNEXA-4 [15]. The original study recruited 352 patients with major bleeding whilst taking a DOAC who all received the reversal agent andexanet alfa [8]. In the current study the authors sought to clarify whether any benefit or harm could be observed in patients from the ANNEXA-4 trial where the treating clinician recommenced therapeutic OAC within 30 days. This was summarised in terms of event rates of thrombosis, haemorrhage (at least 3 days after primary bleed) and death. There were 100 patients who restarted OAC within 30 days, at a median of 10 days, with 83% restarting DOACs and 17% vitamin K antagonists.

The authors endeavour to understand the time-dependant relevance of anticoagulation resumption, firstly through a *landmark* analysis. This works by the authors stipulating a landmark time point, in this case day 14 (as a mid-point to day 30) and only patients who have had *no* events (thrombotic or haemorrhagic) by that time point are included. This select group is then divided into those who had re-started OAC by 14 days and those who had not. By nature of the fact that no events had occurred, this ensures all patients who had started

OAC did so entirely to prevent thrombosis, and not for treatment of a thrombotic event. The findings are important and demonstrate that no subsequent thrombotic events occurred in the patients who had restarted OAC by day 14, whilst 12 thrombotic events (12/234, 5.1%) occurred in those who had not (regardless of whether they started it shortly there-after). Haemorrhagic events occurred in 3 patients (3/67, 4.5%) who had restarted by day 14 and 2 (2/234, 0.9%) who had not. This gives a strong impression that earlier OAC recommencement (<14 days from the original bleeding event) plays a role in thrombosis prevention, although this is potentially at the cost of an increased haemorrhage rate. A time-dependant Cox Regression model was applied to all patients, to understand how the length of time spent on "restarted" OAC during the 30-days after the original bleed related to events. This was congruous with the landmark analysis, suggesting that earlier restarting of OAC was associated with a lower thrombotic event rate, and in addition found a lower combined (thrombosis, haemorrhage and death) event rate. This proposed a net benefit of restarting earlier. This is unsurprising, given that the median time to first thrombotic event was 10 days, relatively early recommencement would be required in order to prevent thrombosis. This certainly invites clinicians to be more aware of the potential benefits surrounding proactive, early OAC recommencement.

Capturing event data within a trial setting provides a reliable source of event rates, none-the-less the authors have taken care not to overestimate their findings, which are limited by the nature of it being a post-hoc analysis. There will inevitably be unknown confounders and the trial was not powered to answer the question of this paper. Selection bias due to the clinician-led decision making on timing of OAC recommencement is certainly a drawback, reflected by the lower proportion of patients with ICH as the primary bleed in the recommencement group (41%) compared to the non-recommencement group (74%). This is likely due to a

higher perceived harm from an ICH rebleed secondary to early OAC recommencement, than other sources of major bleeding, leading to a more cautious approach. This also highlights a wider issue of collecting data in challenging patient groups such as ICH, where various factors can influence the ongoing bleeding risk. This includes original ICH location, size and source (spontaneous or traumatic), with neurosurgeons also interested in those surgically evacuated, who are often excluded from trials, as was the case in the ANNEXA-4 trial.

An important question in interpreting the study findings is how relevant each event is to an individual patient. Whilst the overall thrombotic rate might outweigh the haemorrhage rate, this is insufficient to determine a positive net benefit for the patient, as the effect on functional outcome and quality of life of each event remains unknown. Previous research has reported that patient perception of risk varies widely, but many patients would accept several major systemic bleeding events over one stroke [16]. This highlights the importance of neurological function to patients, and the inadequacies of comparing event rates alone. For future randomised studies in this field to be successful, understanding patient perceptions of health events must improve, with consideration of the impact on quality of life and health-economic costs.

The findings of this study emphasise the challenges in clinical decision making for patients who have had a major bleed whilst on OAC. Efforts at improving the prescription of OAC for thromboprophylaxis in (say) AF should continue [17], as should awareness that delay in OAC recommencement due to clinician uncertainty may be inadvertently harmful. There is a critical need to answer this question more fully through a randomised clinical trial, where the data reported herein will be valuable for informing trial design.

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