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Gaining experience with the NOACs

Pieter W. Kamphuisen UNIVERSITY MEDICAL CENTER GRONINGEN

In this issue of *Blood*, Beyer-Westendorf et al analyzed the safety of long-term treatment with the novel oral anticoagulant (NOAC) factor Xa inhibitor, rivaroxaban, in a large registry of patients from their clinical practice with either venous thromboembolism (VTE) or atrial fibrillation.[1] During treatment, the annual major bleeding rate associated with rivaroxaban treatment was 3% to 4%, and did not differ between patients with VTE or atrial fibrillation. In addition, 60% of the major bleeding events were treated conservatively, by compression therapy or blood transfusion. Finally, the mortality rate due to bleeding after 90 days of treatment was 6.3%. All together, this study provides valuable data on the safety of rivoraxaban. Valuable, because most data on the safety of NOACs come from the phase 3 trials and not from clinical practice.

Since the worldwide registration for the prevention and treatment of VTE and the prevention of ischemic stroke in patients with atrial fibrillation, an increasing use with these anticoagulants has been reported.[2] The great advantage of the NOACs is the simplicity of the treatment, where due to the stable therapeutic effect, no routine monitoring is required. Furthermore, the net clinical benefit in terms of efficacy and safety compared with vitamin K antagonists (VKA) was favorable in the large phase 3 trials in patients with VTE and atrial fibrillation, and was recently summarized in 2 meta-analyses.[3,4] On the other hand, especially in patients with atrial fibrillation, gastrointestinal bleeding, the most common major bleeding complication, seems higher with NOAC treatment than with VKA.[3] Insofar as there is no direct antidote available at present, physicians may be reluctant to prescribe NOACs for their patients. In addition, we know that patients in randomized controlled trials may be healthier and carry a lower bleeding risk than the patients seen in clinical practice.[5] So, in order to better guide clinicians in their decision as to which anticoagulant they could prescribe for their patients, real life data are needed.

In the prospective Dresden Registry, over a period of 2 years, Beyer-Westendorf et al assessed the bleeding rate in 1776 patients who were treated with a therapeutic dose of rivaroxaban. A large dataset of patients such as this provides important clinical information on the safety of NOAC treatment, the severity and outcome of the bleeding, as well as how the major bleeding is treated. Most of the events were treated conservatively, while in other cases intervention (endoscopy) or surgery was necessary to stop the bleeding. In 9% (6 patients) prothrombin complex concentrate (PCC) was administered, next to fresh frozen plasma in most cases. Notably, the physicians most often administered a dose of 2000 IU of PCC, which corresponds to approximately 25 IU/kg. This is less than the dose used in the healthy volunteer study with rivaroxaban, where 50 IU/kg was given.[6] Nevertheless, in 5 patients the bleeding stopped and 1 patient died of intracerebral bleeding. None of these patients developed arterial or venous thrombosis as a side effect of PCC treatment. Although the number of patients treated with PCC in the study was small, it provided important information, since data on prohemostatic treatment of NOAC-related bleeding are scarce, and clinical guidelines give no clear recommendation on what type of prohemostatic agent should be administered in the absence of evidence.[7] Recently, a clinical phase 3 study assessing the direct reversal of dabigatran with the antibody idarucizumab in patients with severe bleeding or emergency surgery has just started recruitment (ClinicalTrials.gov identifier: NCT02104947). Also, a phase 2 study with the antibody PRT064445 against direct/indirect factor Xa inhibitors in healthy volunteers has been completed (ClinicalTrials.gov identifier: NCT1758432), and a phase 3 study is being planned. In the meantime, in the absence of a direct antidote for NOACs, it will be important for all hospitals where patients are treated with NOACs to have a local protocol for the treatment of NOAC-related bleeding, where a step-up algorithm for a transfusion strategy and prohemostatic treatment is documented. Hopefully, this will also lead to more outcome data on the reversal of NOACs, such as in the current study, which is a great example of how local initiatives can lead to unique information.

Conflict-of-interest disclosure: P.W.K. is a consultant for Boehringer Ingelheim and is a steering committee member of the ongoing dabigatran reversal study with idarucizumab. ■

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