CORRESPONDENCE

Oral Anticoagulation

Update on Anticoagulation With Vitamin K Antagonists and Non-Vitamin K-Dependent Oral Anticoagulants

by PD Dr. med. Ertunc Altioek and Prof. Dr. med. Nikolaus Marx in issue 46/2018

Suffers From Conflicts of Interest

Although Altioek and Marx cite important statements on non-vitamin K antagonist oral anticoagulants (NOACs), such as the non-necessity of bridging shown in the BRIDGE study, contraindications for artificial heart valves, and not switching treatment for patients who react well to vitamin K antagonists (VKA), the article does not give an objective view of the study situation (1).

In particular, in the abstract, the authors uncritically follow the European Society of Cardiology (ESC) recommendations by favoring NOACs over VKA. However, these recommendations suffer from conflicts of interest. The well-founded opinion of the Drug Commission of the German Medical Association, that VKA should be the first-line drug of choice, are not mentioned.

Despite the supposed superiority of NOACs postulated by the authors, German real-world data shows the opposite situation. The data presented on the quality of anticoagulation using VKA of TTR (time in therapeutic range) of 55%–65% do not agree with the German TTR (of more than 70%). In Germany, NOACs offer no advantages over VKA. DOI: 10.3238/arztebl.2019.0220a

Reference

1. Altioek E, Marx N: Oral anticoagulation—update on anticoagulation with vitamin K antagonists and non-vitamin K-dependent oral anticoagulants. *Dtsch Arztebl Int* 2018; 115: 776–83.

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Conflict of interest statement

Dr. Maibaum has received honoraria from Thieme Medical Publishers.

Cause of Discrepancy

The article describes the findings of the initial studies on the treatment with direct oral anticoagulants (DOACs) (1). Using a health insurance claims-based data following market entry, Ujeyl and co-workers compared the incidence rate of clinical events with DOACs to those with phenprocoumon (2). As in the pivotal trials, significantly less bleeding occurred with dabigatran and apixaban, but not with rivaroxaban.

Gastrointestinal bleeding occurred 21% more frequently with dabigatran, and 28% with rivaroxaban, but intracranial bleeding occurred less frequently (rivaroxaban, –61%; dabigatran, –43%) (2). Surprisingly, ischemic stroke occurred 84% more frequently with apixaban, and the all-cause mortality was higher with rivaroxaban than with phenprocoumon (2).

Which causes can explain this discrepancy? This may be due at least in part to a faulty or too superficial therapy with DOACs, which is still supported by the summary of product characteristics (“no monitoring”) (3). Regular laboratory controls (liver, kidney) are required in order to allow early detection of dysfunctions and possible adaptations of the therapy strategy. Also, metabolism of DOACs in older patients with comorbidities can be profoundly altered. Therefore, regular quantification of DOAC levels should be carried out using anti-Xa activity assays (for all except dabigatran, for which the ecarin clotting time [ECT]/diluted thrombin time [dTT] should be used). It would be helpful if consensus recommendations for actions were developed, to determine when, with which tests, and on the basis of which target values DOAC monitoring should be carried out, and what are the consequences of deviations from the target range (3).

As an aside, it should be noted that the incidence of intracranial bleeding among vitamin K antagonists is more than halved if the target INR range is chosen to be between 1.8–2.4 for atrial fibrillation and venous thromboembolism. At INR values of 2.5–3, the probability of intracranial bleeding is twice as high as thrombosis protection (4). DOI: 10.3238/arztebl.2019.0220b

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1. Altioek E, Marx N: Oral anticoagulation—update on anticoagulation with vitamin K antagonists and non-vitamin K-dependent oral anticoagulants. *Dtsch Arztebl Int* 2018; 115: 776–83.
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3. Der Arzneimittelbrief: Orale Antikoagulationen: besseres Medikationsmanagement erforderlich. www.der-arzneimittelbrief.de/de/Artikel.aspx?J=2018&S=41 (last accessed on 26. February 2019).
4. Hylek EM, Singer DE: Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994; 120: 897–902.

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Conflict of interest statement

The author declares that no conflict of interest exists.

In Reply:

We would like to thank the authors for their contributions to the discussion, which takes into account further data from real-life studies regarding the use of non-vitamin K antagonist oral anticoagulants (NOACs). The data cited by our colleagues Maibaum and Egidi, about the lack of advantages of NOACs as compared to vitamin K antagonists (VKA) with good INR values, support our statement in the section “Differences between the substances” in our article (1). Indeed, the treatment reality of INR values varies between different surveys and studies. Against this background, it should again be noted that INR self-management by patients may increase time in therapeutic range (TTR) and is associated with a lower rate of VKA thromboembolic events, but does not affect frequency of bleeding complications or mortality (2). The differences in the results on bleeding complications and ischemic events between the prospective controlled and randomized pivotal studies and the real-life data, as highlighted by our colleague Kieseewetter, once again demonstrate the limitations of these two approaches for generating results. Furthermore, the author rightly refers to the importance of monitoring liver and kidney values with NOACs, whereby the INR controls with VKA must be much more closely followed, especially in light of the INR-influencing factors of diet and co-medication. This interaction is less pronounced in NOACs. Quantification of the anti-Xa activity or the ecarin clotting time/ diluted thrombin time with NOACs is of therapeutic interest; however, this approach was not chosen in randomized trials, so that there currently is no evidence to support this benefit. Furthermore, the approach of using a decreased INR target range under VKA, which reduces the risk of bleeding, is mentioned as a therapeutic option. However, against the background of possibly of an increased risk of thromboembolism, this approach is not listed in the recommendations of the specialist societies.

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1. Altioek E, Marx N: Oral anticoagulation—update on anticoagulation with vitamin K antagonists and non-vitamin K-dependent oral anticoagulants. *Dtsch Arztebl Int* 2018; 115: 776–83.
2. Heneghan C, Ward A, Perera R, et al.: Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012; 379: 322–34.

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Conflict of interest statement

Dr. Altioek has received reimbursement for conference registration fees and travel and accommodation expenses, as well as speaking honoraria, from Daiichi Sankyo. Fees for conducting clinical contract research studies from Bayer were passed on to the University Hospital RWTH Aachen.

Prof. Marx has carried out lecture and consulting services for Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, and Daiichi Sankyo; the University Hospital RWTH Aachen received the honoraria for these activities. He was also responsible for third-party funding received by the University Hospital RWTH Aachen from Boehringer Ingelheim, Daiichi Sankyo, and Pfizer.

CLINICAL SNAPSHOT

Siphon-Like Gall Bladder Hydrops in Chronic Cholelithiasis

An 87-year-old woman came to our emergency room complaining of diffuse abdominal pain. Laboratory testing revealed microcytic anemia (hemoglobin 5.9 mmol/L) with normal leukocyte and platelet counts, as well as a high C-reactive protein concentration (48.4 mg/L) and elevation of the cholestasis parameters alkaline phosphatase (12.32 $\mu\text{mol/L/s}$) and gamma-glutamyltransferase (33.03 $\mu\text{mol/L/s}$), with normal bilirubin and transaminase values. Abdominal ultrasonography revealed intra- and extrahepatic cholestasis with a markedly enlarged gall bladder containing large concretions. Computed tomography then yielded the finding illustrated at left, a siphon-like, hydropic, stone-filled gall bladder extending into the pelvis, with a tortuous and enlarged cystic duct and a papillary concretion in the common hepatic duct (arrow). The latter was then removed via endoscopic retrograde cholangiopancreatography. Histological examination of the prominent papilla revealed a florid, longstanding erosive papillitis, most likely due to recurrent outflow of concretions. After removal of the concretion and insertion of a stent, the biliary pathways were promptly unblocked and the cholestasis parameters reverted to normal. Elective cholecystectomy was recommended.

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