

Direct Oral Anticoagulants for Inferior Vena Cava Agenesis

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Abstract

Deep vein thrombosis (DVT) is common in the general population, with an annual incidence of 1 to 2 per 1000 people. Inferior vena cava agenesis (IVCA) increased the risk of developing DVT and is found in approximately 5% of young adults (20-40-year-olds) diagnosed with unprovoked proximal DVT. IVCA can be caused by a defective embryological process, or be a result of intrauterine or perinatal thrombosis. Its estimated incidence in the general population ranges from 0.0005% to 1%, usually involving a partial absence of one of the four segments of the inferior vena cava (IVC). The management during the extended phase of patients with DVT associated with IVCA is not yet harmonized, as it is poorly described in the literature. Patients with IVCA are considered to be at high risk of DVT occurrence, prompting physicians to continue extended anticoagulation, often using vitamin K antagonists. In this retrospective study, we present a cohort of 11 patients diagnosed with IVCA following a DVT, who subsequently received extended treatment with a direct oral anticoagulants. These findings offer reassuring insights into the extended utilization of direct oral anticoagulants, demonstrating both antithrombotic efficacy and a favorable safety profile.

Keywords

direct oral anticoagulant, extended anticoagulation, inferior vena cava agenesis

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Introduction

Deep vein thrombosis (DVT) is common in the general population, occurring at an annual incidence of 1 to 2 per 1000 people. Given its prevalence across various settings, it is crucial for healthcare practitioners in primary and secondary care to be familiar with the clinical signs that suggest DVT.¹ The formation of a venous thrombus is influenced by multiple risk factors, as outlined in Virchow's triad. These risk factors can be related to venous stasis, a hypercoagulable state, or any damage to the vessel wall.² A recent report has highlighted the significant role of inferior vena cava agenesis (IVCA) in contributing to DVT. IVCA is found in approximately 5% of young adults (20-40-year-olds) diagnosed with unprovoked proximal DVT.³ When managing suspected DVT cases, the primary goals should be to reduce the risk of local complications, such as post-thrombotic syndrome, as well as to prevent potentially life-threatening complications associated with pulmonary embolism. Following an initial duration (ranging from 5 to 21 days) and subsequently, a treatment phase (lasting 3-6 months), the option of extended therapy

may be considered for particular patients identified as having a heightened likelihood of recurrence.⁴

The development of the IVC is a complex process that occurs during the sixth to eighth week of gestation. It involves the merging of three pairs of primitive veins, namely the post-cardinal, sub-cardinal, and supra-cardinal veins. This fusion gives rise to the four segments of the IVC, which include the hepatic, suprarenal, renal, and infrarenal segments. If these structures fail to fuse during the designated period, malformations of the IVC can occur. It should be noted, however, that IVC malformation may also be secondary to intrauterine or

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perinatal thrombosis of IVC, unrelated to any abnormality in embryogenesis.⁵

Congenital IVC anomalies are observed in an estimated prevalence ranging from 0.07% to 8.7% in the general population. These anomalies encompass various types of malformations, such as left IVC, double IVC, continuation of the IVC to the azygos vein, or retro-aortic left renal vein. The incidence of IVCA is estimated to be between 0.0005% and 1% in the general population. It usually involves a partial absence of the IVC, with the most common abnormalities occurring in the liver segment (90%), followed by the renal or infrarenal segment (10%).⁶ IVCA may coexist with other congenital anomalies, including dextrocardia, atrial septal defect, atrioventricular septal defect, atrioventricular canal, pulmonary artery stenosis, as well as transposition of abdominal viscera.

The extended phase management of patients with DVT secondary to IVCA remains a topic that lacks consensus and comprehensive understanding in the literature. These patients are at high risk of DVT recurrence, prompting physicians to administer a prolonged prophylactic anticoagulation, usually with vitamin K antagonists (VKAs).⁷ In this study, we present a cohort of 11 patients who were diagnosed with IVCA following DVT. Our aim was to assess the efficacy and safety of an extended treatment with direct oral anticoagulants (DOAC).

Material and Methods

We conducted a retrospective study including all patients with IVCA treated with DOAC, who were referred to the Hemostasis and Thrombosis Unit of a tertiary level hospital between 2006 and 2023. A total of 11 patients with previously diagnosed DVT associated with IVCA were identified, and their medical records were retrospectively reviewed. Demographic data, initial clinical presentation, inherited and acquired thrombophilia (factor V Leiden, prothrombin gene polymorphisms G20210A, plasma anti-cardiolipin and anti- β_2 glycoprotein 1 antibodies, lupus anticoagulant, antithrombin, protein C and protein S), triggering conditions (eg, surgery, trauma, immobilization, oral contraceptives, or pregnancy), other acquired thromboembolic and cardiovascular risk factors (eg, obesity, inflammatory or neoplastic disease, smoking, hypertension, diabetes mellitus, etc.) were collected. Diagnostic modalities used to confirm IVCA, including, phlebography, computed tomography, or magnetic resonance imaging, were recorded. Information regarding acute treatment options (low-molecular-weight heparin, VKA, or DOAC), treatment duration (long-term or extended treatment) and any bleeding complications were documented. Blood parameters, such as blood count, renal function, liver tests, and D-dimers (DD), were measured regularly (once a year) during follow-up. The choice of DOAC dosage was left to the discretion of the physician. Qualitative variables were presented using frequency distribution, while quantitative variables were describe using median and 25th to 75th (P25-P75) percentiles. Data collection was approved by the ethics committee of the Saint-Luc university Hospital (UCLouvain, Brussels, Belgium).

Cohort Description

The study included a total of 11 participants (eight males and three females), the median age of the participants was 64 years (range: 18-70; Q1-Q3: 30.5-44.5). The first DVT was diagnosed at a median age of 23 years (range: 17-64; Q1-Q3: 19-36). The median duration of follow-up in our hospital was 4.3 years (range: 0.5-16; Q1-Q3: 2.4-7.5). The initial presentation was either a unilateral ($n=4$) or bilateral ($n=6$) proximal DVT, involving the femoral or iliac veins. One case of recurrent superficial thrombosis was also observed. Bilateral involvement was common (55%) in our cohort. No pulmonary embolism was recorded.

During the initiation phase, VKAs were used in two cases, while rivaroxaban was employed in nine cases. The median duration of treatment phase was 5 months (range: 3-12; Q1-Q3: 4.5-6). In situ thrombolysis was performed only twice. Among the patients who did not undergo extended treatment, four experienced recurrent thrombosis within a median period of 10 years (range: 2-11; Q1-Q3: 7.25-10.25).

In all cases, investigations were conducted to evaluate hereditary and acquired thrombophilia. A factor V Leiden mutation was diagnosed in one patient. No triggering factors were noted in 73% of cases (8/11). Among the remaining three patients, triggering factors included the use of combined oral contraceptive pills ($n=1$), exploratory laparoscopy ($n=1$), and post-trauma immobilization ($n=1$). Additional risk factors observed were overweight ($n=1$), active smoking ($n=1$), arterial hypertension ($n=1$), and inflammatory bowel disease ($n=1$). No events during the neonatal period, such as umbilical catheters, were identified as potential explanations for IVCA.

In our institution, all patients received extended treatment with either rivaroxaban ($n=9$) or apixaban ($n=2$), as shown in Table 1. Among the patients receiving rivaroxaban, five were prescribed a daily dose of 10 mg, while four were prescribed a daily dose of 20 mg. The patients receiving apixaban were given a twice-daily dose of 2.5 mg. The median duration of follow-up under DOAC therapy was 4.5 years (range: 0.09-6.6; Q1-Q3: 0.85-5.35). The DOAC treatment was well tolerated by all patients, and no complications were reported. One significant bleeding episode was reported during the previous treatment with VKA before switching to DOAC. The bleeding episode was characterized by hematuria (clinically relevant non-major bleeding according to the ISTH classification), requiring hospitalization. Throughout the treatment period, DD levels remained consistently below the measurable threshold (<250 ng/mL) in all patients. None of the patients experienced renal insufficiency. Clinically, no thromboembolic events were reported during the study period.

Discussion

The majority of patients with IVCA do not experience symptoms as long as they have adequate collateral venous drainage. However, when venous drainage is inadequate or when there

Table 1. Cohort Description.

Age at First DVT			Clinical Presentation	Congenital Malformation	Precipitating Factors	Acquired or Hereditary Thrombophilia	Additional Risk Factors for		Follow-Up			
Patient	Sex						Thrombosis	Relapse	Prophylactic Anticoagulation	Under DOAC (Days)	Relapse Under DOAC	Bleeding Complication
1	M	19	Unilateral iliac vein thrombosis	Infrarenal agenesis	Post-traumatic immobilization	No	No	Yes, without prophylactic treatment	Rivaroxaban 10 mg q.d.	817	No	No
2	F	39	Unilateral iliac and femoral vein thrombosis	Infrarenal agenesis	No	FVL ^a	No	Yes, without prophylactic treatment	Rivaroxaban 10 mg q.d.	730	No	No
3	M	48	Bilateral iliac vein thrombosis	Infrarenal agenesis	No	No	IBD ^b , HBP ^c	No	Rivaroxaban 20 mg q.d.	1645	No	No
4	M	21	Bilateral recurrent superficial venous thrombosis	Infrarenal agenesis	No	No	No	Yes, without prophylactic treatment	Rivaroxaban 10 mg q.d.	153	No	No
5	M	27	Bilateral iliac vein thrombosis	Infrarenal agenesis	No	No	Smoking	Yes, without prophylactic treatment	Apixaban 2.5 mg b.i.d.	2239	No	No
6	F	33	Bilateral iliac and femoral vein thrombosis	Infrarenal agenesis	Exploratory laparoscopy	No	No	No	Rivaroxaban 10 mg q.d.	68	No	Yes under VKA
7	M	18	Unilateral iliac and femoral vein thrombosis	Infrarenal agenesis	No	No	No	No	Rivaroxaban 20 mg q.d.	19	No	No
8	F	17	Bilateral iliac vein thrombosis	Infrarenal agenesis	COCP ^d	No	Obesity	No	Apixaban 2.5 mg b.i.d.	421	No	No
9	M	64	Bilateral iliac vein thrombosis	Infrarenal agenesis	No	No	No	No	Rivaroxaban 10 mg q.d.	1057	No	No
12	M	19	Bilateral iliac vein thrombosis	Infrarenal agenesis	No	No	No	No	Rivaroxaban 20 mg q.d.	3502	No	No
11	M	27	Unilateral iliac and femoral vein thrombosis	Infrarenal agenesis	No	No	Obesity	No	Rivaroxaban 20 mg q.d.	2406	No	No

^a Factor V Leiden.

^b Inflammatory bowel disease.

^c High blood pressure.

^d Combined oral contraceptive pill.

are other risk factor for thrombosis, symptoms may arise. These symptoms can include collateral circulation, lower limb edema, pelvic congestion syndrome, varicocele, compression syndrome resulting from the dilation of collateral vessels (eg, sciatic neuropathy caused by dilated epidural veins, obstructive pyelonephritis) or a thrombotic event.⁸ Thrombosis is often diagnoses incidentally during abdominal imaging, abdominal surgery, or failed catheterization.⁹ In our cohort, we observed that the diagnosis of IVCA is frequently made after the occurrence of proximal DVT at a young age. Indeed, up to 5% of patients under 30 years of age with unprovoked proximal DVT have an IVCA. Therefore, it is crucial to actively investigate the presence of IVCA in this population, particularly in cases of bilateral thrombosis.¹⁰

The increased risk of thrombosis is likely attributed to venous stasis caused by insufficient venous return.¹¹ These patients are prone to developing bilateral DVT, which is in stark contrast to the reported incidence of less than 10% in patients with DVT and a normal IVC. Moreover, the risk of pulmonary embolism in these patients is relatively low (9.67%) compared to those with proximal DVT and normal IVC. This is because emboli get trapped in the azygos-hemiazygos system before reaching the pulmonary circulation.¹² It is important to note that IVCA is likely underdiagnosed since it cannot be detected through Doppler ultrasound. In cases where suspicion arises, it is crucial to perform computed tomography or magnetic resonance imaging to confirm the diagnosis.

In cases where patients present with thrombosis and ICVA, we recommend conducting a thorough thrombophilia work-up, despite its infrequent positivity, as it seldom alters the therapeutic management. Among the identified thrombophilias, Factor V Leiden is the most commonly observed, reaching up to 20% in certain cohorts.¹³ Additionally, it is important to investigate the possibility of a secondary cause of IVCA that may have contributed to IVC thrombosis during the peri-natal period. In instances where a congenital origin is suspected, it is crucial to bear in mind the potential presence of other associated malformations.¹⁴

Due to the rarity of IVCA and the absence of clinical trials, there is currently no scientific consensus on the optimal treatment strategy. Oral anticoagulant therapy with either VKAs or DOACs is commonly employed as the mainstay for the initial treatment. In select cases, interventions such as in situ thrombolysis or thrombectomy may be considered to minimize long-term complications. It is important to note that vena cava reconstructions are possible; however, the indications for such procedures must be limited due to the inherent complexity involved.¹⁵ In our cohort, this procedure was only performed once and was justified by the presence of a severe post-thrombotic syndrome that significantly impaired the patient's daily life activities.

Following a prolonged treatment period, an extended phase is frequently recommended to prevent recurrent DVT, as patients with IVCA are at high risk for recurrence. Our cohort demonstrated that patients without preventive anticoagulation experienced a second thrombotic event. Therefore,

extended anticoagulation has been suggested to reduce the risk of recurrence. Historically, treatment with VKAs was proposed.^{12,13} The use of DOACs in this context lacks sufficient data, and there has even been a case report describing the lack of efficacy of rivaroxaban.¹³ Large-scale validation studies on DOACs,^{16–18} and studies evaluating the continuation of half-dose therapeutic anticoagulation for patients without major thrombophilia have not included any IVCA patients.^{19,20} Therefore only case reports have evaluated the use of extended DOAC therapy.^{8,21,22} In addition to anticoagulation, the use of elastic stockings should be encouraged as adjuvant therapy in order to prevent venous insufficiency and ulceration in these patients. Patients should also be advised to avoid additional risk factors, such as prolonged immobilization and oral contraceptives.¹²

Given the limitations of VKA monitoring, the use of DOAC presents an appealing alternative for extended anticoagulation in young individuals. There is no evidence to suggest that this congenital defect would lead to DOAC resistance. In absence of robust data, it has been so far difficult for practitioners to recommend DOAC. In this study, we present retrospective data from 11 patients who were effectively treated with DOACs, including the use of half-therapeutic doses. It is important to acknowledge the limitations of our study, including its retrospective design and small sample size. Furthermore, the relatively short duration of treatment surveillance should be noted in comparison to a median recurrence rate of 10 years in the absence of treatment. Lastly, the treatment regimens employed in our study were quite diverse. Therefore, further research is necessary to confirm both the effectiveness and safety of DOACs in this specific setting.

Conclusion

Our cohort yields promising findings regarding the effectiveness of DOACs in extended phase to prevent thromboembolic events, even when using half-therapeutic doses, among patients with venous thrombosis and underlying IVCA. These results provide encouraging evidence for the use of DOACs in this specific population, considering that these patients often require extended anticoagulation despite the limited clinical evidence supporting its use.

Author Contributions

Conceptualization: C. Hermans/Data collection: C. Hermans/Data curation and analysis: M. Iarossi/Writing—original draft: M. Iarossi/Writing review and editing: C. Hermans and M. Iarossi.

Declaration of Conflicting Interests

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Statement of Ethics

The study protocol was approved by the ethical committee of the Saint-Luc University Hospital (UCLouvain, Brussels, Belgium)

Data Availability Statement

All data generated or analyzed during this study were included in this article. Further enquiries can be directed to the corresponding author.

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