

# Thrombosis of atypical location: how to treat patients in the era of direct oral anticoagulants?

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## KEY WORDS

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## ABSTRACT

In 4% of cases, venous thromboembolism (VTE) involves organ-related venous territories such as splanchnic, renal, gonadal, and cerebral venous segments, and is often called venous thromboembolism of atypical location (VTE-AL). Recommendations regarding the method, intensity, and duration of anticoagulant therapy for VTE-AL are not well established. Direct oral anticoagulants (DOACs) have been a promising alternative to vitamin K antagonists in the treatment of acute VTE. However, all major clinical trials on DOACs excluded patients with VTE-AL. Therefore, data on the use of DOACs in patients with VTE-AL are still limited to case reports and small clinical series, with a relative predominance of publications on splanchnic vein thrombosis including mesenteric, splenic, portal, and hepatic vein thrombosis. The only randomized clinical trial comparing a clinical outcome of patients with acute portal vein thrombosis randomized to either rivaroxaban or warfarin treatment yielded significantly impaired results due to the use of an atypical rivaroxaban dose. A prospective registration of clinical outcome for DOACs used in patients with VTE-AL, in those with VTE of typical location, and in those with VTE-AL treated with enoxaparin showed similar VTE recurrence and major bleeding rates in all 3 groups. High cancer prevalence, typical for VTE-AL, significantly impacted survival as well as VTE recurrence rates and major bleeding outcomes in this study. In general, although still limited, the results for DOAC use in VTE-AL are encouraging and we do not hesitate to use DOACs, particularly rivaroxaban or apixaban, in selected patients with VTE-AL.

**Introduction** Venous thromboembolism (VTE) is a common clinical entity affecting approximately 1 to 2 per 1000 patients.<sup>1</sup> These events primarily involve the deep veins of the lower extremities (deep vein thrombosis [DVT]), which may lead to embolization to the pulmonary arteries (pulmonary embolism [PE]). The risk of mortality associated with a PE is high, and prompt identification and treatment initiation with anticoagulants is a medical emergency.<sup>2</sup> About 4% of VTE cases involve other venous territories, sometimes called venous thromboembolism of atypical location (VTE-AL), with sites that include<sup>3</sup> splanchnic,<sup>4</sup> renal,<sup>5</sup> gonadal,<sup>6,7</sup> and cerebral venous segments.<sup>8</sup> Although relatively infrequent, VTE-AL cases are commonly associated with malignancy and have a direct bearing on the organ drained by the thrombosed vein,

making this type of thrombosis clinically important and challenging. As opposed to proximal leg DVT and PE, which have well established therapeutic recommendations based on randomized clinical trial (RCT) data,<sup>2</sup> recommendations regarding the method, intensity, and duration of anticoagulation for VTE-AL are less well established.

Direct oral anticoagulants (DOACs) have been a promising alternative to vitamin K antagonists (VKAs) in the treatment of acute VTE. The main causes of their growing popularity are the ease of administration, lack of routine monitoring, dietary freedom, and in the case of rivaroxaban and apixaban, avoidance of initial parenteral pretreatment with heparinoids. DOACs have been thoroughly tested and are as effective for initial treatment of DVT and PE as VKAs.<sup>9-13</sup> Dabigatran and edoxaban were found to have the rate

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of major bleeding similar to that for VKAs,<sup>12,13</sup> while apixaban therapy was associated with a lower rate of major bleeding.<sup>11</sup> Treatment with rivaroxaban showed a lower rate of major bleeding in patients with PE<sup>10</sup> but a similar rate of major bleeding in DVT patients as compared with VKA-treated individuals.<sup>9</sup> All major clinical trials with DOACs have studied only patients with proximal leg DVT, PE, or both. As a result, no RCT data are available for the efficacy and safety for VTE-AL.

**Cerebral venous sinus thrombosis** Cerebral venous sinus thrombosis (CVST) predominantly involves women (75%), often on hormonal stimulation, and is a relatively rare type of VTE, with an annual incidence of 3 to 4 cases per million.<sup>14</sup> The effect of treatment with heparinoids has been examined in 3 small RCTs. The first RCT was prematurely closed because of interim analysis showing a significant benefit with heparin.<sup>15</sup> The second one compared low-molecular-weight heparin (LMWH) with placebo for 3 weeks with subsequent warfarin therapy for both groups. It showed no clear benefit of anticoagulation with LMWH.<sup>16</sup> The third one used inaccurate diagnostic methods.<sup>17</sup>

The most recent search of the Cochrane Stroke Group Trials database found limited evidence on anticoagulant treatment for CVST, but anticoagulation appeared to be safe and was associated with a nonsignificant tendency for reduction in the risk of death or dependency.<sup>18</sup> More aggressive treatment, particularly in CVST patients who show no improvement on anticoagulation therapy, can be implemented. Endovascular aspiration thrombectomy with or without lytic therapy showed promising results in small clinical series.<sup>19-21</sup> Currently, most patients with CVST are treated with anticoagulation. In the biggest prospective study, International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), more than 80% of the 624 patients received anticoagulation. The optimal duration of oral anticoagulant treatment after the acute phase is unknown. Recurrent sinus thrombosis occurs in 2% of patients, and about 4% of patients have an extracranial thrombotic event within 1 year.<sup>22</sup> A retrospective analysis of patients with CVST and controls with leg DVT or PE treated at Mayo Clinic revealed a similar rate of VTE recurrence; therefore, a strategy of duration and intensity of anticoagulation comparable to patients with VTE of typical location was suggested.<sup>8</sup>

As of now, experience with DOACs in CVST is limited to case reports and small clinical series.<sup>23-25</sup> The first trial comparing VKAs with dabigatran is in progress, and final results are expected to be published by the end of 2018.<sup>26</sup> Our current therapeutic strategy for acute CVST is anticoagulation therapy including the use of DOACs,<sup>27</sup> with the duration and intensity similar to VTE of typical location according to the presence and persistency of a provoking factor.

**Gonadal vein thrombosis** Gonadal vein thrombosis (GVT) consists of 2 sex-dependent diagnoses: ovarian vein thrombosis in women<sup>6</sup> and testicular vein thrombosis in men.<sup>7</sup> GVT is associated with a high prevalence of cancer (over twice as frequent compared with control groups with leg DVT). GVT has also shown similar VTE recurrence and major bleeding rates compared with leg DVT.<sup>6,7</sup> Given the relative rarity of ovarian vein thrombosis and, even more so, testicular vein thrombosis, it is unlikely that an RCT of anticoagulant therapy will be forthcoming. Current clinical practice is that patients with acute GVT are treated with anticoagulation for 3 to 6 months.<sup>6,7,28,29</sup> Information about the use of DOACs for GVT is limited to a few case reports.<sup>27,30</sup> It continues to be the practice of Mayo Thrombophilia Clinic to provide anticoagulant therapy that includes also DOACs to patients with GVT in the absence of a direct contraindication, such as major bleeding.<sup>6,27</sup>

**Renal vein thrombosis** Renal vein thrombosis (RVT) is highly associated with underlying malignancy, particularly renal cell carcinoma.<sup>5</sup> Invasion of this cancer to the renal vein with extension to the inferior vena cava is often called tumor thrombus and thought not to require anticoagulation. However, thromboembolic complications of tumor thrombus have been reported.<sup>5,31</sup> Membranous nephropathy is another common cause of RVT, the prothrombotic potential of which and the need for anticoagulation are often overemphasized.<sup>5,32</sup> A comparison of RVT patients with leg DVT group showed that the recurrence rate of RVT was lower ( $P < 0.001$ ). This lower rate could be at least partially explained by the higher rate of mortality in the RVT group.<sup>5</sup>

Due to wide ranges of etiologies and varying potential risk of recurrent thrombosis and major bleeding, therapeutic decisions about anticoagulant therapy should be individualized. In general, it is reasonable to decide on duration and intensity of anticoagulation for RVT based on treatment guidelines applied for patients with leg DVT or PE.<sup>5</sup> Experience with DOAC use in patients with RVT is limited.<sup>27,33</sup> RVT may be associated with renal failure, limiting the use of some anticoagulants. For this reason, we favor apixaban from the group of DOACs and suggest caution in using dabigatran in these patients.

**Splanchnic vein thrombosis** Splanchnic vein thrombosis (SVT) consists of 4 types: mesenteric vein, splenic vein, portal vein, and hepatic vein thrombosis.<sup>3</sup> SVT is the most common form of VTE-AL. It is often associated with pathology in the adjacent or drained organ (eg, liver cirrhosis, pancreatitis, or malignancy including myeloproliferative neoplasm). It is the most studied type of VTE-AL.<sup>3,34-39</sup> Management of SVT is difficult. On the one hand, the high incidence of malignancy confers a high prothrombotic risk, and on the other, coexistence of liver cirrhosis with varices (secondary to portal hypertension) and

thrombocytopenia (secondary to hypersplenism) increases the risk of bleeding. In a prospective cohort study of 465 patients with SVT treated with anticoagulation (37.6%, parenteral treatment; 62.4%, VKAs), the rate of thromboembolism was 7.3 per 100 patient-years.<sup>34</sup> In a multivariable analysis, liver cirrhosis was found to be associated with an increasing risk of major bleeding. Yet, within the group of patients with cirrhosis, patients who were treated with anticoagulation had lower hemorrhagic risk compared with patients who were not anticoagulated.

The experts from the 9th edition of the American College of Chest Physicians Practice Guidelines<sup>40</sup> recommended treatment with anticoagulants for patients with symptomatic SVT (Grade 1B) but suggested no anticoagulation for those with asymptomatic thrombosis (Grade 2C). However, in a study by Tufano et al,<sup>35</sup> 212 patients with symptomatic SVT had a ratio between VTE recurrence and major bleeding of 5 to 10, while in 309 patients with incidental SVT, this ratio was 15 to 16. The authors of this study proposed that patients with incidental thrombosis should be treated with anticoagulants after a careful analysis of risk factors for hemorrhagic complications. There are several publications supporting the use of anticoagulation for patients with SVT with and without cirrhosis.<sup>4,15,34-39</sup> The European Society of Vascular Surgery recommends anticoagulation with heparin as first-line treatment, followed by a VKA or DOAC, for mesenteric vein thrombosis without peritonitis, in the absence of major contraindications.<sup>41</sup>

Although the use of DOACs in patients with SVT is still limited, it is better documented than in any other group of VTE-AL. In the current literature, we identified a single clinical trial, 3 retrospective clinical series,<sup>42-45</sup> and some case reports on the use of novel anticoagulants in this group of patients,<sup>46-50</sup> including case reports of clinical failure.<sup>51-53</sup> In an open-labeled clinical trial, 80 patients who developed acute portal vein thrombosis (PVT) after splenectomy or due to portal pyemia were randomly assigned either to rivaroxaban at an atypical dose of 10 mg every 12 hours or to warfarin.<sup>42</sup> In the rivaroxaban group, the resolution of PVT was achieved in 85% of patients, without VTE recurrence, major bleeding, or death. Among patients treated with warfarin, complete resolution of PVT was observed in 45% of cases; major bleeding, in 43.3%; recurrent VTE, in 10%; and death during follow-up, in 20%. In a study involving 39 patients with cirrhosis, there were 12 patients treated for SVT with apixaban or rivaroxaban (some received preventive doses) and 6 treated with warfarin or LMWH.<sup>43</sup> There was 1 major bleeding episode in the group receiving rivaroxaban or apixaban and 2 episodes in the latter group ( $P = 0.9$ ). No VTE recurrence was reported. Three deaths occurred during the study: in 2 patients, secondary to cirrhosis, and in 1 patient, due to intracerebral hemorrhage while on warfarin. In another retrospective analysis of patients

with cirrhosis, 27 received DOACs and 18 warfarin or LMWH.<sup>44</sup> There were fewer major bleeding episodes in the first group (1 vs 5,  $P = 0.03$ ). VTE recurrence occurred in 1 patient receiving DOACs and 1 patient receiving traditional anticoagulation ( $P = 1.0$ ). Investigators of the Vascular Liver Disease Interest Group Consortium<sup>45</sup> retrospectively reviewed clinical outcomes of 94 patients (including 75% of patients with SVT and 38% with cirrhosis) who were treated with rivaroxaban (83%), dabigatran (11%), or apixaban (6%). During a median duration of 15 (in cirrhotic patients) and 26.5 months (in noncirrhotic patients), there was 1 case of recurrent PVT and 5 cases of bleeding.

In summary, these limited data seem to indicate that DOACs can be used in patients with SVT. However, the results of the only RCT published so far are significantly impacted by the open-label design and, more importantly, the use of an atypical rivaroxaban dose that is not approved for VTE therapy. The other studies are limited by their retrospective design, lack of adequate control group, and inconsistency in dosing and duration of anticoagulation.

#### Direct oral anticoagulants in venous thrombosis of atypical location compared with venous thrombosis of typical location

The first and, so far, the only publication comparing clinical outcome of DOACs between patients with VTE-AL and those with VTE of typical location (DVT, PE, or both) is the prospective study of the Mayo Thrombophilia Clinic Direct Oral Anticoagulants Registry.<sup>27</sup> VTE recurrence, major bleeding, clinically relevant nonmajor bleeding, composite of major or clinically relevant nonmajor bleeding, and mortality of patients with VTE-AL treated with DOACs (cases) were compared to patients with DVT or PE or both treated with DOACs (first control group) and to VTE-AL patients treated with enoxaparin (second control group). Patients were seen promptly after diagnosis of acute VTE. Consistent information about guideline-endorsed anticoagulation therapy was uniformly provided based on a standardized script for providers and a short summary table for patients. This system operated on the basis of the uniformity of treatment process and reliability of follow-up organization, based on guideline recommendations, and yet was oriented at a patient clinical situation (including comorbidities such as renal and liver failure), willingness to take medication once or twice a day, as well as insurance situation. Among the 1038 patients enrolled into the registry during the analyzed period, there were 63 patients with acute VTE-AL and 560 patients with acute VTE of typical location. Within the VTE-AL group, there were 36 patients receiving a DOAC (rivaroxaban,  $n = 22$ ; apixaban,  $n = 14$ ), while 23 and 4 patients were treated with enoxaparin and warfarin, respectively. Patients with VTE-AL treated with a DOAC or enoxaparin had the following venous territories involved: splanchnic (DOAC,  $n =$

26; enoxaparin, n = 22), ovarian (n = 8; n = 2), renal (n = 3; n = 5), and cerebral veins (n = 1; n = 1). Two patients in the VTE-AL group treated with DOACs and 7 patients in the VTE-AL group treated with enoxaparin had thrombi in multiple locations. In the group with VTE of typical location, there were 352 patients treated with a DOAC (rivaroxaban, n = 219; apixaban, n = 133).

The VTE recurrence rate for the VTE-AL group receiving a DOAC was not different from that in patients with DVT or PE (7.3 vs 2.4 per 100 person-years,  $P = 0.13$ ) or that in the VTE-AL group receiving enoxaparin (7.3 vs 23.7 per 100 person-years,  $P = 0.37$ ).<sup>27</sup> In patients with underlying malignancy, the VTE recurrence rate was higher in VTE-AL patients treated with DOACs compared with patients with leg DVT or PE (25.4 vs 2.6 per 100 person-years,  $P = 0.02$ ) but comparable to that in VTE-AL patients treated with enoxaparin (25.4 vs 24.5 per 100 person-years,  $P = 0.81$ ). The rate of VTE recurrence was also comparable to the results previously reported in VTE-AL patients treated with a VKA or LMWH.<sup>4,34-36</sup>

Major bleeding rates were not different among VTE-AL patients compared with the group of patients with VTE of typical location treated with DOACs (7.2 vs 3.0 per 100 person-years,  $P = 0.26$ ) and compared with VTE-AL patients treated with enoxaparin (7.2 vs 22.4 per 100 person-years,  $P = 0.31$ ). Neither clinically relevant nonmajor bleeding rates nor the composite of major plus clinically relevant nonmajor bleeding rates differed between study groups. These results were also similar to the safety measures previously observed in patients with SVT treated with LMWH or VKAs.<sup>4,34-36</sup>

Mortality rates in VTE-AL patients treated with rivaroxaban and apixaban were higher than in patients with DVT, PE, or both, but not different from those in VTE-AL patients treated with enoxaparin. This difference reflected a higher proportion of patients with cancer in both VTE-AL groups. Mortality rates were also comparable to the previously reported rates for patients with SVT treated with LMWH or VKAs.<sup>4,34-36</sup>

In summary, clinical outcomes of apixaban- and rivaroxaban-treated patients with acute VTE-AL were not different when compared with patients treated for acute VTE of typical location and with enoxaparin-treated patients with VTE-AL, and was comparable to previously reported outcomes with traditional therapy with VKAs or LMWH. High cancer prevalence in this study impacted survival as well as VTE recurrence rates and major bleeding outcomes. Indeed, in VTE-AL group all adverse events occurred in cancer patients irrespective of treatment type. Nevertheless, the high proportion of patients with cancer in VTE-AL group reflects the demographic background of this population and was previously reported.<sup>3-8,35,36</sup>

**General remarks** There are still limited data on the use of DOACs in patients with VTE-AL. VTE-AL is relatively infrequent and it is difficult to

perform RCTs for this clinical entity. We also do not have adequately powered RCTs for “traditional” therapy of VTE-AL. It is encouraging that a clinical trial with dabigatran in patients with CVST is ongoing, with data becoming available by the end of 2018.

Use of DOACs in VTE-AL patients, particularly with SVT, can be potentially problematic. PVT could lead to severe liver failure and can significantly affect DOAC metabolism. Mesenteric vein thrombosis can be associated with venous congestion and impaired mesenteric perfusion and drug absorption. Very low gastrointestinal absorption of dabigatran (6%–7%) implies that slight fluctuations in absorption or elimination may have profound impact on plasma levels. Poor intestinal absorption also results in high concentrations of the prodrug dabigatran etexilate in feces, and once activated to dabigatran by intestinal or colonic mucosal esterases, it can significantly increase the tendency for gastrointestinal bleeding. RVT could be associated with renal failure and drug accumulation. Without reliable drug monitoring and close clinical surveillance, these problems could seriously affect the effectiveness and safety of therapy.

Despite all these concerns, limited results for DOAC use in VTE-AL are encouraging. The necessity of pretreatment with heparinoids for dabigatran and edoxaban significantly decreases the patient’s enthusiasm to use them for VTE therapy. Consequently, we have very limited experience with these 2 DOACs for VTE therapy of whatever location. We do not hesitate to use DOACs, particularly rivaroxaban or apixaban in selected patients with VTE-AL. Patients with VTE-AL frequently have underlying malignancy, and the recently published clinical trials on cancer-related VTE, although for venous thrombosis of typical location,<sup>54,55</sup> provide additional indirect support for the use of DOACs for cancer related VTE-AL.

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