Balancing Risks and Benefits When Recommencing Oral Anticoagulants after Major Bleeding

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A significant growth in the prescribing of oral anticoagulants (OACs) has occurred over the last decade, largely due to their increasing role in stroke prevention, especially in the aging patients diagnosed with atrial fibrillation (AF).[1] Indeed, there has been a move away from traditional OACs (i.e., vitamin K antagonists) toward the more contemporary direct OACs (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 hemorrhage (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 hemorrhage risk in those that are. Safe, effective, and rapid-onset nonvitamin K oral anticoagulant (NOAC)-reversal agents are required should major hemorrhage 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 bleeding and ICH, with evidence in both cases that subsequent anticoagulation 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 aim to provide data around this challenging topic by performing a posthoc analysis on the DOAC reversal study, ANNEXA-4.[15] The original study recruited 352 patients with major bleeding while 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 summarized in terms of event rates of thrombosis, hemorrhage (at least 3 days after primary bleed), and death (►**Fig. 1**). 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 endeavor to understand the time-dependent relevance of anticoagulation resumption, first through a *landmark* analysis. This works by the authors stipulating a landmark time point, in this case day 14 (as a midpoint to day 30) and only patients who have had *no* events (thrombotic or hemorrhagic) by that time point are included. This select group is then divided into those who had restarted 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, while 12 thrombotic events (12/234, 5.1%) occurred in those who had not (regardless of whether they started it shortly thereafter). Hemorrhagic events occurred in three patients (3/67, 4.5%) who had restarted by day 14 and two (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 hemorrhage rate. A time-dependent 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

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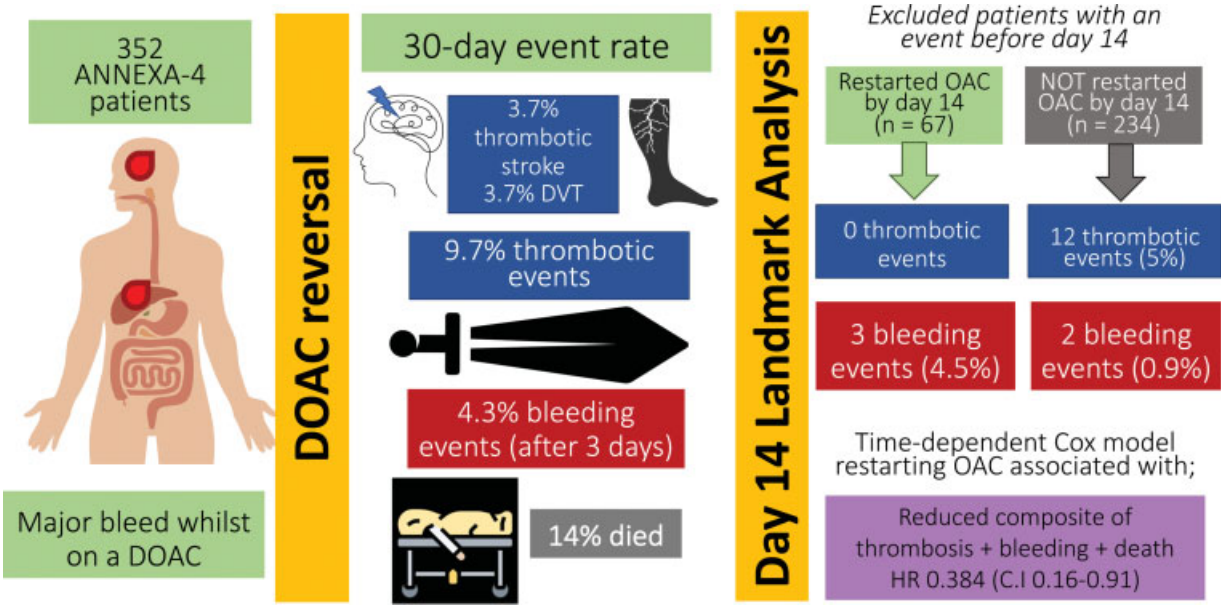

Fig. 1 Summary event rates of thrombosis, bleeding, and death in relation to restarting oral anticoagulants (OACs) following direct oral anticoagulant (DOAC) reversal in patients recruited to the ANNEXA-4 study. This contains images from Flaticon.com, Freepik, and AdobeStock. DVT, deep vein thrombosis.

analysis, suggesting that earlier restarting of OAC was associated with a lower thrombotic event rate, and in addition found a lower combined (thrombosis, hemorrhage, 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 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, nonetheless the authors have taken care not to overestimate their findings, which are limited by the nature of it being a posthoc analysis. There will inevitably be unknown confounders and the trial was not powered to answer the question of this article. 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 with the nonrecommencement 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 patients with 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. While the overall thrombotic rate might outweigh the hemorrhage 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 randomized 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 emphasize the challenges in clinical decision making for patients who have had a major bleed while 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 randomized clinical trial, where the data reported herein will be valuable for informing trial design.

Conflict of Interest
None declared.

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