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Cite this as: *BMJ* 2025;391:r2334
http://doi.org/10.1136/bmj.r2334

Duration of anticoagulation for unprovoked venous thromboembolism

Patient preferences key to weighing benefits and risks of indefinite treatment

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Determining the optimal duration of anticoagulation treatment after a first event of unprovoked venous thromboembolism (VTE) remains challenging.[1] Part of the difficulty lies in identifying patients who are most likely to benefit from extended anticoagulation, a treatment associated with lower VTE recurrence rates but at the cost of higher bleeding risk.[2-4] Uncertainty remains because clinical trials and prospective studies on this topic offer a limited duration of follow-up and often include highly selected participants.[5-7]

In a linked study, Lin and colleagues (doi:10.1136/bmj-2025-084380) provide further real world data to help determine the risk-benefit balance of indefinite anticoagulation treatment in patients with a first, unprovoked VTE by analysing two large American databases, Optum Clinformatics Data Mart and Medicare.[8] Within these databases, adults without reversible risk factors for a first VTE were identified. Patients who continued oral anticoagulant (OAC) treatment were matched 1:1 to those who discontinued treatment using a propensity score, after having completed at least 90 days of anticoagulation. Patients who discontinued treatment were defined as those who did not refill an anticoagulation prescription within a 30 day period, at any time beyond the initial 90 day anticoagulation treatment phase for a first VTE event. Matching was done based on duration from the index VTE and type of index VTE (pulmonary embolism or deep vein thrombosis), as well as 89 relevant baseline characteristics. Through this method, the authors identified 30 554 propensity score matched pairs. Compared with patients who discontinued OAC treatment, patients who continued treatment had lower rates of VTE recurrence (adjusted hazard ratio 0.19 (95% confidence interval (CI) 0.13 to 0.29), and adjusted risk difference per 1000 person years −25.50 (95% CI −39.38 to −11.63)), but higher rates of major bleeding (1.75 (1.52 to 2.02), and 4.78 (1.95 to 7.61)). The net clinical benefit, accounting for both VTE recurrence and major bleeding events, favoured OAC continuation regardless of OAC type or length of anticoagulation, even beyond 1080 days. Additionally, patients who continued treatment had a lower mortality rate compared with those who discontinued treatment (0.74 (0.69 to 0.79), and −14.31 (−22.02 to −6.59)). The results were not explained by the presence of unmeasured confounders, as expressed by the E value (a measure to assess the robustness of causality against potential confounding).[9]

This study adds to the literature on this topic by using a target trial emulation analysis with a large sample size of more than 60 000 patients. More importantly, it provides long term follow-up data, which show that the net clinical benefit persists when OACs are continued even beyond three years. However, despite the extensive propensity matching, limitations remain unavoidable when using such retrospective databases, which the authors acknowledge. Residual confounding may still be present and could contribute to the mortality benefit seen in patients who continued OAC treatment. Furthermore, the risk-benefit calculations provided here do not necessarily translate to improved quality of life, respect of patient values and preferences, or cost-benefit to the healthcare system. Such perspectives are beyond the scope of this study but can be important for further investigation.

What clinical implications can be derived from this current paper? It is generally accepted that major bleeding events in patients receiving extended anticoagulation confer a 2-3 times higher mortality risk than recurrent VTE.[10-12] As such, one would expect continuation of OACs to confer a VTE risk difference to be at least 2-3 times larger than the risk difference of increased major bleeding events, to make this intervention worthwhile from a mortality perspective. When balancing the risks and benefits of continued anticoagulation, clinicians can provide patients with such a framework to help guide decision making on treatment duration. The results from this study are consistent with previous studies on this topic and do support the use of continued oral anticoagulation based on the point estimate of risk difference, although some uncertainty remains when considering the full width of the 95% CI. The risk differences described here might be useful to clinicians when counselling patients on the expected risks and benefits of continued oral anticoagulation treatment. Engaging with patients, however, remains necessary to account for personal preferences and values about the duration of treatment in view of this persistent uncertainty. Furthermore, the choice of anticoagulant could matter. This study showed that among the those who continued OAC treatment, direct oral anticoagulants (DOACs) seemed safer compared with warfarin. Additional areas of clinical equipoise to consider, not covered here, include the impact of DOAC dose reduction in the extended phase, which could further reduce the bleeding risks. Recently, the RENOVE trial showed that after at least six months of initial anticoagulation, continuing either full or reduced dose DOAC was associated with a low rate of recurrent VTE (five year cumulative incidence 1.8-2.2%), with the reduced dose regimen resulting in fewer clinically relevant bleeding events compared with full dose (five year cumulative incidence 9.9% *v* 15.2%, hazard ratio 0.61 (95% CI 0.48 to 0.79).)[13] Additionally, use of biomarkers such

as D-dimer, if available, could be helpful in the risk stratification for recurrent VTE.[14 15]

In summary, Lin and colleagues' study provides clinicians and patients with good insight on the effectiveness and safety of long term OAC treatment, by leveraging large, real world databases to summarise the net clinical benefit associated with this intervention. Additional research to better identify patients who can benefit from continuing OAC treatment after a first unprovoked VTE will help clinicians counsel and support patients who are faced with the prospect of indefinite anticoagulation treatment.

Competing interests: The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: None.

Further details of The BMJ policy on financial interests is here: https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf

Provenance and peer review: Commissioned; not externally peer reviewed.

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