CORRESPONDENCE

Deep Vein Thrombosis of the Upper Extremity

A Systematic Review

by Jan Heil, Prof. Dr. med. Dr. med. habil. Wolfgang Miesbach, Prof. Dr. med. Thomas Vogl, Prof. Dr. med. Wolf O. Bechstein, and Dr. med. Alexander Reinisch in issue 14/2017

In Accordance With Guidelines?

Is therapy of deep vein thrombosis of the upper extremity with non–vitamin K oral anticoagulants (NOACs) covered by approval or by guidelines? The licensing studies have only included patients with deep vein thrombosis of the lower limb. However, the prescribing information for Apixaban and Xarelto state broadly "for the treatment of deep vein thrombosis". The guidelines refer even more generally to "vein thrombosis", and each has a section on upper-extremity thrombosis, jugular vein thrombosis, and catheter-associated thrombosis. However, they do not specifically address the use of NAOCs in these types of thrombosis. For me, both the prescribing information and the guidelines appear to deem the use of NOACs as appropriate for all of these manifestations. Not mentioned in the guidelines are, for example, mesenteric vein thrombosis and hepatic vein thrombosis (Budd–Chiari syndrome). However, these are also deep vein thromboses. Is their treatment with NOACs also covered by the approval of NOACs, which indicates they are "for treatment of deep vein thrombosis"?

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Equivalent Treatment Options

In their systematic review, Heil et al. point to an issue that is also important in primary care, which we too seldom consider when presented with complaints about the upper extremity (1).

However, the subjective assessment of the authors regarding maintenance therapy, which compares the use of vitamin K antagonists (VKA) (usually phenprocoumon in Germany) with NOACs/DOACs, cannot remain unchallenged. Although major bleeding events for NOACs/DOACs occur less frequently, the risk of gastrointestinal bleeding is significantly higher (at least in the studies comparing VKAs with NOACs/DOACs in treating nonvalvular atrial fibrillation) (2). The authors furthermore omit to mention the fact that the number needed to treat to prevent a fetal bleeding with NOACs/DOACs as compared to VKA is 1:111 (3). Also, in contrast to the German guideline, the authors do not point out that there are no NOAC/DOAC studies on upper-extremity deep vein thrombosis. Additionally, during 2016, the number of reports of serious side effects for phenprocoumon submitted to the Drug Commission of the German Medical Association (28 reports) was clearly exceeded by the more than 175 reports for NOACs/DOACs (excluding those for edoxaban) (although this may be due to willingness to report new substances rather than established ones) (4).

It is therefore difficult to understand why VKAs are not listed in the Table. Thus, VKA therapy—which in my opinion is as valid for this indication as other drugs—should remain an option.

Finally, the fact that low-molecular-weight heparins are not approved for maintenance therapy of thromboembolism, and that doing so would formally be an off-label use, is not mentioned.

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Additional Information Necessary

The authors state that, after catheter-related upper extremity vein thrombosis, a functional catheter that is still required can continue to be used together with anticoagulation (1). We have many patients with portal vein thrombosis who do not want to have their port removed even after treatment completion, due to a risk of relapse (for example, breast cancer patients after adjuvant chemotherapy). If the port stays in place for a few years, how long would the authors recommend

using anticoagulant drugs for these patients—for the entire time? Would a therapeutic anticoagulant dose be administered the entire time, or would it be "dialed down" to a prophylaxis dose? Which drug should be used (vitamin K antagonist, direct oral anticoagulant)? No study data exist for this. It would certainly be interesting to hear how the authors proceed in their daily practices.

In the prophylaxis section, the authors state that it is unclear whether prophylaxis has a positive influence on the incidence of deep vein thrombosis (DVT) of the upper extremity but that prophylactic anticoagulation is indicated, as tumor patients are also threatened by DVT of the lower extremity. No distinctions are made between outpatients and inpatients, or surgery patients and patients with cancer. However, there is no indication for thrombosis prophylaxis for cancer outpatients (perhaps with the exception of patients with pancreatic carcinoma treated with chemotherapy or myeloma treated with IMiDs). The guidelines also advise against thrombosis prophylaxis for cancer outpatients. For which patients would the authors then recommend a prophylactic anticoagulation, and with which anticoagulant?

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Further Conditions in Young Patients

Thankfully, Heil et al. have now addressed in their work a clinical picture that frequently occurs in everyday clinical practice yet has a therapy that raises many questions, which are often insufficiently answered by reliable data (1). In addition, an important causal complex should be pointed out here.

Especially for younger patients, the compression syndromes of the upper thoracic outlet (the so-called thoracic outlet syndrome [TOS]) may give rise not only to lesions of the arterial tract but also to compression and damage of the subclavian or axillary vein. This may have a constitutional basis (compression of the anterior scalene muscle, presence of a cervical rib) or be due to excessive physical stress (bodybuilding, effort-induced thrombosis) in terms of a Paget–von Schrötter disease. In addition to anticoagulation and potentially recanalization, elimination of the anatomical obstruction (for example, the cervical rib) also plays a role in therapy (2, 3).

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In Reply:

We would like to thank Prof. Kröger for his comment on the therapy of deep vein thrombosis of the upper extremity (DVT-UE). Not only the German S2k guideline but also the more current, English-language recommendations and guidelines list direct oral anticoagulants (DOAC) as a therapy option for deep vein thrombosis without distinguishing between upper and lower extremities. It was pointed out that these substances have not been tested separately for the therapy of DVT-UE (1, 2). In February 2017, a phase IV study was initiated that explicitly assesses using Apixaban for the treatment of DVT-UE with respect to the endpoints "thromboembolism-related deaths," "symptomatic recurrences," and "bleeding complications." Results are expected for 2019 (Apixaban for Routine Management of Upper Extremity Deep Venous Thrombosis [ARM-DVT]; NCT02945280).

DOACs cannot currently be recommended as a therapy for mesenteric vein thrombosis or Budd–Chiari syndrome: the efficacy of these substance classes has not been investigated, and the alterations of the liver function that are frequently associated with these diseases can lead to pharmacological problems (3).

Dr. Maibaum rightly points out that vitamin K antagonists (VKA) are not listed in the Table in our article. We mention this drug group in the text and have in no way made a judgement for or against VKAs in the treatment of DVT-UE. We believe that the anticoagulation therapy for DVT-UE must be individually adapted to the clinical circumstances of each patient, and that VKA is an important treatment option. Regarding the licensing conditions of low-molecular-weight heparins, we point out in the footnotes to the Table that the pertinent licensing conditions of substances need to be considered.

The question posed by Prof. Matzdorff regarding the duration of anticoagulation in the presence of foreign bodies (for example, a port system) and DVT-UE is frequently asked in the everyday clinical practice. According to the current recommendations, published by Streiff and Rajasekhar, we carry out anticoagulation until the removal of the foreign body, but for at least

three months (4, 5). For indispensable foreign bodies, such as heart pacemakers, we stop anticoagulation after three months. On the other hand, we would not leave in a port system for DVT-UE in case of tumor recurrence but rather would remove it and stop the anticoagulation therapy. Prolonged maintenance therapy may be indicated, following the criteria published in the S2k guideline. Here, no distinction is made between leg and arm vein thrombosis (2).

The indication for thrombosis prophylaxis follows the S3 guideline "Prophylaxis of venous thromboembolism (VTE)." This recommends thrombosis prophylaxis for specific risk factors for non-immobilized cancer outpatients. For example, patients who are discharged following abdominal tumor surgery receive a drug-based thrombosis prophylaxis for about 4 weeks postoperatively. In the absence of contraindications and side effects, low-molecular-weight heparins are used for this (6).

In his contribution, Dr. Hertting explicitly mentions again thrombosis of the upper limb caused by compression syndromes or overexertion and their treatment. This is important to note. Due to the size limitations for the printed edition of our article, we included these points as part of the eSupplement of the article (7).

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