The changing landscape of anticoagulant-related intracerebral hemorrhage

Hailed as a milestone in the management of patients with nonvalvular atrial fibrillation, new oral anticoagulants (NOACs) demonstrated comparable efficacy and similar or improved safety to vitamin K antagonists (VKAs) in randomized clinical trials.1 Their ensuing approvals by central regulatory agencies provoked reservations and caution by many in the medical community. Despite the consistent observation of a lower incidence of intracerebral hemorrhage (ICH) among users of various NOACs,1 the unexplored questions regarding the natural course and prognosis of NOAC-associated ICH, combined with an absence of specific treatment and management options during the initial phases of marketing, heightened the concern related to the safety of these agents. However, a closer look into the trial data was suggestive of similar mortality rates among patients experiencing ICH while using VKAs or NOACs.2–4

Real-world data originating from small single-center studies5–9 and administrative databases10 also showed no sign of excess mortality in NOAC-related ICH. Moreover, hematoma volume, the imaging marker most closely associated with clinical outcome, was smaller in those treated with NOACs, and hence suggested a more favorable profile compared to VKA users.7,8

In this issue of Neurology®, Wilson et al.7 attempt to shed more light on this matter by an international multicenter effort where they compare a number of clinical and imaging endpoints in patients with VKA- and NOAC-related ICH. In their retrospectively collected cohort of 500 ICH patients, consisting of 403 VKA and 97 NOAC users, similar groupwise event rates were observed for the primary outcome measure of 90-day all-cause mortality (31% for VKA group vs 33% for NOAC group). All the analyzed secondary outcome measures, including ICH volume at baseline, mortality at 30 days, proportion of patients with hematoma expansion within 72 hours, and functional outcome at discharge, also proved similar in both patient groups.

Although the study could be criticized from a number of perspectives, such as its retrospective design, inevitable bias associated with choice of a certain anticoagulant for a specific patient, heterogeneity among centers with respect to image analyses, and lack of functional outcome information after discharge, it provides us with further information regarding the real-world prognosis of NOAC-related ICH. Even in the presence of important confounders like an unexpectedly low mortality rate in the VKA group, and lack of specific reversal agent therapy options in the NOAC group, this study did not show any difference in clinical and imaging measures between study groups, and, considered together with results of previous publications in the literature, suggests that there is ample evidence that the prognosis of NOAC-related ICH is not worse than VKA-related ICH.

The increased use of NOACs in lieu of VKAs in upcoming years will trigger a shift in the clinical phenotype of patients experiencing anticoagulant-related ICH.10 Although this might translate into an overall decrease in the frequency of anticoagulant-related ICH, the fact remains that, regardless of the type of anticoagulant, this clinical entity has high morbidity and mortality. We therefore need further studies from real-world settings to characterize this complication better, especially related to NOAC use. These studies might help us elucidate predictors and define short- and long-term prognoses. The applicability of risk assessment tools developed in VKA-treated populations to NOAC users requires systematic reassessment, because these tools form the backbone of a multitude of clinical decision algorithms. Similarly, imaging features including location, growth, and edema dynamics, or interplay with classical metrics suggestive of enlargement, such as spot sign or hematoma density heterogeneity, also need reevaluation in this specific clinical setting. Ideally studies should include other neurologic complications like NOAC-related subarachnoid or subdural hemorrhage. All these achievements will hopefully then pave the way for successful management of these patients, where the development of reversal agents was an important step in the right direction, but needs to be followed by additional therapeutic advancements.
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REFERENCES