

Direct oral anticoagulants for unusual-site venous thromboembolism

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Abstract

Direct oral anticoagulants (DOACs) are currently the preferred oral anticoagulant treatment for most of the patients with deep vein thrombosis of the lower extremities and/or pulmonary embolism. DOACs have several advantages over vitamin K antagonists, such as availability of fixed dosages, fewer drug interactions, faster onset of action, shorter half-life, and lower risk of major and intracranial bleeding. Although the evidence on the use of DOACs in patients with unusual-site venous thromboembolism (VTE) is limited to a few, small randomized controlled trials, these drugs are increasingly used in clinical practice, and several observational cohort studies have been published recently. This narrative review will describe the latest evidence for the use of the DOACs in patients with thrombosis in atypical locations (splanchnic, cerebral, upper extremity, ovarian, and renal vein thrombosis) and will provide some practical advice for their use in patients with unusual-site VTE.

KEYWORDS

Budd-Chiari syndrome, cranial sinus thrombosis, direct-acting oral anticoagulants, portal vein, upper extremity deep vein thrombosis, venous thromboembolism

1 | INTRODUCTION

Unusual-site venous thromboembolism (VTE) refers to thrombosis occurring in venous districts outside the veins of the lower limbs and the pulmonary arteries. Examples of atypical locations include abdominal veins (eg, splanchnic, renal, and ovarian), cerebral veins and venous dural sinuses, and the upper extremity venous system.¹

Direct oral anticoagulants (DOACs) are the preferred treatment for the majority of patients with deep vein thrombosis (DVT) of the lower extremities and/or pulmonary embolism (PE),^{2,3} and their advantages over vitamin K antagonists (VKAs) can also be relevant for patients with unusual-site VTE. For instance, DOACs have a more predictable anticoagulant response and fewer drug interactions, and thus can be administered at fixed doses.⁴ They have a faster onset of action and a shorter half-life, which can simplify the management

of the acute phase of VTE and preoperative interruptions, respectively.⁴ Furthermore, they are associated with a lower risk of major bleeding (MB), particularly intracranial hemorrhages (ICHs).^{5,6} Although DOACs simplify the management of anticoagulated patients, specific laboratory assays may be useful in some situations where there is a need to assess the anticoagulant plasma concentrations (eg, recurrent VTE on treatment) and there is still limited experience with the use of specific antidotes.⁴ Additionally, other types of bleeding might be increased, at least with certain DOACs, such as gastrointestinal (GI)⁶ and menstrual bleeding.⁷

DOACs were not extensively evaluated in patients with VTE in atypical locations, since these patients were not included in the pivotal phase III randomized controlled trials (RCT).⁵ Thus, the recommended anticoagulant treatment for unusual-site VTE still includes parenteral anticoagulation with unfractionated heparin (UFH) or

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low-molecular-weight heparin (LMWH), eventually followed by VKAs.^{8,9} However, in the past 5 years, some evidence has emerged from a few small RCTs and a number of observational studies assessing the safety and effectiveness of DOACs in patients with unusual VTE.¹⁰⁻¹² We also recently conducted a vignette-based survey showing that DOACs were considered by 23%-28% of physicians for patients with thrombosis of the splanchnic or cerebral veins and low bleeding risk.¹³

The aim of this narrative review is to provide an update on the latest evidence for the use of the DOACs in the most common sites of unusual VTE, namely, splanchnic, cerebral, upper extremity, ovarian, and renal venous thrombosis.

2 | SPLANCHNIC VEIN THROMBOSIS

2.1 | Overview

Splanchnic vein thrombosis (SVT) is a heterogeneous disorder that includes thrombosis of the portal, mesenteric, and splenic veins and Budd-Chiari syndrome (BCS). The most common risk factors for SVT are liver cirrhosis and solid cancer, which together account for ~50% of cases.^{14,15} Other risk factors include myeloproliferative neoplasm (MPN) or JAK2V617F mutation, abdominal surgery, abdominal inflammatory disorders or infections, and thrombophilia, while in 15%-27% of cases SVT is unprovoked.^{14,15} SVT can have different clinical presentations, including abdominal pain (48%-55%), GI bleeding (9%-26%), and ascites (10%-29%)^{14,15}; however, up to a third of cases are incidentally detected at abdominal imaging tests performed for other reasons.

SVT prognosis can also be challenging. These patients have a higher risk of bleeding events compared to those with usual-site VTE,¹⁶ but at the same time the risk of recurrent thrombosis is not negligible.¹⁵ In particular, patients with cirrhosis have the highest risk of both thrombotic and bleeding complications.¹⁵ Mesenteric vein thrombosis (MVT) can evolve into acute intestinal infarction and can be life-threatening, with very high short-term mortality rates (63% at 30-day).¹⁷ BCS is a particularly severe entity that can present with or rapidly progress to liver failure, and requires liver transplantation in >10% of patients.¹⁸

2.2 | General principles of treatment

In the absence of absolute contraindications, anticoagulation should be started early after SVT diagnosis, together with adequate prophylaxis for gastroesophageal varices bleeding, if needed,¹⁹ to improve recanalization rates and reduce the risk of GI bleeding.²⁰ A recent guidance document from the International Society on Thrombosis and Haemostasis (ISTH) suggested the possibility of prescribing DOACs for non-cirrhotic patients with acute symptomatic SVT and considering standard treatment with LMWH/VKAs if contraindications to DOACs are present.¹⁹ In cancer-associated SVT, LMWH/

Essentials

- Venous thromboembolism (VTE) may involve atypical locations.
- There is limited evidence on direct oral anticoagulants (DOACs) for unusual-site VTE.
- Published studies reported heterogeneity of dosages and starting time of DOACs.
- In selected patients with unusual-site VTE, DOACs showed good efficacy and safety profile.

DOACs were recommended over VKAs, with a preference for LMWH if luminal GI cancer, genitourinary neoplasm at high bleeding risk, or concomitant chemotherapy interacted with the DOACs.¹⁹ Finally, LMWH was suggested for cirrhotic SVT, with a switch to VKAs/DOACs if not contraindicated by severe liver dysfunction.¹⁹ Conversely, the recent guidelines of the American College of Gastroenterology suggested starting with parenteral anticoagulation and continuing with standard treatment (LMWH/VKAs), giving more importance to the limited experience with DOACs and the potential malabsorption due to intestinal edema.²¹

It has been debated whether patients with asymptomatic, incidentally detected SVT need the same therapeutic approach. While the 2012 guidelines of the American College of Chest Physicians (ACCP) suggested no anticoagulation,²² several studies published afterwards have shown that symptomatic and incidentally detected SVT share a similar risk of recurrent VTE.^{23,24} Thus, in the 2020 ISTH guidance, we suggested that the same therapeutic approach as for patients with symptomatic SVT should be followed.¹⁹

While general antithrombotic guidelines advocated an anticoagulant treatment duration of at least 3 months,²² gastroenterological guidelines indicated a minimum of 6 months.^{8,21} Factors associated with indefinite anticoagulant treatment duration included persistent risk factors (eg, MPN, severe thrombophilia), unprovoked SVT, or VTE recurrence.^{8,19,21}

Due to its severity, BCS often requires a stepwise approach starting with medical treatment (anticoagulation, diuretics), followed by interventional procedures (angioplasty, stenting, thrombolysis, transjugular intrahepatic portosystemic shunt), up to orthotopic liver transplantation.⁸ There is consensus that BCS patients require indefinite anticoagulation.^{8,19}

2.3 | Evidence regarding DOACs

There is only one RCT that evaluated one of the DOACs in the treatment of SVT. Hanafy et al¹¹ enrolled 80 patients with acute non-neoplastic portal vein thrombosis (PVT) in the context of hepatitis C virus-related compensated liver cirrhosis (Child-Pugh classes A-B) from two tertiary referral centers in Egypt. Patients were treated with enoxaparin 1 mg/kg twice daily for 3 days, then randomized to rivaroxaban 10 mg twice

daily or warfarin (target international normalized ratio [INR] range 2.0-2.5). During the 1-year follow-up, complete or partial recanalization was obtained by all patients in the rivaroxaban groups versus 45% in the warfarin group. There was no severe GI bleeding or recurrent PVT in the rivaroxaban group, whereas these events occurred in 17 and 4 patients, respectively, in the warfarin group.¹¹ While the results of this study suggested that rivaroxaban could be safe and effective in cirrhotic PVT, several limitations should be considered, such as the small sample size, the low dose of rivaroxaban tested during the acute phase of PVT, and the unclear transition from parenteral to oral anticoagulation in the control group. Furthermore, despite the randomization process, baseline characteristics of the two cohorts were not completely balanced. For instance, there was a higher prevalence of grade 3-4 esophageal varices in the rivaroxaban group,¹¹ which might have resulted in different therapeutic approaches, since varices at high risk of bleeding were managed with endoscopic band ligation and there was no mention of prophylactic beta-blockers. In addition, the fact that other outcome events (such as ascites, hepatic encephalopathy, and mortality) occurred only in patients on VKA suggested that also the degree of hepatic dysfunction might have been different, despite similar Child-Pugh and Model for End-Stage Liver Disease scores at baseline.

Several small observational cohort studies²⁵⁻³² described the use of DOACs in patients with SVT. However, most of them had a retrospective design or used radiological (eg, vein recanalization) instead of clinical outcomes; thus, high-quality evidence on this topic is limited. The largest cohort, so far, was recently published by Naymagon et al³⁰ and included 93 patients with non-cirrhotic PVT treated with apixaban (n = 20), dabigatran (n = 8), or rivaroxaban (n = 65) in the years 2000-2019. This study also included two groups of patients receiving standard treatment (70 enoxaparin, 108 warfarin). The primary outcome was complete resolution of the thrombosis at imaging and was achieved by 66% of patients in the DOAC group. This result was similar to the LMWH group (57%) and significantly better than the VKA group (31%, corresponding to hazard ratio [HR] 2.91; 95% confidence interval [CI], 1.87-4.52, for DOACs vs VKAs).³⁰ Among the secondary outcomes, MB occurred in 2% of patients receiving DOACs, 14% receiving enoxaparin, and 24% receiving warfarin (corresponding to HR, 0.20; 95% CI, 0.05-0.86, for DOACs vs VKAs).³⁰ Given the retrospective design, these results could be partly explained by a selection bias in the choice of which patients were treated with DOACs and a temporal bias, since the DOACs were more commonly prescribed in recent years, resulting in a shorter follow-up duration. However, a potential advantage of DOACs is the more stable anticoagulant levels obtained during the early phase of treatment, when proper anticoagulation is crucial to prevent the development of portal hypertension and VKA levels are generally unstable. The same authors also analyzed a subset of 23 patients with PVT and inflammatory bowel disease and similarly reported good safety and effectiveness of DOACs.²⁹

Some studies focused on patients with liver cirrhosis treated with DOACs for different indications and highlighted that a broad range of daily dosages were used (eg, apixaban 2.5-10 mg; rivaroxaban 5-20 mg; dabigatran 110-220 mg),^{33,34} while another study

reported that patients with gastroesophageal varices were more likely to receive VKAs.³⁵

Among those studies specifically considering patients with cirrhosis and SVT, Nagaoki et al²⁵ evaluated 50 patients with PVT who were initially treated with parenteral danaparoid for 2 weeks. From 2011 to November 2014 they were subsequently switched to warfarin with a target INR range of 1.5-2.0 (n = 30), while from December 2014 to 2016 they were subsequently switched to edoxaban 60 mg once daily, eventually reduced to 30 mg once daily as per edoxaban's posology (n = 20). At 6-month follow-up, PVT volume was decreased in the edoxaban group, while it was increased in the warfarin group; however, warfarin was targeted at a lower range than usually recommended, and the rates of clinically significant GI bleeding were nonsignificantly higher in the edoxaban group (15% vs 7%).²⁵

Ai et al³¹ performed a prospective cohort study of patients with cirrhosis and chronic PVT, defined as a diagnosis >1 month before and absence of symptoms of portal hypertension or abdominal pain. Using propensity-score matching, they matched 40 patients receiving DOACs (rivaroxaban 20 mg once daily as first choice, or dabigatran 150 mg twice daily if contraindications to rivaroxaban existed, such as Child-Pugh classes B-C), with 40 patients receiving no anticoagulant treatment. The rates of partial or complete recanalization were higher in the DOAC group both at 3-month (12.8% vs 0%) and 6-month (28.2% vs 2.6%) follow-up, with low and not significantly different rates of overall bleeding (7.7% vs 2.5%).³¹

Salim et al²⁶ considered patients with acute symptomatic MVT, 22 treated with different DOACs and 56 with VKAs. During a median follow-up of 4 years, the two groups showed similar rates of bowel resection (9% vs 23%) and vessel recanalization (69% vs 71%), and no recurrent VTE on treatment. However, it should be noted that MB rates in this study were relatively high in both groups (9.1% vs 14.3%, respectively), although with different patterns (more GI bleeding with DOACs vs more ICH with VKAs).²⁶

Sharma et al²⁸ evaluated a cohort of patients with BCS after endovascular intervention, 36 treated with dabigatran and 62 with VKAs, matched by age, sex, and site of obstruction. Dabigatran resulted in similar rates of stent patency compared to VKAs (91% vs 93% at 1-year follow-up), without increasing MB (3.5% vs 6.5%).²⁸

Finally, in a recently published meta-analysis, the proportion of SVT patients receiving DOACs and experiencing recurrent VTE (8%; 95% CI, 2-28) or MB (7%; 95% CI, 2-23) was similar to patients receiving VKAs (recurrent VTE, 8%; 95% CI, 4-13; MB, 11%; 95% CI, 7-18).³⁶

3 | CEREBRAL VEIN THROMBOSIS

3.1 | Overview

Cerebral vein thrombosis (CVT) includes thrombosis of the dural venous sinuses and thrombosis of the cortical or deep cerebral veins. The superior sagittal sinus and the lateral sinuses are the most frequently involved (37%-62% and 31%-44%, respectively).^{37,38}

A number of different underlying risk factors may be present in CVT, the most common being pregnancy/puerperium, estrogen-containing oral contraceptives, and thrombophilia.³⁹ Other risk factors include central nervous system (CNS) infections, malignancies, trauma, and surgery.³⁹ Finally, in 13%-21% of cases, CVT is unprovoked.³⁷

CVT has different clinical presentations, varying from headache (89%) to seizures (20%-30%) to stupor or coma (14%).³⁷ A concomitant ICH at CVT onset is reported in a third of patients.^{37,38} CVT has generally a good prognosis, with an overall mortality rate < 10%, and 5%-10% of patients maintaining a certain level of dependency.³⁹ Approximately 80% of patients achieve recanalization, which is associated with favorable outcome.⁴⁰

3.2 | General principles of treatment

The latest guidelines on the treatment of CVT were published by the European Stroke Organization (ESO) in 2017 and recommended standard treatment with parenteral anticoagulation followed by VKAs.⁹ LMWH was suggested as first choice over UFH, except in patients with renal failure or other contraindications to LMWH, or in cases that might require rapid reversal of anticoagulation.⁹ DOACs were not recommended in these guidelines; however, it was a weak recommendation based on the very low quality of evidence available at the time of publication.⁹

The presence of ICH at CVT onset is not a contraindication to anticoagulation, because the hemorrhagic transformation of a venous infarct is likely due to the venous outflow blockage with increased venous pressure and rupture of venules.⁴¹ For this reason, therapeutic doses of heparin were also recommended for patients presenting with ICH.⁹

The 2017 ESO guidelines suggested an anticoagulant treatment duration of 3-12 months for the majority of patients with CVT, except those with recurrent VTE or persistent prothrombotic risk factors that might necessitate lifelong treatment.⁹ Previous guidelines published by the European Federation of Neurological Societies in 2010⁴² and the American Heart Association/American Stroke Association in 2011⁴³ suggested 3-6 months for CVT secondary to transient risk factors, 6-12 months for unprovoked CVT, and indefinitely for recurrent VTE or severe thrombophilic status.

3.3 | Evidence regarding DOACs

There is only one RCT that evaluated one of the DOACs in CVT. RE-SPECT CVT was a multicenter, parallel-group, open-label with blinded-endpoint adjudication clinical trial that enrolled 120 patients with acute CVT.¹² After 5-15 days of parenteral UFH/LMWH, patients were randomly assigned to dabigatran 150 mg twice daily or warfarin (target INR range, 2.0-3.0) for 24 weeks.¹² The primary outcome was a composite of MB and recurrent VTE and occurred in one (1.7%) patient in the dabigatran group versus two (3.3%)

patients in the warfarin group. Since there was no recurrent VTE on treatment, the outcome events were all bleeding and involved different sites: GI bleeding in the dabigatran group and ICH in the warfarin group.¹² Recanalization occurred in 60.0% and 67.3% of patients in the two groups, while excellent functional outcome at 24 weeks, defined as modified Rankin scale 0-1 points, in 91.5% and 91.4%, respectively.¹²

The RE-SPECT CVT trial showed with a rigorous study design that dabigatran has a safety and efficacy profile similar to warfarin in these patients. However, the long list of exclusion criteria (such as CNS infections, major head trauma, active malignancy, recent MB, inability to swallow, planned surgical procedures for CVT)¹² allows generalizability of the results only to patients with CVT of mild/moderate severity. Furthermore, due to the relatively small sample size and relatively short follow-up duration, this trial could not provide information on the risk of recurrent VTE and on the long-term safety of dabigatran for patients necessitating indefinite anticoagulation. This information, however, could be derived from the studies conducted for the treatment of DVT and PE, where dabigatran showed similar rates of VTE recurrence and a nonsignificant trend toward lower MB events than warfarin,⁴⁴ even during the extended treatment period.⁴⁵

A number of small observational cohort studies on the use of the DOACs in patients with CVT have been published in recent years,⁴⁶⁻⁵⁷ mostly with a retrospective design. Some of these studies included a control group of patients receiving standard treatment,^{46,50-53,56,57} although a selection bias cannot be excluded due to the observational design. In addition, DOACs were usually started after an initial treatment with UFH/LMWH^{46-53,55,56} to achieve stable clinical conditions. There was only one study that evaluated rivaroxaban directly initiated as a single-drug approach.⁵⁴ Shankar Iyer et al⁵⁴ prospectively enrolled 20 patients with CVT who were treated with rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily. At 6-month follow-up, all patients obtained either complete (12 patients; 60%) or partial recanalization (8 patients; 40%), without any MB. Furthermore, 19 (95%) patients obtained excellent neurological outcome.⁵⁴ The other two prospective studies evaluated different DOACs after approximately a week of heparin lead-in, and highlighted the variety of dosages used (eg, apixaban 5 mg twice daily, dabigatran 75-150 mg twice daily, rivaroxaban 15-20 mg once daily).^{55,56} Of note, the study by Wasay et al⁵⁶ included 45 patients treated with DOACs and 66 patients treated with VKAs (target INR range, 2.0-3.0) and showed similar rates of excellent functional outcome in the two groups at 6-month follow-up (64.1% vs 62.5%, respectively), with low rates of MB. Rusin et al⁵⁵ enrolled 36 patients with CVT treated with DOACs and reported similar efficacy outcomes (vessel recanalization in 94.4% of patients and excellent neurological outcome in 66.7%). However, in this study the rates of MB during a median treatment duration of 8.5 months was high (three patients; 8.3%), even though none of the events was life threatening.⁵⁵ A recently published meta-analysis of six studies comparing DOACs and VKAs highlighted similar rates of excellent functional outcome (81.8% vs 76.1%, respectively; risk ratio [RR], 1.02; 95% CI,

0.93-1.13) and a nonsignificant trend toward lower MB in the DOAC group (1.32% vs 3.45%, respectively; RR, 0.44; 95% CI, 0.12-1.59).⁵⁸

Since in previous studies DOACs were associated with a risk of ICH at least halved compared to VKAs,^{5,6} their safety benefit was expected to be particularly relevant in patients with CVT. In the RESPECT CVT study, randomization was stratified by the presence/absence of ICH, thus resulting in 20 patients in each group with ICH at baseline.¹² In this subgroup of patients, there was one new ICH during treatment in the warfarin group and one enlargement of the baseline ICH in the dabigatran group,¹² thus confirming the similar safety profile of these two oral anticoagulants. In addition, the multicenter prospective observational study by Wasay et al highlighted that the presence of ICH at baseline was more common in patients receiving DOACs (either rivaroxaban or dabigatran), than in those receiving warfarin (25/45 [55.6%] vs 20/66 [30.3%]; $P = .01$).⁵⁶ This finding suggested that physicians feel more comfortable prescribing DOACs for patients with CVT and concomitant ICH.

4 | UPPER EXTREMITY DEEP VEIN THROMBOSIS

4.1 | Overview

Upper extremity deep vein thrombosis (UEDVT) includes thrombosis of the axillary, subclavian, internal jugular, or brachiocephalic veins (proximal veins) and thrombosis of the brachial, radial, or ulnar veins (distal veins) and represents around 5%-10% of all DVTs.^{59,60} UEDVT can be classified as primary (~25% of cases) or secondary (~75%), based on the pathophysiology.²² Primary UEDVT refers to effort-related thrombosis (Paget-von Schrötter syndrome), thoracic outlet syndrome, and unprovoked thrombotic events.⁵⁹ The most common risk factors in secondary UEDVT are malignancy (22%-64%) and central venous catheters (CVC) (10%-93%).⁵⁹ Other risk factors include implantable pacemakers, recent surgery or trauma, and thrombophilia.

Among the possible complications, PE and postthrombotic syndrome (PTS) were less frequently reported in patients with UEDVT compared to those with lower extremity DVT (LEDVT). In fact, PE was detected in 3% of UEDVT vs 16% of LEDVT ($P < .001$),⁶¹ while PTS was described in 15%-25% of cases after UEDVT versus 20%-50% after LEDVT.⁶² Mortality was higher in patients with UEDVT versus LEDVT (9.7 vs 6.7 per 100 person-years),⁶³ which might reflect the higher prevalence and the greater severity of underlying cancer.

4.2 | General principles of treatment

Guidelines for the treatment of UEDVT are scarce. The 2012 ACCP guidelines recommended parenteral anticoagulation (UFH, LMWH, or fondaparinux) in patients with acute UEDVT involving the axillary vein or more proximal venous districts.²² While a minimum

anticoagulant duration of 3 months was suggested,²² some underlying factors may favor definite (such as unprovoked UEDVT or removed CVC) or indefinite (such as malignancy or persistent CVC) treatment duration. In clinical practice, the majority of patients are usually treated for 3-6 months and switched to VKAs after the initial heparin treatment, except those with active malignancy.¹

In CVC-associated UEDVT, there is no need to remove the catheter if well positioned, functional, and required; however, anticoagulation has to be continued as long as the CVC is in place.^{22,64} If the CVC is nonfunctional or infected, a short course of anticoagulation (3-7 days) is suggested before removal, if not contraindicated by high bleeding risk.^{64,65} However, the results of a large retrospective study conducted in the United States showed that early catheter removal (<48 hours) did not increase the risk of developing PE.⁶⁶

4.3 | Evidence regarding DOACs

There are no RCTs evaluating the DOACs for the treatment of UEDVT; however, several prospective⁶⁷⁻⁷⁰ or retrospective⁷¹⁻⁷³ cohort studies were published in the past few years. Houghton et al⁷⁰ prospectively assessed a cohort of 210 patients with acute UEDVT evaluated at the Mayo Clinic in the years 2013-2019: 102 treated with DOACs (63 apixaban, 39 rivaroxaban) and 108 treated with LMWH/VKAs. At 3-month follow-up, the DOAC group showed similar outcomes compared to the LMWH/VKA group in terms of VTE recurrence (1.0% vs 0.9%), MB (0% vs 2.8%) and mortality (2.0% vs 4.6%).⁷⁰ However, the presence of active cancer was more common in the standard treatment group. In this study, there was also a group of 843 patients with LEDVT treated with DOACs, who showed similar outcome rates (VTE recurrence, 0.7%; MB, 1.7%; mortality, 2.4%).⁷⁰ Montiel et al⁷² described another unselected cohort of UEDVT consisting of 55 patients from the Swedish national anticoagulation registry and similarly reported low rates of event at 6-month follow-up (VTE recurrence on treatment, 2%; MB, 0%; mortality, 0%).

The Italian multicenter retrospective study by Porfidia et al⁷³ enrolled 61 patients with non-cancer non-CVC-related UEDVT treated with the four different DOACs. The DOACs were usually preceded by LMWH/fondaparinux; however, a single-drug approach was used in 9 of 37 (24.3%) patients receiving rivaroxaban and in 4 of 11 (36.4%) patients receiving apixaban. In two-thirds of cases, a treatment duration of 3-6 months was chosen, while the remaining patients were treated for >6 months. Partial or complete recanalization was obtained in all patients, and there were no episodes of VTE recurrence, MB, or mortality.⁷³

Cancer and CVC-related UEDVT have been the focus of specific studies. The retrospective single-institution study by Laube et al⁷¹ analyzed 83 patients treated with rivaroxaban and highlighted a non-negligible rate of line dysfunction (3.6%) and high rate of mortality (7.2%). In a Canadian prospective multicenter study (CATHETER-2), 70 patients received rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily, in 51% of cases preceded by LMWH.⁶⁸

While there were no episodes of line dysfunction and there was only one episode of recurrent VTE (fatal PE), this trial raised concern with regard to the risk of MB and clinically relevant nonmajor bleeding, which occurred in 13% of patients during the 3-month follow-up.⁶⁸ This finding could be partly explained by the loading dose of rivaroxaban, since most of the events occurred in the first month, and partly by the severity of the underlying active malignancy.⁶⁸

5 | OVARIAN VEIN THROMBOSIS

5.1 | Overview

Ovarian vein thrombosis (OVT) is around 60 times less frequent than lower extremity DVT.⁷⁴ OVT can complicate 0.01%-0.18% of pregnancies and occurs typically in the postpartum period, with a peak 2-6 days after delivery.⁷⁵ Pregnancy-related OVT involves the right ovarian vein in 70%-80% of cases, due to differences in venous drainage.⁷⁶ Other risk factors for OVT include estrogen-containing oral contraceptives, malignancies, recent abdominopelvic surgery, pelvic inflammatory diseases, and infections (septic pelvic thrombophlebitis),⁷⁷ while 4%-16% of cases are classified as unprovoked.^{74,75}

OVT usually manifests with lower abdominal pain, sometimes associated with abdominal tenderness. A palpable cordlike abdominal mass is a specific finding, although reported in < 50% of cases.⁷⁸ In addition, nonspecific GI symptoms (eg, anorexia, nausea, vomiting, ileus) were reported.⁷⁵ In patients with septic pelvic thrombophlebitis, the classic symptom triad includes spiking fever, pelvic pain, and palpable mass.⁷⁹ OVT can also be an incidental finding in women with gynecological malignancies undergoing abdominal imaging as part of routine follow-up.⁸⁰ OVT has nowadays a good prognosis, with mortality rates <5%.⁷⁸ In a recent study, at the time of OVT diagnosis 25% of patients showed thrombus extension into the inferior vena cava or the left renal vein, while <10% presented with PE.⁷⁵ In another study, the risk of recurrent VTE in OVT was 2.3 per 100 patient-years, similar to lower extremity DVT; however, recurrences were more frequently located in atypical venous locations.⁷⁴

5.2 | General principles of treatment

Antibiotics and anticoagulation represent the main treatment options for OVT. In pregnancy-related OVT, the 2014 guidelines of the Society of Obstetricians and Gynaecologists of Canada recommended parenteral broad-spectrum antibiotic treatment until at least 48 hours after defervescence and anticoagulation for 1-3 months.⁸¹ The 2012 Guidelines of the British Committee for Standards in Haematology recommended anticoagulation for 3-6 months for patients with postpartum OVT and suggested no anticoagulation for incidentally detected cancer-associated isolated OVT.⁸²

The important role of anticoagulation in OVT is nowadays well recognized,^{1,83} despite the limited evidence available. A small clinical trial conducted in the 1990s, in which 14 women with puerperal

septic pelvic thrombophlebitis and OVT were randomly assigned to antibiotic treatment alone or with the adjunct of UFH, did not show any difference in the rates of recurrent VTE or in the length of hospitalization.⁸⁴ The study by Lenz et al⁷⁴ showed that despite OVT being less frequently anticoagulated than lower limb DVT (54% vs 98%, $P < .001$), VTE recurrences were similar (2.3 vs 1.8 per 100 patient-years, respectively; $P = .49$). Assal et al⁸⁵ reported a nonsignificant trend toward reduction of VTE recurrence rates with anticoagulation in patients with OVT (5.9% in anticoagulated patients vs 9.9% in patients who were not anticoagulated; $P = .59$). In general, data from observational studies suggest that the antithrombotic management of OVT is similar to usual-site VTE, with parenteral anticoagulation during the acute phase, followed by oral anticoagulants (mainly VKAs) in approximately two-thirds of patients.^{74,85}

5.3 | Evidence regarding DOACs

Eight patients with OVT treated with DOACs were included in the study by Janczak et al assessing the treatment of VTE in atypical locations,¹⁰ while 5% of 219 women with OVT included in the study by Lenz et al⁷⁴ received direct factor Xa inhibitors; however, separate outcome data were not provided. There are 3 published case reports evaluating the use of rivaroxaban^{86,87} or apixaban⁸⁸ in young women with OVT, with promising results. Finally, Covut et al⁸⁹ retrospectively assessed the treatment of 36 women with OVT evaluated at the Cleveland Clinic (United States) in the years 2012-2018. They found that 10 women received DOACs (rivaroxaban or apixaban), 11 VKAs and 15 enoxaparin.⁸⁹ During follow-up, recanalization was achieved in 70% of women in the DOAC group versus 55% in the VKA group versus 93% in the LMWH group. The 1-year cumulative incidence of clinically significant bleeding events was 10% versus 18% versus 25% in the three groups, respectively.⁸⁹

6 | RENAL VEIN THROMBOSIS

6.1 | Overview

Renal vein thrombosis (RVT) is around 30 times less frequent than lower limb DVT⁹⁰ but is the most frequent non-catheter-related thrombosis in neonates.^{91,92} The most common risk factor for RVT is nephrotic syndrome, especially membranous glomerulonephritis.⁹³ Other risk factors include malignancies (particularly renal cell carcinoma), surgery (including urological procedures and kidney transplantation), and abdominal trauma or infections.^{90,94,95} Finally, approximately 12% of RVTs are classified as unprovoked.^{90,94}

Typical manifestations of RVT include flank pain and tenderness, microscopic or gross hematuria, proteinuria and worsening of renal function.⁹⁵ In infants, a painful palpable mass corresponding to the enlarged kidney can be seen. However, acute manifestations are rare, and RVT has usually a chronic onset or can be an incidental finding.⁹⁶ Possible complications of RVT include progression into

the inferior vena cava (43%-65% of cases), which increases the risk of embolization.^{90,93,94} Long-term renal damage and hypertension have also been described.^{91,97} Bilateral RVT can lead to acute renal failure and can be life threatening, especially in small infants.^{95,97} Prognosis of RVT depends on the etiology, being favorable in patients with nephrotic syndrome and poor in those with underlying malignancies.^{90,94}

6.2 | General principles of treatment

There is little evidence on the treatment of RVT. In line with the management of usual-site VTE, acute RVT is usually treated with parenteral anticoagulation (UFH/LMWH), eventually followed by VKAs.⁸² Recent studies reported a definite anticoagulant treatment duration of 3-12 months in patients with RVT provoked by a transient risk factor and a longer indefinite duration in those with permanent hypercoagulable states (including persistent nephrotic syndrome) or unprovoked RVT.^{93,94,96}

There are two guidelines mentioning the treatment of pediatric RVT. The 2018 Guidelines of the American Society of Hematology suggested anticoagulation in neonates with RVT and considered thrombolysis followed by anticoagulation for life-threatening RVT (eg, bilateral thrombosis).⁹⁷ Previously, the 2012 ACCP guidelines considered either anticoagulation or radiologic monitoring for unilateral RVT without renal impairment or involvement of the inferior vena cava, and suggested either anticoagulation or thrombolysis followed by anticoagulation in bilateral RVT with renal impairment.⁹⁸

6.3 | Evidence regarding DOACs

Three patients with RVT treated with the DOACs were included in the study by Janczak et al¹⁰ evaluating the use of the DOACs in unusual site VTE. Furthermore, there are four published case reports evaluating the use of rivaroxaban,^{99,100} apixaban¹⁰¹ or edoxaban¹⁰² in patients with RVT with good clinical outcomes. However, the DOACs should be used with caution in patients with RVT due to their risk of accumulation in renal insufficiency.

7 | PRACTICAL ADVICE REGARDING DOACs IN UNUSUAL-SITE VTE

Based on the available evidence, DOACs seem to be a promising option for selected SVT patients, especially those with non-malignant, non-cirrhotic thrombosis. Given the high hemorrhagic risk of these patients, factor Xa inhibitors might be preferred over thrombin inhibitors, due to their lower risk of GI bleeding.¹⁰³ However, there are some conditions frequently associated with SVT in which DOACs are contraindicated or caution is needed (Figure 1). First, since liver failure can affect drug metabolism, all the DOACs are contraindicated in patients with Child-Pugh class C cirrhosis, and rivaroxaban has

been reported to accumulate also in patients with Child-Pugh class B.¹⁰⁴ Second, since the DOACs have mainly renal excretion, they are contraindicated in severe renal failure (creatinine clearance [CrCl] <30 mL/min for dabigatran; CrCl < 15 mL/min for the factor Xa inhibitors). Recent data from pharmacokinetic and retrospective studies suggest that the safety profile of apixaban might be confirmed also in patients with severe chronic kidney disease,¹⁰⁵⁻¹⁰⁷ and several RCTs are assessing this population (RENAL-AF, NCT02942407; AXADIA, NCT02933697; SAFE-HD; NCT03987711). Of note, also LMWH is not recommended if CrCl is < 15 mL/min and requires anti-Xa monitoring or dose reduction if CrCl is 15-29 mL/min.¹⁰⁴ Third, liver cirrhosis and hypersplenism are frequently associated with thrombocytopenia. Both DOACs and VKAs are not recommended if platelet count is <50 × 10⁹/L, and in this situation LMWH would be the treatment of choice because the dosage can be modulated.¹⁰⁴ There are some concerns regarding the use of DOACs in patients with luminal GI cancer, due to local mucosal damage, which can be associated with poor absorption and higher risk of GI bleeding. Thus, LMWH is usually preferred in these patients.¹⁹

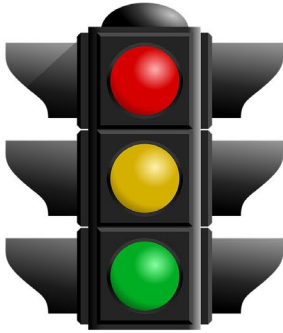
The presence of esophageal varices should not represent a contraindication to the anticoagulant treatment and to the use of DOACs, especially if adequate prophylaxis is considered (beta-blockers or endoscopic band ligation). However, since gastroesophageal varices might represent a more advanced liver dysfunction, caution should be applied to these patients.

In severe MVT, the presence of small bowel congestion may result in malabsorption of drugs.¹⁰⁸ With the exception of rivaroxaban, which is primarily absorbed in the stomach, the other DOACs are, at least partially, absorbed in the small intestine.¹⁰⁹ Although retrospective clinical data suggest that DOACs had an efficacy profile similar to VKAs in MVT patients,²⁶ the potential for malabsorption cannot be excluded.

Given their favorable safety profile, DOACs are a therapeutic option for selected patients with CVT, especially those with mild/moderate clinical manifestations. In this context, dabigatran might be the preferred choice because of its lowest potential for crossing the blood-brain barrier, compared to the other DOACs.¹¹⁰ However, more evidence is needed to understand whether these pharmacologic properties translate into different outcomes in clinical practice. Some contraindications to DOACs can also be identified among patients with CVT (Figure 2). First, patients presenting with seizures may receive antiepileptic drugs that interfere with DOACs (eg carbamazepine, phenytoin).¹¹¹ Second, the oral administration may be problematic in comatose patients with CVT or those unable to swallow. There is limited evidence for the use of DOACs in CVT associated with CNS malignancies, infections, or trauma; thus, caution should be applied.

DOACs are a promising treatment for selected patients with UEDVT, especially those with non-cancer, non-CVC-related thrombosis. All four available DOACs might be considered, and the management of UEDVT follows the recommendations for LEDVT. Caution should be applied to patients with cancer- and CVC-related UEDVT, due to the high risk of bleeding.⁶⁸ A recently

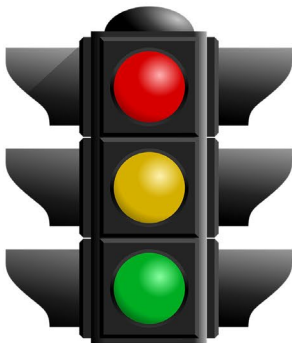
DOACs in specific SVT patients



- **Hepatic dysfunction**
 - DOACs contraindicated if Child-Pugh class C (rivaroxaban if Child-Pugh classes B-C)
 - **Severe renal insufficiency**
 - DOACs contraindicated if CrCl <15 mL/min* (dabigatran if CrCl <30 mL/min)
 - **Thrombocytopenia**
 - DOACs not recommended if platelet count <50×10⁹/L
-
- **Luminal GI cancer**
 - Higher risk of GI bleed, poor absorption, CHT interference, vomiting/nausea
 - **MVT complicated by bowel ischemia**
 - Potential DOACs malabsorption
 - **Chronic SVT or portal cavernoma**
 - Case-by-case evaluation
 - **Gastroesophageal varices**
 - Not a contraindication to anticoagulant therapy (consider EGDS, beta-blockers, EBL)
 - Frequently associated with severe liver disease
-
- **Incidentally detected SVT**
 - Similar rates of event than symptomatic SVT

FIGURE 1 Use of the DOACs in specific patients with SVT. *The US Food and Drug Administration (FDA) removed this contraindication for apixaban in 2019, while as of November 2020 the European Medicine Agency (EMA) still considers apixaban not recommended in this population. The red color on the traffic light refers to situations in which DOACs are contraindicated; yellow refers to debated situations; green refers to situations in which DOACs can be considered. CHT, chemotherapy; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; EBL, endoscopic band ligation; EGDS, esophagogastroduodenoscopy; GI, gastrointestinal; MVT, mesenteric vein thrombosis; SVT, splanchnic vein thrombosis

DOACs in specific CVT patients



- **Seizures**
 - Pharmacokinetic interactions between DOACs and antiepileptic drugs (e.g. carbamazepine, phenytoin, phenobarbital, valproate)
 - **Coma**
 - Unable to swallowing
-
- **CVT associated with CNS malignancies, infections, trauma**
 - Not enough evidence either to support or refute the use of DOACs
-
- **Concomitant ICH**
 - Not a contraindication to anticoagulant therapy & DOACs have lower risk of ICH
 - Eventually start with LMWH/UFH until clinical stability

FIGURE 2 Use of the DOACs in specific CVT patients. The red color on the traffic light refers to situations in which DOACs are contraindicated; yellow refers to debated situations; green refers to situations in which DOACs can be considered. CNS, central nervous system; CVT, cerebral vein thrombosis; DOACs, direct oral anticoagulants; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin

published meta-analysis of RCTs evaluating cancer-associated usual-site VTE showed a (nonsignificant) lower risk of recurrent VTE, balanced by a (nonsignificant) higher risk of MB with the DOACs compared to LMWH,¹¹² thus supporting the use of the DOACs also in patients with cancer. However, certain conditions (such as GI or genitourinary tumors or CNS metastasis) carry a particularly high bleeding risk, and these patients may not be candidates for DOACs.

Finally, among the different risk factors for unusual-site VTE, pregnancy and the puerperium represent general contraindications to DOACs because these drugs cross the placenta and are excreted in breast milk.¹¹³ Since warfarin also crosses the placenta, LMWH is the preferred drug antenatally; however, warfarin can be considered during the puerperium. In addition, DOACs are not recommended in patients with severe forms of thrombophilia, such as antiphospholipid syndrome with triple positivity.¹¹⁴

8 | ISTH 2020 CONGRESS REPORT

The results of several studies on the use of the DOACs in unusual-site VTE were presented during the ISTH 2020 virtual congress. Serrao et al¹¹⁵ evaluated patients with SVT who were candidates for long-term anticoagulation and described similar rates of recurrent thrombosis between those shifted to DOACs and those continued on VKAs. De Stefano et al¹¹⁶ reported that, among patients with MPN treated with DOACs for secondary prevention after different types of VTE, there were also a number of patients with SVT or CVT as primary events.

A case series by Barbar et al¹¹⁷ confirmed the good safety and efficacy profile of DOACs (mainly dabigatran) in patients with CVT, with no thrombosis recurrence or major or clinically relevant bleeding recorded during treatment. Conversely, the study by Capocchi et al¹¹⁸ raised some concerns that the risk of bleeding might be higher in patients with CVT treated with anti-factor Xa inhibitors compared to VKAs.

Two abstracts, by Pannu et al¹¹⁹ and Cohen et al,¹²⁰ highlighted that DOACs were used in more than a third of patients with non-cancer-associated UEDVT, while the collaborative prospective study by Vedovati et al¹²¹ confirmed the safety and effectiveness of the DOACs in these patients, showing low rates of recurrent VTE and MB during follow-up.

9 | FUTURE DIRECTIONS

More evidence will emerge in the next few years, when the results of ongoing studies will become available. There is an ongoing interventional, prospective cohort study evaluating rivaroxaban as a single-drug approach in patients with acute symptomatic non-cirrhotic SVT (RIVASVT-100, NCT02627053) and an open-label RCT comparing rivaroxaban versus no treatment in patients with chronic non-cirrhotic PVT without high-risk thrombophilia (RIPORT, NCT02555111). In

acute CVT, there is an ongoing open-label RCT comparing the use of rivaroxaban versus standard treatment with UFH/LMWH eventually switched to warfarin (SECRET, NCT03178864). There are two ongoing interventional studies assessing the use of the DOACs in patients with UEDVT: the ARM DVT study (NCT02945280) is investigating apixaban as a single-drug approach in patients with acute symptomatic UEDVT,¹²² while CATHETER-3 is evaluating apixaban after LMWH in patients with cancer and CVC-related UEDVT (NCT03100071). Finally, we are conducting a collaborative prospective registry on the use of DOACs in unusual-site VTE (DUST, NCT03778502).

10 | CONCLUSIONS

The evidence on the use of DOACs for the treatment of unusual-site VTE is limited and derived from a few RCTs (one using rivaroxaban in SVT and the other using dabigatran in CVT) and several observational cohort studies. In general, patients enrolled in these studies had unusual-site VTE of mild/moderate severity and low bleeding risk. The DOACs were prescribed at different dosages and usually started after an initial treatment with parenteral anticoagulation to achieve clinical stability.

Given the limited and low-quality available evidence on the use of the DOACs in this setting, some authors would still prefer traditional anticoagulant treatment for these patients.¹²³ However, RCTs in patients with unusual-site VTE are difficult to conduct, mainly because of the rarity and the severity of these conditions.

We believe that, taken together, the available results suggest that DOACs can be used in selected patients with unusual-site VTE, since they showed comparable effectiveness and a trend toward better safety than the VKAs. However, caution should be exerted in special categories of patients (such as those with liver cirrhosis, malignancy, CNS infections or trauma, or CVC-related UEDVT). Ongoing collaborative studies will provide additional data on the safety and efficacy of DOACs in these patients.

RELATIONSHIP DISCLOSURE

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AUTHOR CONTRIBUTIONS

NR reviewed the literature and wrote the first draft of the manuscript. WA critically revised and edited the manuscript. All authors provided final approval of the manuscript.

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