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Letter to the Editors-in-Chief

Evidence for resumption of anticoagulation after a previous major gastrointestinal bleeding

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Dear Editors,

In a recent article in Thrombosis Research, Little et al. [1] update a meta-analysis assessing the risk of recurrent bleeding, thromboembolism and mortality in patients with gastrointestinal bleeding under anticoagulant treatment (mostly vitamin K antagonists). They report that patients resuming anticoagulation have a higher risk of recurrent bleeding but lower risk of thromboembolism, and lower risk of death.

As the authors emphasize, the quality of the evidence for all endpoints is low. The authors also mention a potential bias we are deeply concerned about, i.e., that patients in better general health would be preferentially recommended resumption of anticoagulation and that this, rather than resuming anticoagulation, could be what leads to a lower mortality. Indeed, studies in patients with previous intracranial as well as gastrointestinal bleeding have almost uniformly shown that patients who resume are younger, less comorbid and/or have a less severe bleeding event, among other findings [2–5]. Although most studies made an effort to match patients in the two groups, residual bias has to remain a major consideration [3]. Of note, the difference between the overall survival curves in patients who resume anticoagulation vs. those who do not (in large studies of patients with intracranial or gastrointestinal hemorrhage) seems greater than those of thromboembolism [2,4,5]. This could be explained by mortality related to factors other than thromboembolic events (e.g., more severe bleeding or otherwise poorer health and lower homeostatic reserve). Importantly, the factors mentioned above may also place patients who do not resume at greater risk of stroke, meaning that the decreased risk of stroke among patients who resume may not all be due to anticoagulation.

In patients with intracranial bleeding (anticoagulated for atrial fibrillation [AF]) there are ongoing efforts to obtain higher quality evidence. A large randomized trial testing a resumption of anticoagulation vs. antiplatelet/no treatment strategy (NCT03153150) is ongoing and results are expected by 2023. Two smaller trials with apixaban (vs. antiplatelet/no treatment [NCT02565693] and vs. left atrial appendage closure vs. antiplatelet/no treatment [NCT03243175]) are also ongoing. Conversely, we are unaware of any such studies in patient with gastrointestinal bleeding. We imagine that the main reason is that the prognosis of cardioembolism (in terms of death and disability) is similar to that of an intracranial hemorrhage while that of gastrointestinal bleeding is significantly better. However, we believe the aforementioned bias may be great enough to abrogate the reported survival benefit. A randomized trial in these patients would provide high quality evidence to answer this question. Importantly, even if resumption of anticoagulation was generally a better option, which we would hypothesize is the most likely outcome, a randomized trial would also allow relevant subanalyses to find subsets of patients who might not benefit from anticoagulation resumption, at least for some months after the event.

The authors mention the need for prospective studies. Do they mean that randomized trials are imperative, particularly in patients with AF? Would they be satisfied with a prospective observational study? Are they aware of any such trials that might be ongoing or planned? And, based on the available evidence, do they currently recommend resumption of anticoagulation to all patients with AF or are there any specific patient-related or event-related factors that would make them recommend against anticoagulation (if not indefinitely, at least for more than 3 months)?

The author reports no conflict of interest.

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