REVIEW ARTICLE

How to treat isolated distal deep vein thrombosis

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KEY WORDS

anticoagulant therapy, calf deep vein thrombosis, direct oral anticoagulants, isolated distal deep vein thrombosis, venous thromboembolism

ABSTRACT

Isolated distal deep vein thrombosis (IDDVT) is a frequent manifestation of venous thromboembolism (VTE), accounting for up to 50% cases of lower-extremity deep vein thrombosis (DVT). As compared with proximal DVT, IDDVT is more frequently associated with transient risk factors and less often occurs unprovoked or in the presence of permanent risk factors. IDDVT generally carries a significantly lower risk of proximal extension, post-thrombotic syndrome, and recurrence than proximal DVT. Nevertheless, some patient subgroups, such as those with active cancer, other predisposing permanent risk factors, prior VTE, unprovoked IDDVT, persistently restricted mobility, and trifurcation or bilateral involvement, exhibit a non-negligible recurrence risk. Unlike in proximal DVT, the optimal therapeutic management of IDDVT remains uncertain. In clinical practice, the vast majority of IDDVT patients are managed with anticoagulation rather than with surveillance serial compression ultrasonography, which tends to be reserved to individuals at a high bleeding risk. Available data seem to favor anticoagulant therapy over no anticoagulation, thanks to a significant reduction in the risk for proximal extension and recurrence, without increased bleeding risk. Recent results of the RIDTS (Rivaroxaban for the Treatment of Symptomatic Isolated Distal Deep Vein Thrombosis) randomized clinical trial with rivaroxaban further support the use of anticoagulant therapy for 3 months over shorter durations (eg, ≤6 weeks). In this review, we offer an updated overview of the epidemiology, risk factors, and clinical course of IDDVT, with a focus on the therapeutic management in light of current guideline recommendations and most recent evidence. We also present real-life clinical cases of IDDVT with proposed therapeutic approaches, and highlight major challenges and gaps in this field.

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Isolated distal deep vein thrombosis Isolated distal deep vein thrombosis (IDDVT) refers to deep vein thrombosis (DVT) below the knee (ie, below the popliteal vein) in the absence of concomitant thrombosis in other venous districts.[1-3] Despite interindividual variability, the deep veins of the calf, comprising the anterior and posterior tibial veins, the peroneal vein, and the muscular (soleal and gastrocnemius muscle) veins, merge proximally to form the trifurcation area, followed by the popliteal vein (FIGURE 1).[1-3] Due to its anatomical closeness to the proximal deep veins and clinical characteristics shared with proximal DVT, it is still under debate whether trifurcation DVT should be managed as proximal or distal.[1-4]

IDDVT reportedly represents the most frequent presentation of lower-extremity DVT.[1-4] IDDVT has been long considered benign; however, a number of studies reported a non-negligible rate of complications following IDDVT, including recurrent venous thromboembolism (VTE), proximal extension, and post-thrombotic syndrome (PTS).[1-3] This was particularly noticeable among selected patient subgroups, such as those with active cancer.[5,6] Despite its relatively high prevalence and clinical relevance, as compared with proximal DVT and pulmonary embolism (PE), far fewer prospective studies have specifically addressed IDDVT, and its optimal therapeutic management remains uncertain, as reflected by scarce and heterogenous guideline recommendations. Recently, the RIDTS (Rivaroxaban for the Treatment of Symptomatic Isolated Distal Deep Vein Thrombosis) trial,[7] a randomized trial comparing 2 different durations (6 weeks vs 3 months) of anticoagulant therapy with the factor Xa inhibitor

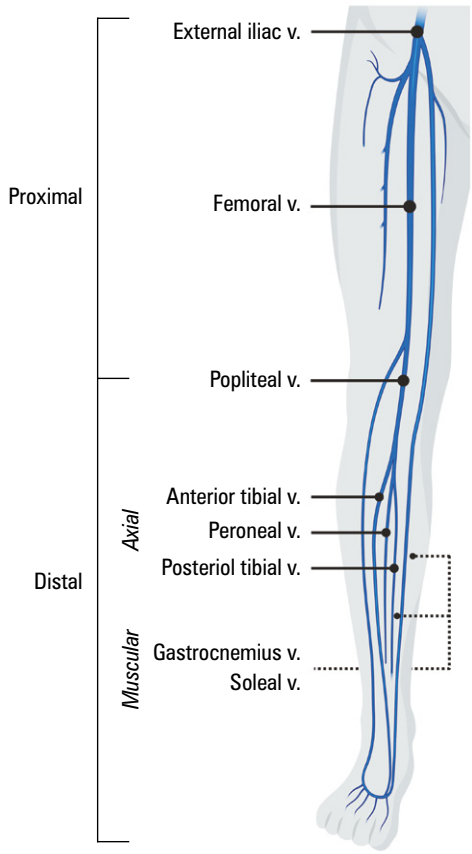

FIGURE 1 Proximal and distal veins of the lower extremity
Abbreviations: v, vein

rivaroxaban in 402 individuals with symptomatic IDDVT has been completed, providing implications for future studies and clinical practice.

Isolated distal deep vein thrombosis: epidemiology and risk factors Wide variability exists around the estimated prevalence of IDDVT, mainly due to factors such as differences in the study design, clinical setting, patient populations examined, and strategies used to diagnose IDDVT.[1-3] Among hospitalized patients, IDDVT reportedly accounts for up to 60% of all DVTs, while this proportion may reach 50% in ambulatory patients.[8-10] In studies in which whole-leg compression ultrasonography (CUS) was systematically performed, IDDVT represented about half of all DVTs, with significantly lower rates found when distal veins were were not systematically scanned upon initial imaging assessment.[1,2,11,12]

IDDVT and proximal DVT share common pathogenic mechanisms. However, the prevalence and contribution of each risk factor appear to be different between these 2 conditions. As compared with proximal DVT, IDDVT is more frequently associated with transient risk factors, such as recent surgery, trauma, hospitalization, travel, immobilization, or hormonal therapy.[13-17] Conversely, IDDVT less frequently occurs unprovoked, or in the presence of persistent risk factors, such as cancer, antiphospholipid syndrome, or heart failure.[13-18] The proportion of IDDVT cases is higher in women, especially those aged 40 to 49 years, whereas proximal DVT tends to be more frequent among men.[19] Individuals affected by IDDVT are generally younger, and less frequently exhibit comorbidities including renal impairment, as compared with patients with proximal DVT.[15,16] Pre-existing varicose veins and venous insufficiency are more frequent among IDDVT versus proximal DVT patients.[20] Individuals with IDDVT are also less likely to be diagnosed in the emergency department or to be hospitalized, as compared with patients with proximal DVT or PE.[20] Evidence also suggested that symptomatic IDDVT involving the deep calf and muscular veins exhibit slightly different symptoms at presentation, but share similar risk factors.[21]

Natural history of isolated distal deep vein thrombosis and comparisons with proximal deep vein thrombosis **Venous thromboembolism recurrence** The estimated risk for recurrent VTE is lower following IDDVT than proximal DVT.[13-20] Nevertheless, selected patient subgroups with IDDVT exhibit a clinically relevant recurrence risk despite generally lower rates. For example, individuals with bilateral IDDVT have a 2-fold increased risk for recurrent VTE, as compared with those with unilateral IDDVT.[22] The recurrence risk markedly increases in IDDVT patients with an active malignancy. Among individuals with 13 common cancer types, IDDVT represented 11% of cancer-associated VTE, being associated with a recurrence burden similar to that conferred by proximal DVT or PE.[6] In the OPTIMEV (Optimising History Taking for Evaluating the Risk of Venous Thromboembolism) prospective study, the overall annual recurrence rates were 5.2% and 2.7% in patients with proximal DVT and IDDVT, respectively.[4] In comparison with cancer-associated isolated proximal DVT, cancer-associated IDDVT had a higher risk for recurrent VTE (5.4% vs 11.5% per patient-year, respectively; adjusted hazard ratio [aHR], 1.8; 95% CI, 0.7–4.5). Accordingly, when comparing IDDVT patients with or without cancer, the former group exhibited a 2-fold higher recurrence risk (11.5% vs 5% per patient-year, respectively; aHR, 2.0; 95% CI, 1.0–3.7), independent of VTE history.[23] IDDVT in the deep calf or muscular veins exhibited comparable recurrence rates, whereas trifurcation IDDVT had a yearly recurrence rate similar to proximal DVT.[4] In a retrospective study[24] enrolling 831 patients with first acute, symptomatic isolated proximal or distal DVT followed for a median of 7.6 years, recurrent VTE was diagnosed in 17.3% and 7.9% of the participants, respectively. In agreement with other studies, when compared with their counterparts with proximal DVT, patients with cancer-associated IDDVT had a similar risk for recurrent VTE, whereas this risk was considerably lower following an unprovoked episode.[25] A recent meta-analysis[26] comprising 8160 patients with cancer-associated IDDVT estimated an incidence rate for recurrent VTE of 5.65 (95% CI, 2.09–15.30) per 100 person-years, regardless of

the type and duration of anticoagulant therapy, confirming a high recurrence risk of IDDVT in cancer patients.

In the XALIA (Xarelto for Long-term and Initial Anticoagulation in Venous Thromboembolism) study[18] including over 4000 individuals treated with rivaroxaban, recurrence rates for IDDVT and proximal DVT were 1% and 2.4% (aHR, 0.56; 95% CI, 0.29–1.08) on-treatment, and 1.1% and 2.1% (aHR, 0.65; 95% CI, 0.32–1.35) off-treatment, respectively. In the large GARFIED-VTE registry[16] comprising participants with IDDVT (n = 2123), proximal DVT (n = 3830), or PE (n = 4066), the vast majority (>98%) of whom were receiving anticoagulation, the 1-year recurrence rate was 4.8 (95% CI, 3.9–5.9) per 100 person-years for IDDVT, which was lower than for proximal DVT (HR, 0.76; 95% CI, 0.60–0.97; P = 0.003), but higher than for PE (HR, 1.16; 95% CI, 0.89–1.51; P = 0.003). These findings were confirmed by recent data from the RIETE (Registro Informatizado Enfermedad Tromboembólica)[17] registry involving approximately 6000 patients with IDDVT and 28 000 with isolated proximal DVT, demonstrating a lower risk for recurrent VTE (HR, 0.83; 95% CI, 0.69–0.99) at 1 year following IDDVT. When considering individuals who did not experience adverse events within the first 3 months of index DVT, this risk was further reduced (aHR, 0.48 for IDDVT vs proximal DVT; 95% CI, 0.24–0.97).[17] Evidence also suggests that IDDVT more likely tends to recur as IDDVT, with a similar behavior observed for proximal DVT.[4] In another study[24] involving 202 individuals with symptomatic IDDVT and 629 with proximal DVT, IDDVT was associated with a 69% lower risk for recurrent VTE, as compared with proximal DVT. Similar findings were obtained in the AUREC (Austrian Study on Recurrent Venous Thromboembolism) study.[27] In a patient-level meta-analysis of 7 prospective studies including 2554 individuals with a first VTE followed after discontinuation of anticoagulation, the participants with proximal DVT had a 4.8-fold higher recurrence rate than those with distal DVT (HR, 4.8; 95% CI, 2.1–11.0).[28] Conversely, a retrospective analysis of Mayo Clinic databases[29] comprising patients with IDDVT (n = 746) or proximal DVT (n = 1176) found no differences in VTE recurrence (4.60 vs 5.77 per 100 person-years, respectively), although baseline characteristics differed between the 2 cohorts.[29] Recently published data from the TROLL (Venous Thrombosis Registry in Østfold Hospital) registry,[30] comprising 475 patients with IDDVT without active cancer, reported cumulative incidences of recurrent VTE of 5.6%, 14.7%, and 27.2% at 1, 5, and 10 years, respectively. The rates were significantly higher in the patients with an unprovoked than those with a provoked event, thus confirming a high long-term risk of VTE recurrence after IDDVT, which is still considerable in the absence of cancer.

Proximal extension Proximal extension of IDDVT appears of critical clinical relevance due to the higher embolic potential and subsequent implications for treatment.[1-3] The natural course of IDDVT can be outlined based on studies in which IDDVT was managed with ultrasound surveillance without anticoagulation. These studies reported highly variable rates of proximal extension, ranging from 0% to 28%, possibly due to the low quality of the study design (mainly small, retrospective studies), and wide heterogeneity in patient populations, diagnostic strategies, and length of follow-up.[31] Studies comparing different diagnostic strategies (eg, serial proximal vs single complete [proximal and distal] CUS) in patients with suspected DVT have been reviewed elsewhere.[1-3] More recent studies have suggested that the risk for proximal extension following IDDVT appears to be lower than 10%, with substantial differences across patient subgroups.[32] In the CALTHRO prospective study[33] evaluating outpatients with symptomatic IDDVT managed with serial CUS, the majority of the participants exhibited complete thrombus resolution, while proximal extension occurred in about 3% of cases between 5 and 7 days of the diagnosis. Conversely, the risk for proximal extension appears considerably higher in patients with cancer or other persistent risk factors. In a randomized trial[34] comparing serial proximal to whole-leg CUS, proximal propagation occurred in 28% of IDDVT patients managed without anticoagulation, of whom almost 30% had cancer. In the CACTUS (Anticoagulant Therapy for Symptomatic Calf Deep Vein Thrombosis) trial,[35] comparing 6-week low-molecular-weight heparin (LMWH) nadroparin to placebo in IDDVT patients without malignancy or prior VTE, the rate of proximal extension at 3 months was 5.4% in the placebo group. Hence, proximal extension appears to be lower in outpatients with IDDVT associated with noncancer risk factors. Some studies suggested that individuals with muscular IDDVT might be at lower risk (<2%) for proximal extension than those with axial IDDVT, although this was not observed in other works.[36]

Post-thrombotic syndrome PTS is a disabling complication of DVT presenting with signs and symptoms of chronic venous insufficiency.[37] PTS negatively impacts quality of life, and accounts for significant utilization of health care resources.[38,39] PTS develops frequently following proximal DVT, while it is relatively less frequent after IDDVT.[37] Among the RIETE registry participants, PTS was found in 47.6% and 60.5% at 1 year following IDDVT and proximal DVT, respectively.[17] In the TULIPA (Thrombosis and Pulmonary Embolism in Out-Patients) registry,[40] which included 135 patients with a first DVT episode prospectively followed for 3 years, the rates of PTS were 15.6% and 32% following IDDVT and proximal DVT, respectively, suggesting that the PTS risk after IDDVT is approximately half of that associated with proximal

DVT.[40] Among the 178 CACTUS trial participants with a PTS assessment, no significant differences in PTS incidence were found between nadroparin and placebo after a median follow-up of 6 years.[41] However, when considering only participants without prior chronic venous insufficiency, PTS incidence was lower in the anticoagulation group (9% vs 24% for placebo; $P = 0.04$).[41] The beneficial effects of anticoagulant therapy on PTS prevention are well-recognized, with direct oral anticoagulants (DOACs) and LMWHs appearing superior to vitamin K antagonists (VKAs), presumably due to their anti-inflammatory properties, although direct comparisons are lacking.[42] Accumulating evidence points to a pathogenetic role of inflammation in PTS.[43] Statins reduce the occurrence of VTE,[44] and may help prevent PTS.[45] The ongoing SAVER (Statins for Venous Event Reduction in Patients With Venous Thromboembolism) randomized trial[46] with rosuvastatin is testing this hypothesis (NCT04319627). Elastic compression stockings may relieve edema and pain after acute DVT, although their effect on PTS prevention and treatment appears limited.[47,48] Hence, most guidelines suggest against routine use of compression therapy, which should be considered in high-risk individuals.[47,48] Additional research is warranted to establish the role of distinct anticoagulants, anti-inflammatory agents (including statins), and compression therapy in PTS prevention and management, which remain a significant unmet clinical need.[42]

Incident cancer VTE can be the first manifestation of occult cancer.[49] In a large, population-based Danish study,[50] patients with VTE were at increased risk for cancer, as compared with the general population, regardless of VTE location. Comparable findings were provided by the OPTIMEV study,[51] in which participants with isolated distal or proximal DVT had a similar likelihood of being diagnosed with cancer during the 3-year follow-up (3.9% for both groups). Conversely, data from the GARFIELD-VTE registry[16] suggested that the 12-month risk for incident cancer was significantly lower in patients with IDDVT than in those with proximal DVT or PE. Since the estimates around new cancer diagnosis following IDDVT may vary depending on the patient population and the strategy used to exclude cancer at DVT diagnosis or to detect cancer during follow-up, additional research is necessary to clarify the clinical and pathophysiological relationship between IDDVT and subsequent cancer.

Mortality Mortality associated with IDDVT is reportedly lower, although not negligible, than that associated with proximal DVT, being mostly driven by VTE-unrelated causes, thereby reflecting the characteristics of the patient population studied. In the XALIA study,[18] 1-year mortality rates were 0.8% and 2.2% for IDDVT and proximal DVT, respectively. In the RIETE registry,[14] active cancer was the strongest predictor of death among IDDVT patients. IDDVT has been associated with increased mortality across several cancer types, with a prognostic impact similar to that observed in proximal DVT for most cancers.[6] A recent meta-analysis[26] reported the mortality of 30.22 per 100 patient-years (95% CI, 22.60–42.89) in patients with cancer-associated IDDVT. Among 831 patients with either IDDVT or proximal DVT followed for 7.6 years, mortality was respectively 25.7% and 33.5% (aHR, 0.75; 95% CI, 0.55–1.02), thus consistently indicating lower mortality following IDDVT also in the long-term, especially following an unprovoked event (aHR, 0.58; 95% CI, 0.26–1.31).[24] Conversely, in a recent study conducted at the Mayo Clinic,[29] patients with IDDVT or proximal DVT had overall mortality rates of 31.89 and 28.36 per 100 person-years, respectively, and the rates were significantly higher at 3 months in the IDDVT patients. Independent predictors of mortality included increasing age, active cancer, and the use of unfractionated heparin, LMWH, or warfarin (vs DOACs).[29] When considering individuals with cancer, those with IDDVT had a similar, or even greater, risk for death, as compared with those with proximal DVT.[23,29] This observation was recently confirmed in a prospective study showing similar clinical outcomes among 192 patients with either isolated distal or proximal DVT, thus suggesting that the treatment of cancer-associated IDDVT should mirror that of cancer-associated proximal DVT, although dedicated randomized trials are required.[52]

Anticoagulant therapy for isolated distal deep vein thrombosis

Evidence from observational studies A recent study evaluated the outcomes associated with anticoagulation versus serial ultrasound for IDDVT management.[53] Among 483 retrospectively identified patients, VTE recurrence was significantly lower in the ones receiving anticoagulation than in those with ultrasound surveillance (7.3% vs 14.3%, respectively; $P = 0.04$).[53] The rate of DVT propagation was also reduced with anticoagulation (2.8% vs 8.3%; $P = 0.01$), while no differences were found in bleeding or mortality, resulting in a net clinical benefit favoring anticoagulation.[53] This study, together with previous observations showing a non-negligible risk of thrombotic evolution of IDDVT when left untreated, underscores the importance of anticoagulation in this patient population.[33]

In a retrospective study[54] involving an unselected cohort of 384 patients with IDDVT, 63.3% received therapeutic-dose anticoagulation (mostly warfarin and LMWH), while the remaining participants received no or prophylactic-dose anticoagulation. Baseline characteristics differed between the 2 groups, especially with regard to inpatient status, recent surgery, cancer, and use of prophylactic anticoagulation prior to index IDDVT.[54] In comparison with prophylactic anticoagulation, therapeutic anticoagulation was associated with a lower risk for proximal DVT and

PE at 3 months (odds ratio [OR], 0.34; 95% CI, 0.14–0.83), but a higher bleeding risk (OR, 4.35; 95% CI, 1.27–14.9).[54]

Among 308 patients with cancer-associated IDDVT treated with LMWH (93.5%) or VKA for a median of 4.2 months, incidence rates of VTE and major bleeding were 13.2 and 2.0 per 100 person-years, respectively, thus suggesting a high recurrence risk despite anticoagulation.[5] Residual vein obstruction at anticoagulant discontinuation was detected in approximately half of the cases, and was associated with increased recurrence risk.[5] Female sex, obesity, and axial vein involvement correlated with residual vein obstruction after cancer-associated IDDVT.[5]

In a small prospective study[55] evaluating therapeutic-dose nadroparin for 10 days plus compression therapy in comparison with compression therapy alone in IDDVT patients, anticoagulation was associated with reduced thrombus progression and recurrent muscle vein thrombosis, while no symptomatic PE or bleeds occurred. In another prospective cohort of outpatients with symptomatic IDDVT managed according to a prespecified anticoagulant strategy consisting in LMWH for 30 days for provoked events (n = 56) or a VKA for 3 months for unprovoked IDDVT (n = 32), 19.3% of the participants experienced thromboembolic complications during the 2-year follow-up, with cancer and male sex conferring a considerably higher risk.[56] In a single-arm study[57] enrolling 119 patients with IDDVT treated with LMWH for 40 days, 5% of the participants had recurrent DVT, 1.7% had thrombus extension, and 3.4% experienced PTS, with no PE or bleeds occurring after 3 months. Notably, both DVT recurrence and residual vein obstruction correlated with the number of thrombosed veins, suggesting that longer treatment could be necessary when multiple veins are involved.[57] In a retrospective study evaluating LMWH for 4 to 6 weeks in 280 patients with IDDVT, recurrence rates per 100 person-years were, 7.2, 5.9, and 3.5, respectively, in patients with an unprovoked event, cancer-associated IDDVT, or IDDVT associated with transient risk factors.[58] Prior VTE and unprovoked event conferred a 2-fold increased risk, indicating a non-negligible recurrence risk associated with short-term anticoagulation.[58] In the START registry,[59] among 421 participants with IDDVT receiving anticoagulation (49% DOAC, 45% VKA), the incidences of thromboembolic and bleeding complications were 1.1% and 5.6% patient-years, respectively. The vast majority of IDDVT patients received anticoagulant therapy for over 3 months, but were less likely to be treated for more than 6 months, as compared with patients with proximal DVT (70.7% vs 52.7%, respectively).[59] Bleeding was more frequent among individuals with IDDVT than those with proximal DVT, and was significantly higher among warfarin users.[59] Interestingly, most bleeding and thromboembolic events occurred after 3 months of therapy, suggesting that anticoagulation for longer than 90 days in unselected IDDVT patients could be associated with an increased rate of complications.[59] In the prospective, multicenter TWISTER (Two Weeks of Low Molecular Weight Heparin for Isolated Symptomatic Distal Vein Thrombosis) study,[60] low-risk ambulatory patients with IDDVT (eg, cancer and prior VTE excluded) were managed with therapeutic-dose anticoagulation (enoxaparin or rivaroxaban) for 2 weeks, stopped in the case of complete symptom resolution and no radiological extension, otherwise continued for another 4 weeks. The findings of this study, although limited by the small event number and lack of randomization, suggested that this strategy might be safe in low-risk individuals.[60] In another recent prospective study conducted in Japan (J'xactly),[61] enrolling 288 individuals with IDDVT treated with rivaroxaban (42.7% therapeutic-dose with mean treatment duration, 4.5 months), the incidences of symptomatic recurrent VTE and major bleeding were, respectively, 2.9% and 1.55%, with comparable effectiveness and safety observed with 15 and 30 mg/day rivaroxaban dosages. The use of DOACs (n = 444; 63% apixaban, 36% rivaroxaban, 1% edoxaban or dabigatran) vs unfractionated heparin, LMWH, or warfarin (n = 302) in an unselected IDDVT cohort was found to be associated with significantly reduced rates of recurrent VTE, major bleeding, and death, thus suggesting that DOACs represent valid options for IDDVT treatment.[29] Among 475 individuals with IDDVT without cancer enrolled in the TROLL registry,[30] the 3-month incidence of major bleeding was 1.5% overall, and 0.8% in those receiving DOACs, suggesting lower bleeding risk with DOACs.

The risk of bleeding associated with IDDVT is largely affected by anticoagulation (eg, anticoagulant type, treatment duration) and patient characteristics. Evidence suggests that individuals with IDDVT may exhibit an overall lower risk for bleeding than those with proximal DVT.[14,16,18] The 1-year rates of major bleeding and any bleeding were, respectively, 1.2 (95% CI, 0.8–1.8) and 7.5 (95% CI, 6.3–8.8) per 100 person-years among over 2000 anticoagulated IDDVT patients enrolled in the GARFIELD-VTE registry.[16] As compared with individuals with proximal DVT, those with IDDVT were significantly less likely to experience major or any bleeding (HR, 0.69; 95% CI, 0.57–0.84; P = 0.0002), while major bleeding did not significantly differ between the groups (HR, 0.8; 95% CI, 0.49–1.28; P = 0.3503).[16] In the XALIA study,[18] on-treatment major bleeding occurred in 0.9% and 1.4% of patients with IDDVT and proximal DVT, respectively. Median anticoagulant treatment duration for IDDVT was shorter than for proximal DVT (102 vs 192 days, respectively), in line with other studies.[17,24,29] Comparing participants with IDDVT or proximal DVT in the GARFIELD-VTE registry,[16] the former group had a numerically lower risk for major bleeding (HR, 0.80; 95% CI, 0.49–1.28; P = 0.35), and a significantly lower risk for any bleeding complication

(HR, 0.69; 95% CI, 0.57–0.84; P = 0.0002).[16] Accordingly, patients with IDDVT enrolled in the RIETE registry,[14] most of whom receiving anticoagulation, exhibited lower 3-month rates of major bleeding than the patients with proximal DVT (1% vs 2.2%, respectively; P <0.01). Despite abundant evidence indicating lower bleeding risk in patients with IDDVT versus proximal DVT, it is possible that residual confounders due to differences in patient characteristics and anticoagulation may influence, at least in part, the risk estimates around bleeding. Additional prospective studies are therefore necessary to better identify high- and low-risk patient-, disease-, and treatment-related characteristics to optimize anticoagulant management.

Among IDDVT patients included in the OPTIMEV study,[23] those with cancer exhibited a 2-fold higher risk for major bleeding, as compared with individuals without cancer (3.6% vs 1.8% per year, respectively; aHR, 2.0; 95% CI, 0.6–6.1). In a recent meta-analysis comprising over 8000 patients with cancer-associated IDDVT, the incidence rates of major bleeding and clinically relevant nonmajor bleeding were 4.08 (95% CI, 2.52–6.61) and 8.11 (95% CI, 5.56–11.83) per 100 patient-years, respectively.[26] While these results require careful interpretation due to the observational nature of the studies included and the wide heterogeneity in background anticoagulant therapy, they highlight a relevant risk for bleeding complications, which, paired with an elevated recurrence risk, makes management of cancer-associated IDDVT highly challenging.

Evidence from randomized controlled trials A number of randomized controlled trials assessing anticoagulant therapy in patients with IDDVT has been conducted (TABLE 1). Some of these studies evaluated anticoagulation in comparison with no anticoagulation or placebo (in addition to usual care, comprising, depending on the study, compression therapy and/or agents including nonsteroidal anti-inflammatory drugs for symptom relief).[35,36,62-64] In a landmark trial conducted by Lagerstedt et al[63] in 1985, which randomized 51 individuals with symptomatic IDDVT without cancer to either warfarin for 3 months or no anticoagulation after an initial course of unfractionated heparin, anticoagulation was associated with a considerably reduced rate of recurrent VTE at 3 and 12 months, without increased bleeding. Schwarz et al[36] evaluated nadroparin for 10 days vs no anticoagulation among 107 patients with symptomatic acute IDDVT without prior VTE, finding no significant reductions in recurrent VTE and vein recanalization at 3 months. Conversely, in the ACT (Anticoagulation of Calf Thrombosis) pilot trial,[64] treatment with therapeutic-dose dalteparin followed by an oral VKA for a total of 3 months was associated with numerically lower, although not significant, recurrent VTE and proximal extension, as compared with no anticoagulation, without a clear increase in major bleeding. The CACTUS trial[35] evaluated 6-week nadroparin vs placebo among 259 low-risk patients with symptomatic acute IDDVT without cancer or prior VTE. In comparison with placebo, LMWH use was associated with a nonsignificant reduction in recurrent VTE at 3 months (3.3% vs 6.2% for placebo; P = 0.28), with a similar rate of major bleeding, but slightly increased rate of clinically relevant nonmajor bleeding. LMWH therapy did not improve pain control in the acute and subacute phases after IDDVT.[65] In a long-term follow-up study of the CACTUS trial,[41] LMWH use was not associated with a reduction in PTS (29% vs 32% for placebo; P = 0.6), except in patients without pre-existing chronic venous insufficiency (9% vs 24% for LMWH and placebo, respectively; P = 0.04). Long-term rates of recurrent VTE in the LMWH and placebo groups were, respectively, 8% and 14% (P = 0.2), possibly suggesting a trend toward lower recurrence risk with LMWH in this low-risk population.

Other randomized controlled trials compared different durations of anticoagulation for IDDVT management.[7,66-68] The DURAC (Duration of Anticoagulation) trial[66] found that 6-month VKA therapy after a first VTE episode (including IDDVT) reduced 2-year recurrences as compared with 6-week therapy. The DOTAVK (Durée Optimale du Traitement AntiVitamines K) study,[67] an open-label randomized trial comparing 6-week versus 3-month VKA therapy in 197 patients with distal DVT without cancer or prior VTE, suggested that short-course anticoagulation could be sufficient in this low-risk population. Another open-label study[68] randomized 192 patients with postsurgical IDDVT to receive LMWH followed by warfarin for either 3 months or 6 weeks. A significant reduction in IDDVT extension was found in patients with 2 or more veins involved receiving longer-duration anticoagulation. While no major bleeds occurred, recurrent VTE events were also numerically lower in those receiving longer-duration anticoagulation.[68] In the recent RIDTS trial,[7] outpatients with symptomatic acute IDDVT were randomized after a 6-week uneventful period of standard-dose rivaroxaban to receive 20 mg of rivaroxaban (n = 200) or placebo (n = 202) once daily for additional 6 weeks. Patients with active cancer and severe renal or liver insufficiency were excluded, and participants were followed for 24 months. The primary efficacy outcome was recurrent VTE after randomization, comprising IDDVT progression, recurrent IDDVT, proximal DVT, and symptomatic or fatal PE, while the primary safety outcome was major bleeding.[7] Recurrent VTE occurred in 11% and 19% of patients in the rivaroxaban and placebo arms, respectively (relative risk [RR], 0.59; 95% CI, 0.36–0.95; P = 0.03; number needed to treat, 13; 95% CI, 7–126).[7] Recurrent IDDVT was also reduced with 3-month as compared with 6-week rivaroxaban (8% vs 15%, respectively; P = 0.02). No significant differences in the rates of proximal DVT or PE were found (3% vs 4% for

TABLE 1 Randomized controlled trials evaluating anticoagulant therapy for isolated distal deep vein thrombosis (continued on the next page)

Study (year)	Study design (sample size)	Main inclusion/(exclusion) criteria	Intervention	Main findings
RCTs comparing AC vs no AC or placebo				
Lagerstedt et al[63] (1985)	Randomized, open-label (n = 51)	Symptomatic IDDVT (PE, malignancy, or prior VTE on anticoagulant therapy excluded)	UFH/warfarin for 3 months vs no warfarin	↓ recurrent VTE at 3 months (0% vs 29% for warfarin vs no warfarin, respectively; $P < 0.01$), and 1 year (4.3% vs 67.9% for warfarin vs no warfarin, respectively; $P < 0.02$); ↓ recurrent DVT (0% vs 28.6% for warfarin vs no warfarin, respectively); ↓ PE (0% vs 3.6% for warfarin vs no warfarin, respectively); ↓ MB (0% vs 7.1% for warfarin vs no warfarin, respectively)
Nielsen et al[62] (1994)	Randomized, open-label (n = 16)	Proximal and distal DVT (clinical symptoms of PE excluded)	UFH/phenprocoumon for 3 months vs no AC	No recurrent VTE at 60 days occurred. 8.3% rate of bleeding events in the AC group
Schwarz et al[36] (2010)	Randomized, open-label (n = 107)	Symptomatic, acute IDDVT (prior VTE excluded)	Nadroparin for 10 days vs no anticoagulation, in addition to compression therapy	←→ recurrent VTE (including proximal extension and PE) (3.7% vs 3.8% for AC vs no AC, respectively); ←→ vein recanalization at 3 months; No symptomatic PE, MB, or death occurred.
Horner et al[64]; Anticoagulation of Calf Thrombosis (ACT) pilot trial (2014)	Randomized, open-label (n = 70)	Symptomatic IDDVT, outpatients (prior VTE excluded)	Dalteparin/VKA for 3 months vs no anticoagulation	↓ recurrent VTE (including symptomatic proximal extension and PE) at 3 months (0% vs 11.4% for AC vs no AC, respectively; $P = 0.11$); ↓ proximal extension (0% vs 8.6% for AC vs no AC, respectively; $P = 0.24$); ←→ PE (0% vs 2.9% for AC vs no AC, respectively); ←→ MB (0% in both groups); No death occurred.
Righini et al[35,41]; Anticoagulant Therapy for Symptomatic Calf Deep Vein Thrombosis (CACTUS) trial (2016)	Randomized, double-blind, placebo-controlled (n = 259)	Symptomatic, acute IDDVT (cancer and prior VTE excluded)	Nadroparin for 6 weeks vs placebo	←→ recurrent VTE at 3 months (3.3% vs 6.2% for AC vs placebo, respectively; $P = 0.28$); ←→ recurrent DVT (1.6 vs 5.4% for AC vs placebo, respectively); ←→ PE (1.6% vs 0.8% for AC vs placebo, respectively); ←→ MB (0.8% vs 0% for AC vs placebo, respectively); ↑ MB or CRNMB (4.0% vs 0% for AC vs placebo, respectively; $P = 0.026$); ←→ PTS at 6 years (28.7% vs 31.9% for AC vs placebo, respectively; $P = 0.6$); ↓ PTS at 6 years, in patients without primary chronic venous insufficiency (9% vs 24% for AC vs placebo, respectively; $P = 0.04$); ←→ all-cause mortality (0.8% vs 0% for AC vs placebo, respectively)
RCTs comparing different durations of AC				
Schulman et al[66]; Duration of Anticoagulation (DURAC) trial (1995)	Randomized, open-label (n = 347)	PE, proximal or distal DVT (cancer and prior VTE excluded)	VKA (warfarin or dicoumarol, target INR 2.0–2.85) for 6 months vs 6 weeks	↓ recurrent VTE at 2 years (5.8% vs 11.4% for long- vs short-course anticoagulation, respectively)
Pinede et al[67]; Durée Optimale du Traitement AntiVitamines K (DOTAVK) study (2001)	Randomized, open-label (n = 197)	Symptomatic PE, proximal or distal DVT (cancer, prior VTE, pregnancy, vena cava filter, surgical thrombectomy, known thrombophilia, and severe PE excluded)	VKA (fluindione, target INR 2–3) for 3 months vs 6 weeks	←→ recurrent VTE (3.2% vs 1.9% for long- vs short-duration AC, respectively); ←→ recurrent DVT (2.2% vs 1.9% for long- vs short-duration AC, respectively); ←→ PE (1.1% vs 0% for long- vs short-duration AC, respectively); ←→ MB (3.3% vs 1.0% for long-vs short-duration AC, respectively); No PE- or MB-related death occurred.

TABLE 1 Randomized controlled trials evaluating anticoagulant therapy for isolated distal deep vein thrombosis (continued from the previous page)

Study (year)	Study design (sample size)	Main inclusion/(exclusion) criteria	Intervention	Main findings
Ferrara et al[68] (2006)	Randomized, open--label (n = 192)	Post-surgical distal DVT (cancer, inherited coagulopathies, hyperviscosity syndromes or antiphospholipid antibodies excluded)	LMWH (nandroparin) followed by VKA (warfarin, target INR 2–3) for 3 months vs 6 weeks	↓ recurrent VTE (8.3% vs 30.2% for long- vs short-duration AC, respectively); ↓ recurrent DVT (7.3% vs 28.1% for long- vs short-duration AC, respectively); ←→ proximal extension, 1 vein involved (2.9% vs 14.7% for long- vs short-duration AC, respectively; $P = 0.197$); ↓ proximal extension, ≥ 2 veins involved (9.7% vs 35.5% for long- vs short-duration AC, respectively; $P = 0.001$); ←→ PE (1.0% vs 2.1% for long- vs short-duration AC, respectively); No MB occurred.
Ageno et al*; Rivaroxaban for the Treatment of Symptomatic Isolated Distal Deep Vein Thrombosis (RIDTS) trial (2022)	Randomized, double-blind, placebo-controlled (n = 402)	Symptomatic, acute IDDVT (parental or oral AC >3 days prior to enrollment excluded)	Rivaroxaban (15 mg twice daily) for 6 weeks, followed by rivaroxaban (20 mg) or placebo for an additional 6 weeks	↓ recurrent VTE (including proximal extension, recurrent IDDVT, proximal DVT, symptomatic PE) at 2 years (11.5% vs 19.3% for long- vs short-duration AC, respectively; $P = 0.03$; NNT = 13); ↓ recurrent IDDVT (8.0% vs 15.3% for long- vs short-duration AC, respectively; $P = 0.02$); ←→ proximal DVT or PE (3.5% vs 4.0% for long- vs short-duration AC, respectively; $P = 0.8$); ←→ all-cause mortality (1% in each group); No fatal PE or MB occurred.

Abbreviations: ↑, increase; ↓, decrease;←→, no change; AC, anticoagulation; CRNMB, clinically relevant nonmajor bleeding; DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MB, major bleeding; NNT, number needed to treat; PE, pulmonary embolism; RCTs, randomized controlled trials; VKA, vitamin K antagonist; VTE, venous thromboembolism

rivaroxaban and placebo, respectively; $P = 0.8$).[7] No major bleeds occurred, and episodes of clinically relevant nonmajor bleeding were overall low, and similar between the groups.[7] Importantly, the benefits of 3-month rivaroxaban were consistent across IDDVT sites (axial vs muscular vein) and nature (provoked vs unprovoked), and obesity status, and were more pronounced in women and patients without prior VTE.[7] Collectively, these findings indicate that additional 6 weeks of rivaroxaban following a 6-week uneventful period of anticoagulation effectively reduce the risk of VTE recurrence without increasing the risk of major bleeding. It is, however, worth noting that the observed benefit was mainly due to a reduction in recurrent IDDVT, while the incidence of proximal DVT or PE was low after 2 years, and not statistically different between the 2 arms.[7] Although recurrent IDDVT might be less clinically relevant than proximal VTE events, its detection in clinical practice leads to re-initiation or extension of anticoagulation for much longer than 6 weeks. Therefore, the reduction in IDDVT recurrences with an additional 6 weeks of treatment may prevent further unnecessary anticoagulation in a substantial proportion of patients. It is also likely that the timely detection of recurrent IDDVT (including asymptomatic events) during follow-up might have prevened subsequent symptomatic proximal events. It is also worth pointing out that, while the RIDTS trial informs on the optimal duration of anticoagulation, it did not address the question whether or not anticoagulation should be used in IDDVT patients, which warrants further investigation.

A meta-analysis[69] comprising 4072 patients showed that anticoagulation (either therapeutic- or prophylactic-dose) reduces the risk for recurrent VTE, comprising proximal propagation, recurrent DVT (OR, 0.5; 95% CI, 0.31–0.79), and PE (OR, 0.48; 95% CI, 0.25– 0.91), without increasing the risk for major bleeding (OR, 0.64; 95% CI, 0.15–2.73). Importantly, a significantly lower risk for recurrent VTE was estimated in individuals receiving over 6 versus 6 weeks of anticoagulant therapy (OR, 0.39; 95% CI, 0.17–0.90).[69] Confirming and further expanding these data, a recent Cochrane meta-analysis comprising a total of 1239 patients with IDDVT from 8 randomized controlled trials found that anticoagulation with a VKA, as compared with no anticoagulation, was associated with significant reductions in recurrent VTE (RR, 0.34, 95% CI, 0.15–0.77; high-certainty evidence) and recurrent DVT (RR, 0.25; 95% CI, 0.10–0.67; high-certainty evidence), with little to no effect on PE or major bleeding (low-certainty evidence).[70] Anticoagulation, as compared with no anticoagulation, was however associated with increased risk for clinically relevant nonmajor bleeding (RR, 3.34; 95% CI, 1.07–10.46; high-certainty evidence).[70] When assessing different anticoagulant durations, anticoagulation with a VKA for 3 months or longer appeared superior to 6-week anticoagulation, showing a reduced risk for VTE

(RR, 0.42; 95% CI, 0.26–0.68; high-certainty evidence) and DVT recurrence (RR, 0.32; 95% CI, 0.16–0.64; high-certainty evidence), with little to no effect on PE, and no clear increase in the risk of major bleeding or clinically relevant nonmajor bleeding (low-certainty evidence).[70]

Guideline recommendations International clinical practice guidelines provide variable recommendations, often weak and with low-to-moderate certainty, reflecting the lack of robust clinical trial evidence.[71-73] In addition, some of the major international societies' guidelines do not provide any specific recommendation for IDDVT management (TABLE 2).[74-78]

For patients with acute IDDVT without severe symptoms or risk factors for extension, the American College of Chest Physicians (ACCP) guidelines suggest serial imaging for 2 weeks (ie, repeated ultrasound once weekly or with worsening symptoms for 2 weeks, starting anticoagulation if IDDVT extends or propagates proximally).[71] Anticoagulation is favored over serial imaging in patients with acute IDDVT presenting with severe symptoms or risk factors for extension (TABLE 3).[71] In patients receiving anticoagulation for IDDVT, the same anticoagulation regimen as that used for acute proximal DVT is recommended, with no distinct duration of therapy.[71]

The European Society for Vascular Surgery guidelines recommend clinical reassessment and repeated whole-leg ultrasonography after 1 week in patients with symptomatic IDDVT not receiving anticoagulation.[72] For patients with symptomatic IDDVT requiring anticoagulation, 3-month treatment is recommended over shorter durations, with DOACs being preferred over LMWH followed by VKA.[72] In patients with symptomatic IDDVT associated with active cancer, extension of anticoagulation beyond 3 months should be considered.[72]

The European Society of Cardiology (ESC) suggests that patients with IDDVT at a high risk of recurrence should receive full-dose anticoagulation for at least 3 months.[73] Conversely, individuals at low risk of recurrence should be anticoagulated with LMWH for a shorter period (4–6 weeks), but lower anticoagulant doses, or ultrasound surveillance may be considered.[73]

The use of compression therapy following acute DVT remains controversial considering the lack of adequate evidence to inform clinical practice. Uncertainty is even greater with respect to IDDVT, as most randomized trials evaluating compression therapies were conducted in patients with proximal DVT. Therefore, guideline recommendations primarily refer to acute proximal DVT, with unclear generalizability to acute IDDVT, underscoring the need for additional research in this area. The ACCP and American Society of Hematology guidelines suggest against routine use of compression stockings in individuals with acute DVT, although they may be considered to reduce edema and pain in selected cases.[71,75] According to the ESC, the use of elastic compression stockings should be individualized, and immediate compression therapy with early mobilization and walking exercise may be proposed to relieve acute venous symptoms after acute DVT.[73]

Management of isolated distal deep vein thrombosis: proposed therapeutic approach The vast majority of IDDVT cases are treated with anticoagulant therapy in real-life clinical practice, as attested by large registries showing that as much as 95% of patients with IDDVT receive anticoagulation.[14,16,18,20] Multiple reasons may account for this trend. These include the therapeutic goal to minimize the risk for proximal extension, recurrent VTE and PTS, but also practical challenges in performing repeated CUS imaging, as well as patient and physician expectations and preferences. When opting for anticoagulation instead of serial imaging in patients with IDDVT, an assessment of the bleeding risk should be performed, carefully evaluating the presence of acquired and inherited risk factors for bleeding and patient characteristics, including renal function, platelet count, and body mass index.[33,53]

In our experience, in the absence of a clinically relevant bleeding risk, patients with unprovoked IDDVT should be treated with therapeutic-dose anticoagulation for 3 months (FIGURE 2). As previously discussed, cancer-associated IDDVT tends to exhibit clinical outcomes similar to those of cancer-associated proximal DVT. Hence, in the absence of an increased bleeding risk, we generally treat patients with IDDVT and active cancer with extended-duration full-dose anticoagulation (eg, as long as cancer is active). When this is the management strategy of choice, periodic clinical and laboratory reassessment of the bleeding risk, as well as prevention and prompt management of potential complications (eg, toxicity due anticancer drugs, including thrombocytopenia, liver or kidney insufficiency, infections, hospitalization, and surgical procedures) are essential to mitigate the risk of bleeding and to tailor anticoagulant therapy.

In the case of IDDVT associated with a transient risk factor (eg, hospitalization, surgery, plaster immobilization, long-haul travel) and no increased bleeding risk, full-dose anticoagulation for 3 months is usually preferred over shorter courses (eg, 4–6 weeks) of therapy, provided that the risk factor is resolved and no symptom worsening or evidence of proximal propagation are observed within this period of time (FIGURE 2). However, we acknowledge that evidence to support anticoagulant treatment for low-risk patients is limited and that repeated ultrasound testing is an acceptable option. Patient opinion and preferences should be carefully considered under these circumstances. We also acknowledge that shorter courses of treatment are used in low-risk patients, but the benefits of this strategy remain uncertain.

To date, indefinite-duration anticoagulation is not indicated following a first episode of unprovoked IDDVT, as most recurrences are expected

TABLE 2 Recommendations from major international clinical practice guidelines and expert consensus statements on the management of patients with isolated distal deep vein thrombosis

Guideline (year)	Recommendations
Second consensus document on diagnosis and management of acute deep vein thrombosis: updated document elaborated by the ESC Working Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function (European Society of Cardiology [ESC], 2022)[73]	1 Patients with IDDVT at high risk of recurrence should be treated with full-dose anticoagulants for at least 3 months, as in the case of proximal DVT. 2 Patients at low risk of recurrence should be treated with shorter LMWH treatment (4–6 weeks), even at lower anticoagulant doses, or ultrasound surveillance may be considered. 3 Low- and high-risk features are shown in **TABLE 3**.
Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report (American College of Chest Physicians [ACCP], 2021)[71]	1 In patients with acute IDDVT: and (i) without severe symptoms or risk factors for extension (**TABLE 3**), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (weak recommendation, moderate-certainty evidence); or (ii) with severe symptoms or risk factors for extension, we suggest anticoagulation over serial imaging of the deep veins (weak recommendation, low-certainty evidence). 2 In patients with acute IDDVT who are treated with serial imaging, we (i) recommend no anticoagulation if the thrombus does not extend (strong recommendation, moderate-certainty evidence); (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins (weak recommendation, very low-certainty evidence); (iii) recommend anticoagulation if the thrombus extends into the proximal veins (strong recommendation, moderate-certainty evidence). 3 In patients with acute IDDVT of the leg treated with anticoagulation, the same anticoagulation regimen as for patients with acute proximal DVT should be used. If anticoagulant therapy is chosen, the same initiation and treatment-phase regimens should be used as for acute proximal DVT. Remarks: Serial imaging refers to repeating ultrasound once weekly, or with worsening symptoms for 2 weeks, anticoagulating only if distal thrombi propagate. Patients at high risk for bleeding are more likely to benefit from serial imaging. Evidence suggests uncertainty that anticoagulation is superior to no anticoagulation. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to favor initial anticoagulation over serial imaging.
European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis[72]	1 For patients with IDDVT, a decision to anticoagulate based on symptoms, risk factors for progression, and bleeding risk should be considered (class IIa, level C). 2 For patients with symptomatic IDDVT requiring anticoagulant treatment, a 3-month therapy is recommended over shorter durations (class I, level A) 3 For patients with IDDVT requiring anticoagulation, DOACs are recommended over LMWH followed by VKA (class I, level C). 4 For patients with symptomatic IDDVT and active cancer, anticoagulation beyond 3 months should be considered (class IIa, level C). 5 For patients with symptomatic IDDVT not receiving anticoagulation, clinical reassessment and repeat whole leg ultrasound after 1 week is recommended (class I, level B).
2022 International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19 (International Initiative on Thrombosis and Cancer [ITAC] advisory panel)[77]	Not discussed
American Society of Hematology (ASH) 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer[74]	Not discussed
American Society of Hematology (ASH) 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism[75]	Not discussed
Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (National Institute of Health and Care Excellence [NICE] guideline 158, 2020)[78]	Not discussed
Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update (American Society of Clinical Oncology [ASCO], 2019)[76]	Not discussed

Abbreviations: DOAC, direct oral anticoagulant; others, see **TABLE 1**

TABLE 3 Main patient- and thrombosis-related characteristics to be considered in the clinical decision-making regarding isolated distal deep vein thrombosis management

Factors favoring serial imaging or anticoagulation after IDDVT	
Favoring serial imaging	Favoring anticoagulation
• Thrombosis confined to the muscular veins (ie, soleus, gastrocnemius vein) • High or moderate risk for bleeding • Patient prefers to avoid anticoagulation	• Highly symptomatic • No reversible provoking factor, active cancer, history of VTE, inpatient status, COVID-19 • Extensive thrombosis (eg, >5 cm in length, multiple calf veins involved, >7 mm in maximum diameter), thrombosis close to the proximal vein • Positive D-dimer (particularly when markedly elevated without alternative reason) • Patient prefers to avoid repeated imaging
Risk factors for VTE recurrence after IDDVT	
Low-risk	High-risk
• Plaster, immobilization, trauma, long trip, etc; provided complete mobilization is achieved • During contraceptive or replacement hormonal therapy (provided the therapy has been interrupted)	• Previous VTE, male sex, age >50 years, active cancer, unprovoked IDDVT, persistently hampered mobilization, known genetic thrombophilia • IDDVT involving: popliteal trifurcation and/or >1 calf vein, bilateral, presence of predisposing disease (eg, inflammatory bowel diseases), axial vs muscular vein
Risk factors and corresponding HRs (95% CIs) for VTE recurrence after IDDVT	
Risk factor	HR (95% CI)
Age >50 vs <50 years	3.7 (1.0–10.6)
Male vs female sex	4.7 (1.6–14.5)
Multiple vs single unilateral thromboses	2.9 (1.4–6.1)
Bilateral vs single unilateral IDDVT	4.0 (1.4–11.1)
Unprovoked vs provoked IDDVT	3.1 (1.4–6.9)
Cancer- vs non–cancer-associated IDDVT	5.5 (1.8–17.6)

Abbreviations: HR, hazard ratio; others, see **TABLE 1**

to be distal, and the recurrence risk is substantially lower than that associated with unprovoked proximal DVT. We do not routinely use intermediate- or reduced-dose anticoagulation in the absence of an elevated bleeding risk; however, these can be considered in patients at a high risk for bleeding in whom anticoagulation is the management of choice.

As for the choice of the anticoagulant agent, the same considerations as for proximal DVT may generally apply. Although clear guideline recommendations in this regard are lacking, DOACs seem to represent safe and effective options, as suggested by the results of large prospective registries and the recent RIDTS trial with rivaroxaban.[7,14,16,18,20] Renal function, potential clinically relevant drug–drug interactions, preferred route of administration, and patient preferences are some of the factors to take into account when deciding on a DOAC versus LMWH as the anticoagulant of choice. To date, rivaroxaban is the only DOAC tested in patients with IDDVT in the setting of a randomized controlled trial.[7] However, it is possible to speculate that other DOACs may exhibit comparable safety and efficacy, and might be used for IDDVT treatment considering the clinical, pharmacokinetic, and pharmacodynamic profile of each DOAC in relation to the specific patient- and disease-related characteristics as well patient and physician preferences.

In patients with a high risk for bleeding (eg, prior major bleeding, concomitant use of antiplatelet drugs, cancer, severe thrombocytopenia, renal or liver insufficiency),[79] surveillance imaging could be considered, withholding anticoagulation unless proximal propagation or recurrent VTE are detected upon serial imaging (eg, after 1–2 weeks, or earlier if there are progressive symptoms). Since some of the factors, such as older age and cancer, are associated with an increased risk for both bleeding and thromboembolic complications, careful and repeated assessment of the risk-to-benefit ratio of anticoagulation should be made as this balance may change over time. Serial imaging could be also considered in ambulatory patients at low thromboembolic risk (eg, physically active young patients, without an unprovoked event, active cancer, or prior VTE); however, only a minority of patients and physicians opt for this therapeutic strategy in routine clinical practice.[14,16,18,20]

Below, we present 3 real-life cases of IDDVT with a proposed therapeutic approach.

Case 1 A 78-year-old man with a history of smoking and pharmacologically-controlled hypertension was diagnosed with isolated gastrocnemius vein thrombosis. No apparent provoking factors were identified upon diagnosis. Standard-dose anticoagulation with a DOAC was started for an intended duration of 3 months. Two months later, he was diagnosed with pancreatic adenocarcinoma with bone and liver metastases, and was scheduled to receive palliative chemotherapy. The anticoagulant therapy was prolonged indefinitely. After the first 2 cycles of

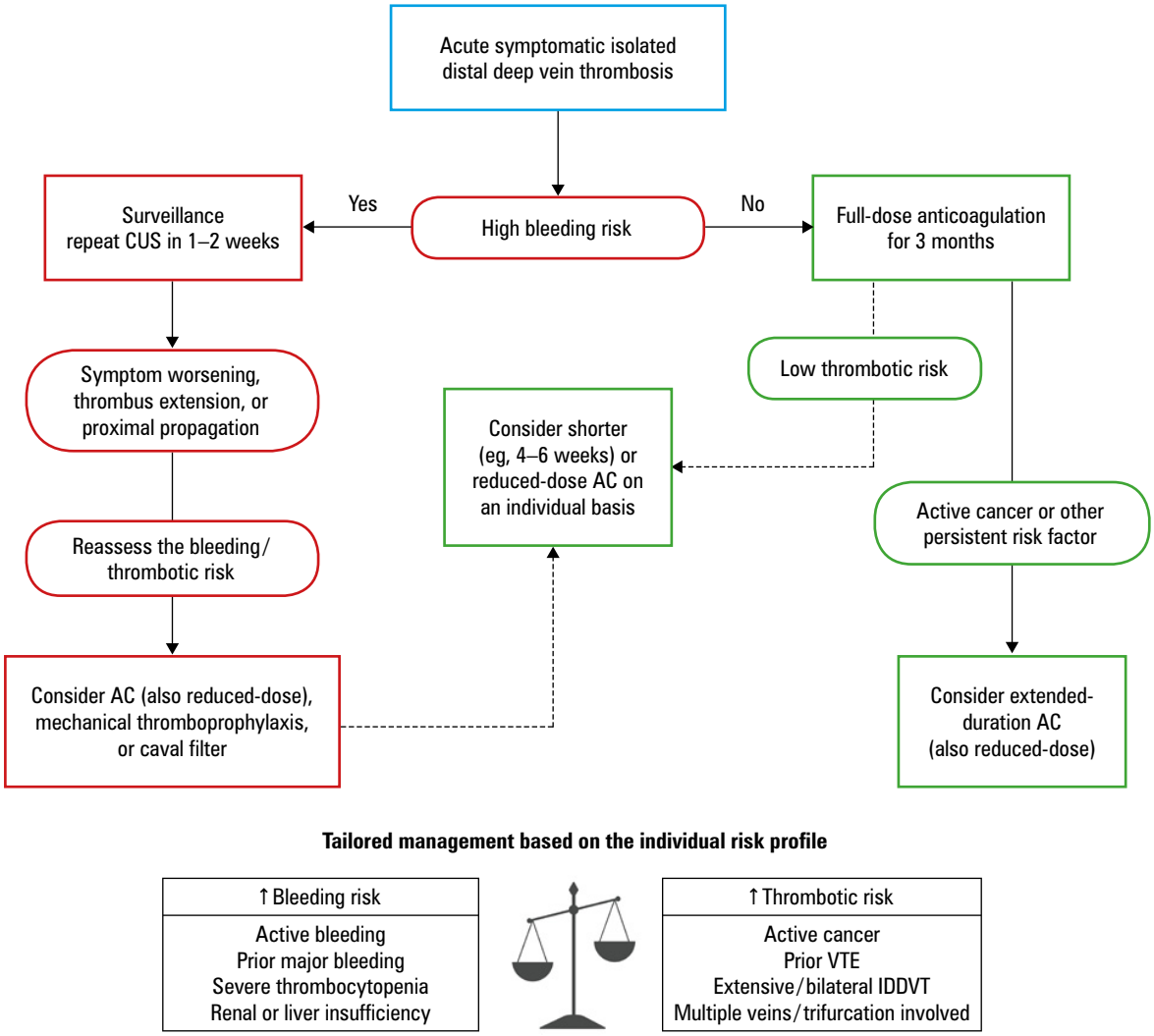

FIGURE 2 Proposed therapeutic approach to isolated distal deep vein thrombosis
Abbreviations: CUS, compression ultrasonography; others, see **TABLE 1**

chemotherapy, the patient developed moderate thrombocytopenia (82 000/μl), and a decision to switch to reduced-dose anticoagulation was made.

Case 2 A 26-year-old female professional cyclist presented with IDDVT involving the calf trifurcation 1 week after an arthroscopic meniscectomy in the ipsilateral leg, for which she had not received anticoagulant thromboprophylaxis and had been hospitalized for 2 days, starting rehabilitation shortly after the procedure. She was prescribed with a full-dose DOAC for 3 months, since trifurcation IDDVT has a recurrence risk similar to that conferred by proximal DVT. She was suggested to refrain from physical exercise for the duration of anticoagulation, also considering the risk for traumatic injury associated with her occupation. At the end of an uneventful 3-month period of the therapy, complete vein recanalization was documented, treatment was stopped, and the patient was allowed to resume sports practice.

Case 3 An 83-year-old community-dwelling man presented to the emergency room due to upper gastrointestinal bleeding with melena and a hemoglobin level of 6.8 g/dl. Past medical history was relevant for New York Heart Association class 2 heart failure with reduced ejection fraction and degenerative osteoarthritis of the spine, for which he was chronically taking nonsteroid anti-inflammatory drugs. Following fluid replacement and hemotransfusion, urgent esophagogastroduodenoscopy revealed an actively bleeding gastric ulcer treated with local epinephrine injection and endoclip placement. Two days after admission to the medical ward, CUS was performed because of progressive bilateral leg swelling, which revealed an otherwise asymptomatic posterior tibial vein thrombosis. Mechanical compression therapy was started and another CUS examination was repeated at discharge from the hospital, showing partial thrombus resolution. No anticoagulant treatment was prescribed. The patient was referred to the Thrombosis Clinic in case symptoms suggestive of DVT extension occurred.

Conclusions IDDVT is a frequent and clinically relevant manifestation of VTE. Proximal propagation, VTE recurrence, PTS, and death are generally less frequent following IDDVT than after

proximal DVT. However, selected patient subgroups, such as those with active cancer, other permanent risk factors, prior VTE, and trifurcation or bilateral IDDVT, exhibit clinical outcomes similar to proximal DVT; hence, careful risk stratification should be made on an individual basis. Two management strategies for symptomatic acute IDDVT are possible: anticoagulation or surveillance imaging, starting anticoagulation if symptoms worsen or thrombus extends during follow-up. Anticoagulant therapy is used in the large majority of patients with IDDVT in real life, and evidence seems to support this approach. Serial imaging is generally reserved to patients at a high bleeding risk or at a very low thromboembolic risk. When anticoagulation is administered, accumulating evidence, including the results of the recent RIDTS trial[7] with rivaroxaban, indicate that 3-month anticoagulation is associated with a lower risk for thromboembolic complications without a clear increase in the bleeding risk, as compared with shorter-duration anticoagulation (eg, ≤6 weeks). DOACs appear to be safe and effective in this setting. In patients with cancer-associated IDDVT, extended-duration anticoagulation is preferred over fixed-duration. IDDVT management remains challenging, and therapeutic decisions should be tailored to the individual risk profile, patient preferences, and physician expectations. Additional research is necessary to improve risk stratification and management, including the type, intensity, and duration of anticoagulation.

ARTICLE INFORMATION

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