When Should We Measure Anti-Xa Activity?

Fixed-dosage apixaban therapy significantly reduces adverse bleeding events compared with adjusted-dosage warfarin with PT monitoring. However, it is still possible that adverse events under apixaban therapy may occur in AF patients with a high risk of bleeding. To reduce bleeding events, it might be reasonable to monitor apixaban plasma concentration in such circumstances. Baglin et al reported that the following situations may be appropriate for monitoring anti-Xa activity: bleeding incidents, perioperative management, and suspicion of overdose because of worsening of renal function. In addition, patients’ non-adherence to anticoagulant NOAC therapy is associated with thromboembolic events. When the thrombotic event occurs, measuring anti-Xa activity may be useful to monitor whether patients are regularly taking NOACs. The cost of measuring anti-Xa activity is another issue to be solved in the future, because it is not covered by insurance.
Does the Therapeutic Range Matter for NOACs?
In the era of anticoagulant therapy with warfarin, the concept of the time in the therapeutic range (TTR) was used to monitor effectiveness of anticoagulant activity. However, titrating the dose of warfarin to maintain a higher TTR was challenging and often unsatisfactory. In fact, clinical trials of NOACs (RE-LY, ROCKET-AF and ARISTOTLE) revealed that NOACs were superior or at least non-inferior for preventing stroke compared with warfarin, the TTR of which was only 55–65% in patients with NVAF. The ARISTOTLE study demonstrated safety and efficacy profiles of apixaban without monitoring anticoagulant activity compared with dose-adjusted warfarin.1 These results led to the conclusion that the concept of therapeutic range does not matter when we use NOACs, even if the plasma concentration may vary according to individual metabolism, unless the patients meet the criteria of recommended dose reduction. However, the RE-LY trial revealed that major bleeding risk, mainly from the intestine, was associated with the trough value of dabigatran plasma concentration.2 Taken together these results suggest that we still should be careful with patients with a high bleeding risk, although the concept of therapeutic range is no longer practical with NOACs.

In this regard, Osanai et al report no significant differences in trough and peak anti-Xa activity in patients with bleeding events compared with those without events, raising the question that measuring anti-Xa activity does not identify high-risk patients. However, it may be associated with the small number of bleeding events in their study and the fact that anti-Xa activity was measured in the steady state, but not when adverse events occurred. Further assessment of anti-Xa activity in patients at high risk of bleeding because of worsening of renal function or age-associated poor drug metabolism is required.

Measurement of Anti-Xa Activity: Peak or Trough?
Apixaban has multiple metabolic pathways, a small volume distribution, a plasma half-life of almost 12 h, and is taken twice daily.3 In contrast, rivaroxaban, another Xa inhibitor, is taken once daily with a similar plasma half-life to apixaban. Median time to peak plasma concentration (Tmax) is 2 h (min taken once daily with a similar plasma half-life to apixaban).4 Than for apixaban (4.7).5

In the present study, Osanai et al point that high dose, age, and serum creatinine were significantly associated with high anti-Xa activity at both the trough and peak level.6 In fact, elderly people have various comorbidities, renal dysfunction, malnutrition, and take many concomitant drugs, including antibiotics, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).7,8 Preexisting malignancies also should not be forgotten in the elderly.9

In summary, to avoid adverse events, it is important to administer the recommended dose of NOACs, to monitor renal function as appropriate, to avoid concomitant use of aspirin and/or NSAIDs, and to exclude malignancy (Figure).

Conflicts of Interest
None declared.

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How to Avoid Adverse Events
Phase III clinical trials of other NOACs, including dabigatran (RE-LY) and rivaroxaban (ROCKET-AF), resulted in increased gastrointestinal bleeding compared with warfarin therapy. Apixaban has been reported to be a safe drug compared with warfarin and other NOACs.1 In the present study, Osanai et al point that high dose, age, and serum creatinine were significantly associated with high anti-Xa activity at both the trough and peak level. In fact, elderly people have various comorbidities, renal dysfunction, malnutrition, and take many concomitant drugs, including antibiotics, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Preexisting malignancies also should not be forgotten in the elderly.

In summary, to avoid adverse events, it is important to administer the recommended dose of NOACs, to monitor renal function as appropriate, to avoid concomitant use of aspirin and/or NSAIDs, and to exclude malignancy (Figure).

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