Anticoagulation in Patients with Isolated Distal Deep Vein Thrombosis: Bringing the Puzzle Together

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Thromb Haemost 2024;124:811–814.

Whether and how to prescribe anticoagulant treatment in patients with acute isolated distal deep vein thrombosis (IDDVT) is a long-lasting, recurring, and debated issue.[1] IDDVT affects the infrapopliteal veins, comprising the axial (peroneal, anterior, and posterior tibial), and muscular (soleal and gastrocnemius muscle) veins, which proximally form the trifurcation area before merging into the popliteal vein. While the trifurcation anatomically belongs to the distal venous district, thrombosis involving this area is often considered as proximal deep vein thrombosis (DVT).[1] IDDVT is a frequent manifestation of venous thromboembolism (VTE) disease, accounting for up to 50% of all DVTs.[1] Traditionally perceived as far more benign than proximal DVT, IDDVT may also result in clot extension, pulmonary emboli, and recurrent VTE if left untreated.[1] Similar to proximal DVT, recurrence risk tends to be higher in patients with cancer-associated or unprovoked IDDVT than in those with transient risk factors.[2–4] In high-risk subgroups, long-term recurrence rates may reach those observed in patients with proximal DVT.[2–4] Despite this, the management of IDDVT remains uncertain and widely heterogenous across centers worldwide. IDDVT has long been understudied until recent times. This Editorial Focus outlines latest relevant research findings with particular attention to two recent randomized controlled studies, namely the RIDTS[5] and ONCO DVT[6] trials, and discusses how these may advance personalized management of patients with IDDVT.

Anticoagulation versus Ultrasound Surveillance

Current clinical practice guidelines suggest anticoagulation in subjects with severe symptoms or risk factors for extension, while ultrasound surveillance for all the remainders (►**Fig. 1**).[7–9] Randomized evidence with this regard was, however, limited to a few, relatively small randomized trials with vitamin K antagonists or low-molecular-weight heparins. When combining observational and interventional studies, the estimated recurrence rate (including IDDVT proximal extension, pulmonary emboli, and new proximal DVT events) in untreated patients was considerably high (11.2% at 3 months).[10] Conversely, recurrence risk was significantly lower among anticoagulant-treated patients (odds ratio: 0.50; 95% confidence interval: 0.31–0.79), without a clear signal for increased major bleeding complications (odds ratio: 0.64; 95% confidence interval: 0.15–2.73), although the small sample size and wide heterogeneity of the included studies precluded definitive conclusions.[10] One of the main reasons for potentially avoiding anticoagulation is the concern for excess bleeding. Nevertheless, the incidence of major bleeding was acceptably low (0.8% at 3 months) in the CACTUS randomized study with nadroparin, the largest available trial comparing anticoagulation to no anticoagulation.[11] It should be also noted that none of these trials used direct oral anticoagulants (DOACs), which may presumably exhibit an even more favorable bleeding risk profile. Supportive of this notion is a recent retrospective study of 483 patients with IDDVT stratified by management strategy.[12] Compared with surveillance, anticoagulant treatment (40.6% DOACs) significantly lowered recurrences (14.3 vs. 7.3%, respectively; $p = 0.04$), with a net clinical benefit, comprising major bleeds, favoring this approach (20.2 vs. 9.8%, respectively; $p < 0.01$).[12] While adequately designed and controlled prospective studies remain needed, the presence of patients managed without anticoagulation despite an objective DVT diagnosis (either proximal or distal) might rise significant safety concerns, and appears nowadays difficult to

received
January 6, 2024
accepted
January 18, 2024
accepted manuscript online
January 19, 2024
article published online
February 7, 2024

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-2250-3298.
ISSN 0340-6245.

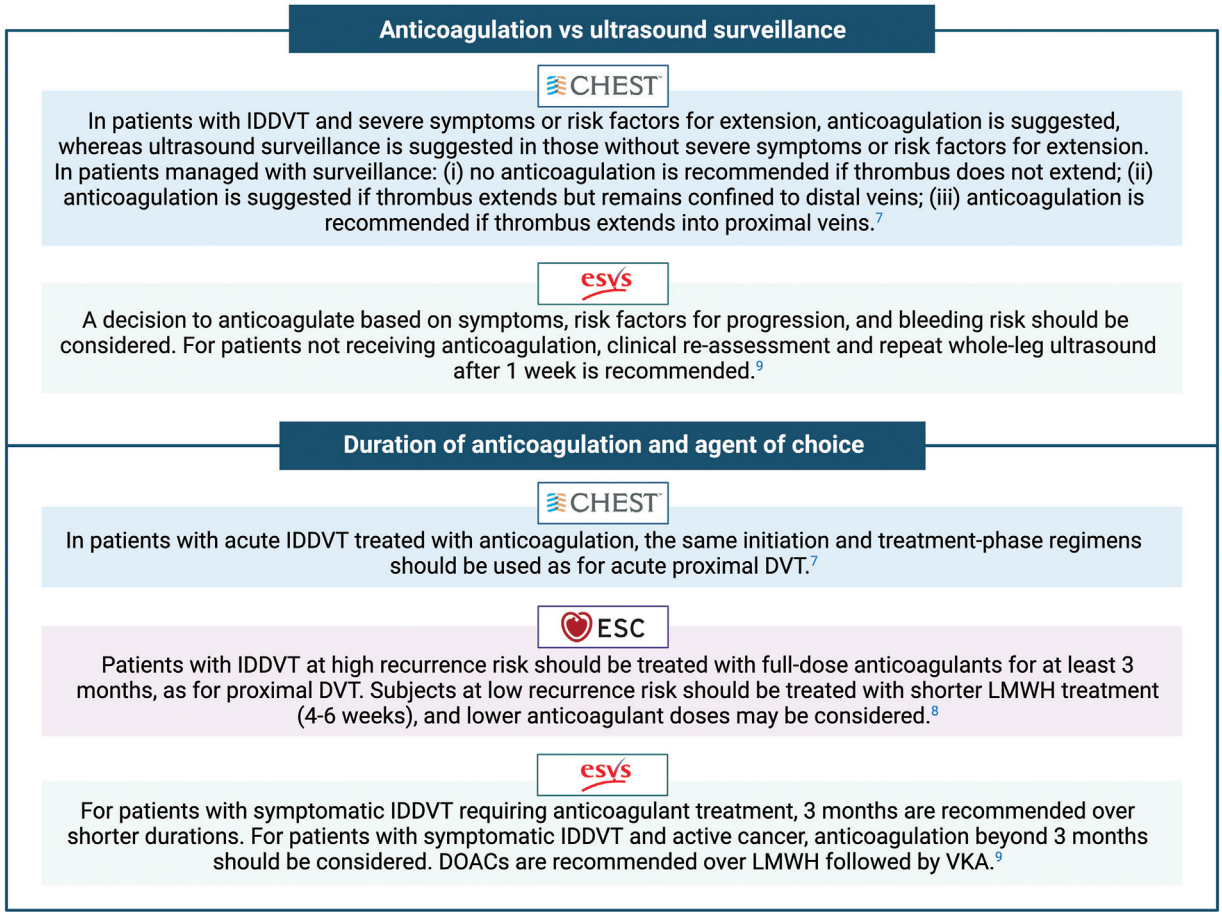

Fig. 1 Overview of current guideline recommendations for the management of patients with IDDVT. DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

implement. In patients with suspected lower extremity DVT, a potentially safer and more viable alternative might be to limit the initial ultrasound evaluation to proximal veins, extending the search for IDDVT only in those with high clinical pretest probability and positive D-dimers, although this approach suggested by the results of a single trial needs to be confirmed by additional studies.[13]

Duration of Anticoagulation

Recent data from large registries show that nearly all patients with IDDVT receive anticoagulation in current clinical practice, hence making the optimal treatment duration a compelling issue.[2–4] In a meta-analysis of studies comparing >6 versus 6 weeks of treatment, longer anticoagulant durations were associated with a 61% reduction in recurrent VTE (risk ratio: 0.42, 95% confidence interval: 0.19–0.90), without evidence of excess bleeding.[10] Hence, guidelines suggest anticoagulation for at least 3 months, as for the acute-phase management of proximal DVT, whereas shorter treatment durations are proposed for low-risk patients (e.g., provoked IDDVT).[7–9] In subjects with symptomatic IDDVT and active cancer, anticoagulation beyond 3 months can be considered (►**Fig. 1**).[7–9] Reflecting the uncertainty around the optimal treatment duration for IDDVT, studies describing real-life management patterns show that most patients are treated for shorter periods than those suggested.[2–4]

Non-Cancer-Associated IDDVT: 6-Week versus 3-Month Anticoagulation

In a recent study of 475 patients with non-cancer-associated IDDVT, the cumulative incidence of recurrent VTE after anticoagulation cessation (median treatment duration: 92 days) was 5.6, 14.7, and 27.2% at 1, 5, and 10 years, respectively.[14] In the same study, the 3-month incidence of major bleeds in anticoagulant-treated patients was 1.5%, and 0.8% when considering DOAC users only.[14]

The RIDTS trial recently addressed the important question of whether anticoagulation for 3 months is superior to 6 weeks in symptomatic outpatients with acute IDDVT and no active cancer.[5] After completing uneventful 6 weeks of standard-dose rivaroxaban (15 mg twice daily), 402 subjects were randomized to receive rivaroxaban 20 mg or placebo once daily for 6 additional weeks, and followed for 2 years.[5] Recurrent VTE occurred in 11 and 19% of subjects in the rivaroxaban and placebo groups, respectively (relative risk: 0.59; 95% confidence interval: 0.36–0.95; $p = 0.03$).[5] This benefit was primarily driven by significant reductions in distal recurrences (8 vs. 15% for placebo; $p = 0.02$), whereas proximal DVT and symptomatic pulmonary emboli were

relatively infrequent, and similar between the two treatment durations (3 vs. 4%, respectively; $p = 0.80$). No major bleeds occurred, and clinically relevant nonmajor bleeds were equally uncommon (0.5% in both groups).[5] Collectively, these findings further support the need of 3-month anticoagulation in patients with non-cancer-associated IDDVT, especially if one or more risk factors for recurrence are present. However, since only a small proportion of trial participants was classified at very low risk based on currently recommended definitions, additional research is warranted to identify selected subgroups who might be safely managed with surveillance or shorter duration of anticoagulation. It should be however noted that results were overall consistent across the study population, including in those participants with lower risk features (e.g., provoked or muscular vein IDDVT).[5]

Cancer-Associated IDDVT: 3- versus 12-Month Anticoagulation

Cancer-associated IDDVT accounts for 11% of all cancer-associated thromboses and negatively impacts prognosis, with an effect similar to that of proximal DVT and pulmonary embolism.[15] In this patient population, recurrences and bleeds are considerably frequent, and have estimated incidence rates of 5.65 and 4.08 per 100 person-years, respectively.[16] A recent study showed that, compared with IDDVT patients without cancer, those with cancer-associated IDDVT have 46 and 53% higher risks for recurrence and bleeding, respectively.[17] In this setting, guidelines suggest longer treatment duration (beyond 3 months) than that recommended for subjects with non-cancer-associated IDDVT (►**Fig. 1**).[7–9] Active cancer was, however, an exclusion criterium for most IDDVT treatment trials, and whether these patients may actually benefit from longer anticoagulation remained unproven.

Recently, the open-label randomized ONCO DVT trial, conducted in Japan, compared the safety and efficacy of 12 versus 3 months of edoxaban among 601 subjects with newly diagnosed cancer-associated IDDVT.[6] The 12-month incidences of symptomatic recurrent VTE or VTE-related death were 1.0 and 7.2% (odds ratio: 0.13, 95% confidence interval: 0.03–0.44) for 12- versus 3-month treatment, respectively.[6] No fatal VTE events occurred. Symptomatic recurrent VTE in the 3-month edoxaban group consisted of 2 pulmonary emboli, 7 proximal DVT events, and 14 distal recurrences. Asymptomatic IDDVT progression, defined as new or worsening thrombi during any follow-up ultrasound evaluation, occurred in 7.8 and 15.0% of patients receiving extended and shorter anticoagulation, respectively ($p < 0.05$).[6] Although numerically higher, the risk for major bleeding with 12-month edoxaban was not significantly increased compared with the shorter regimen (odds ratio: 1.34; 95% confidence interval: 0.75–2.41).[6] Collectively, these relevant findings indicate that anticoagulation for 12 months is superior to 3 months in patients with cancer-associated VTE. An important caveat is, however, that approximately 70% of participants had a body weight <60 kg, and even higher proportions received reduced edoxaban doses (30 mg instead of 60 mg daily), which might have blunted, at least partially, potential bleeding differences.[6] Thus, generalizability of these results to non-Japanese populations is to be determined, together with a potential role for reduced-dose anticoagulation.[18] Moreover, the fact that 80% of subjects was asymptomatic at IDDVT diagnosis, and almost 23% had asymptomatic thrombus progression, might support extended treatment independently from the presence of symptoms[6]; also warrants consideration whether and when routine ultrasound surveillance would be beneficial in this particular scenario.

In sum, anticoagulation is widely preferred over surveillance in most patients with acute IDDVT, and accumulating evidence supports this approach. Two recent large trials indicate that anticoagulation is overall safe and, when administered, this should be preferably done for 3 months in patients without active cancer, and for at least 12 months in those with cancer-associated IDDVT. Although the trial findings specifically apply to rivaroxaban (RITDS) and edoxaban (ONCO DVT), other DOACs might also possess similar safety and efficacy profiles in this setting. Therapeutic decisions should be personalized to each patient, taking into account individual clinical characteristics, preferences, and expectations. Additional research is necessary to improve risk stratification including implementation of risk prediction scores specific to subjects and subgroups with IDDVT. Modified anticoagulant durations and low-intensity DOACs in the acute phase might have a role, but should not be used in daily clinical practice until additional evidence will become available.

Authors' Contribution

All authors contributed to review and editing of the manuscript.

Conflict of Interest

N.P. received, outside of the submitted work, a training fellowship from the International Society on Thrombosis and Haemostasis (ISTH), and research funding from the International Network of VENous Thromboembolism Clinical Research Networks (INVENT). Y.Y. received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo, and grant support from Bayer Healthcare and Daiichi-Sankyo. W.A. received payment or honoraria for lectures from Astra Zeneca, Bayer, BMS/Pfizer, Viatris, Leo Pharma, Sanofi, and for participation on a Data Safety Monitoring Board or Advisory Board for Astra Zeneca, Bayer, Norgine, Leo Pharma, Sanofi, and Techdow.

Acknowledgment

The figure was created using BioRender.com.

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