CORRESPONDENCE

Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) as an Alternative Treatment Option in Tumor-Related Venous Thromboembolism

by PD Dr. med. Jan Beyer-Westendorf, PD Dr. med. Robert Klamroth, PD Dr. med. Stephan Kreher, PD Dr. med. Florian Langer, Prof. Dr. med. Axel Matzdorff, Prof. Dr. med. Hanno Riess in issue 3/2019

Skewed Recommendations Due to Conflicts of Interest

To compare NOAC with low molecular weight heparin (LMWH) in cancer-associated venous thromboembolism (VTE), a randomized, controlled trial has been published for edoxaban as well as for rivaroxaban, including the methodological weaknesses. For instance, neither trial was blinded, and efficacy was evaluated by including VTE, which was evident solely through imaging as it has no clinical symptoms (1, 2). Even these VTEs were significantly reduced only in one study (1), in contrast to the significant increase of major bleeding (2) as well as clinically relevant non-major bleeding (1, 2). The benefit-to-harm ratio of NOAC in cancer-associated VTE is thus at best unclear.

Nonetheless, the authors present NOAC as an alternative treatment option (3). They have numerous conflicts of interest through financial relationships with NOAC manufacturers. According to the Acknowledgments, two other people played a “significant role” in the article who also receive funds from all NOAC manufacturers.

Several statements of the recommendations are distorted in favor of the pharmaceutical entrepreneurs: for instance, the authors do not mention in the conclusion the increased risk of bleeding with NOAC. When presenting a meta-analysis, they omit in a key statement that the reduction in VTE recurrence under NOAC is only a numerical trend, and that only the increased risk of major bleeding is statistically significant. Such a “spin” of the conclusions, in favor of the sponsor, has also been shown in pharmaceutically funded clinical trials (4).

In the interest of cancer patients, reliable data that demonstrate the superiority of NOAC over LMWH and as an oral alternative to vitamin K antagonists would be welcome. The current study situation is not sufficient for this. Especially for clinical situations with insufficient evidence from trials, recommendations should be made by authors who are free from conflicts of interest through financial ties with pharmaceutical companies.

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References

1. Young A, Marshall A, Thirlwall J, et al.: Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018; 36: 2017–23.
2. Raskob G, van Es N, Verhamme P, et al.: Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018; 378: 615–24.

3. Beyer-Westendorf J, Klamroth R, Kreher S, Langer F, Matzdorff A, Riess H: Non-vitamin K antagonist oral anticoagulants (NOAC) as an alternative treatment option in tumor-related venous thromboembolism. *Dtsch Arztebl Int* 2019; 116: 31–8.
4. Schott G, Pacht H, Limbach U, Gundert-Remy U, Ludwig WD, Lieb K: The financing of drug trials by pharmaceutical companies and its consequences: Part 1. A qualitative, systematic review of the literature on possible influences on the findings, protocols, and quality of drug trials. *Dtsch Arztebl Int* 2010; 107: 279–85.

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Conflict of interest statement

Dr. Schott is a member of MEZIS (*Mein Essen zahl ich selbst*, I pay for my own lunch).

Dr. Schurig is on the board of MEZIS and has received reimbursement for conference participation fees as well as travel and accommodation expenses from MEZIS.

Ms. Dannenberg is on the board of MEZIS.

Dr. Wille is a member of the Drug Commission of the German Medical Association and member of the editorial board of the *arznei-telegramm*

In Reply:

In both open-label trials, endpoint assessment was blinded according to the internationally accepted PROBE design (1). The inclusion of VTE incidental imaging findings made sense, as these events are prognostically important in cancer patients (2, 3).

Both studies reported a combined endpoint of efficacy and safety, in light of the increased risk of embolism and bleeding from cancer patients, and in this respect, both NOACs were equivalent to LMWH. The reduction of thromboembolism at the expense of higher rates of bleeding highlights the fact that every patient needs a benefit-risk assessment—even with LMWH treatment.

A LMWH treatment that lasts over several months impairs the quality of life of cancer patients. In the criticized studies, patient-initiated discontinuation of therapy was more common in the LMWH arm. This makes it clear that the recommendations for LMWH (which are also based on pharmaceutically-funded, open-label PROBE trials) as the standard of care are difficult to implement. When it comes to a benefit-to-

harm ratio, patient preference for an oral therapeutic alternative must be recognized.

We neither work for pharmaceutical companies nor skew recommendations. We provide our expertise from years of clinical and scientific work with cancer patients, and an precise knowledge about the benefits and limitations of alternative therapies, not only to patients and medical colleagues but also to the research-based pharmaceutical industry. Expertise is indispensable for the correct execution and interpretation of clinical trials and for improved patient care.

We have clarified when a therapy with NOAC is problematic (4). Transparent disclosure of conflicts of interest does not preclude us from providing medical advice, but it does enable the reader to weigh recommendations against conflicts of interest, to make different recommendations, or to set up studies of their own without pharmaceutical promotion. In clinical research, vigilance, transparency, and critical dispute are important. Rejecting expert opinions and trial results solely on account of potential conflicts of interest is no longer appropriate in light of the increasing specialization in medicine as well as the complexity and costs of modern trial methodology. DOI: 10.3238/arztebl.2019.0420b

References

1. Beyer-Westendorf J, Büller H: External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? *J Thromb Haemost* 2011; 9: 2153–8.
2. Di Nisio M, Carrier M: Incidental venous thromboembolism: is anticoagulation indicated? *Hematology Am Soc Hematol Educ Program* 2017; 2017: 121–7.
3. van der Hulle T, den Exter PL, Planquette B, et al.: Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. *J Thromb Haemost* 2016; 14: 105–13.
4. Beyer-Westendorf J, Klamroth R, Kreher S, Langer F, Matzdorff A, Riess H: Non-vitamin K antagonist oral anticoagulants (NOAC) as an alternative treatment option in tumor-related venous thromboembolism. *Dtsch Arztebl Int* 2019; 116: 31–8.

On behalf of the authors

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Conflict of interest statement

PD Beyer-Westendorf has received speaking and/or consultant honoraria from EO Pharma, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Daiichi Sankyo, and Portola, travel expenses and registration fee reimbursement from LEO Pharma, Bayer, and Daiichi Sankyo, and fees (third-party account) for conducting commissioned clinical trials for LEO Pharma, Bayer, Pfizer, Boehringer Ingelheim, Janssen, Daiichi Sankyo, and Portola.