Literature review of distal deep vein thrombosis

Nedaa Skeik, MD,[a] Jenna E. Smith, BS,[b] Jacob D. Jensen, BA,[b] Meagan E. Nowariak, BA,[b] Jesse M. Manunga, MD,[a] *and* Aleem K. Mirza, MD,[a] *Minneapolis, Minn*

ABSTRACT

Objective: Although distal deep vein thrombosis (DDVT) has been more frequently diagnosed with the availability of better ultrasound imaging quality, the data on the best method to manage DDVT have been conflicting. The aim of the present review was to summarize the current and evidence-based recommendations for the diagnosis and management of DDVT and to provide a summary of the most recent societal guideline recommendations.

Methods: A literature review of DDVT was performed. The PubMed databases were queried for articles on the epidemiology, risk factors, diagnosis, and management of DDVT.

Results: The prevalence of isolated DDVT has been reported in a broad range. The reported risk factors include older age, active malignancy, a low degree of mobility, acute infection, and atrial fibrillation. With more evidence, anticoagulation therapy was found to be associated with a reduced risk of recurrent venous thromboembolism (VTE) and/or thrombus propagation compared with conservative management. However, anticoagulation was associated with an increased risk of bleeding in a number of studies. The rate of VTE recurrence ranged from 7% to 23% during a follow-up period ranging from 3 months to 8 years. The significant risk factors for VTE recurrence included cancer, older age, an unprovoked event, and inpatient status.

Conclusions: Few studies have addressed the diagnosis and management of DDVT. Further research is needed to standardize the best approach to diagnose and treat DDVT. (J Vasc Surg: Venous and Lym Dis 2021;■:1-16.)

Keywords: Diagnosis; Distal deep vein thrombosis; Management; Outcome

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), continues to be a major preventable cause of morbidity and mortality and economic burden on the healthcare system.[1,2] An estimated 100,000 Americans die annually of VTE,[3] of which 80,000 cases are related to DVT. Furthermore, DVT was associated with 600,000 hospitalizations in the United States annually.[4] The prevalence of lower extremity DVT has been estimated to be 0.1% in the general U.S. population, with distal DVT (DDVT) involving posterior or anterior tibial, gastrocnemius, peroneal, or soleus veins believed to represent up to one half of these cases.[5,6] Proximal DVT (PDVT), involving the iliac, femoral, and/or popliteal veins, has been associated with a greater risk of PE than has thrombosis of the distal lower extremities, upper extremities, or renal, splanchnic, cerebral sinus, or ovarian veins.[7]

The Virchow triad of venous stasis, endothelial damage, and inflammation represents the main underlying pathology for the development of VTE.[4] The major risk factors for VTE include recent hospitalization, surgery, malignancy, obesity, immobility, advanced age, hormone use, and inherited thrombophilia.[8] PDVT and DDVT are diagnosed by a combination of symptoms (eg, leg swelling, tenderness, discoloration), laboratory test results (eg, D-dimer levels), and imaging findings (ultrasound findings).

The American College of Chest Physicians guidelines have recommended ≥3 months of anticoagulation therapy for acute symptomatic PDVT and/or PE.[9] Although the guidelines have favored using direct oral anticoagulant (DOAC) agents instead of other agents, the ultimate duration of anticoagulation therapy has often been determined by the risk/benefit findings after the initial 3 months of therapy.[1,9]

Although strong evidence is available to support the use of anticoagulation therapy for PDVT, the reported data on the best clinical management of DDVT have remained scarce. The risk of PE with DDVT is low and usually results from thrombus propagation into the proximal vein group. An estimated 7% of DDVT cases will progress to PDVT and/or PE.[10] The management options should be determined by the risks and benefits and include immediate anticoagulation therapy vs conservative therapy with short interval serial imaging studies. Given the lack of reported data addressing the epidemiology, risk factors, diagnosis, and management of DDVT, we performed an extensive literature search to address this lack. We have summarized the current evidence

From the Section of Vascular and Endovascular Surgery, Minneapolis Heart Institute, Abbott Northwestern Hospital[a]; and the Minneapolis Heart Institute Foundation.[b]

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Correspondence: Nedaa Skeik, MD, Section of Vascular Medicine, Minneapolis Heart Institute, Abbott Northwestern Hospital, A Part of Allina Health, 920 E 28th St, Ste 300, Minneapolis, MN 55407 (e-mail: nedaa.skeik@allina.com).

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and provided recommendations for the diagnosis and management of DDVT.

METHODS

A systematic review of the reported data on the epidemiology, risk factors, diagnosis, and management of DDVT was conducted. The PubMed databases were searched using the following terms: "distal deep vein thrombosis," "distal DVT," "isolated distal deep vein thrombosis," "isolated distal DVT," "IDDVT," "DDVT," "calf deep vein thrombosis," "calf DVT," "CDVT," "below-knee deep vein thrombosis," "below knee deep vein thrombosis," "below knee DVT," "below-knee DVT," "BKDVT," "posterior tibial vein thrombosis," "anterior tibial vein thrombosis," "gastrocnemius vein thrombosis," and "soleal vein thrombosis." English language articles reported from January 1, 2010 to March 1, 2020 were included. The search resulted in 150 studies reported during the study period. Reports with no isolated DDVT, individual case reports, and review articles were excluded, resulting in 42 included reports (Fig 1). The details of the included studies are presented in Table I.

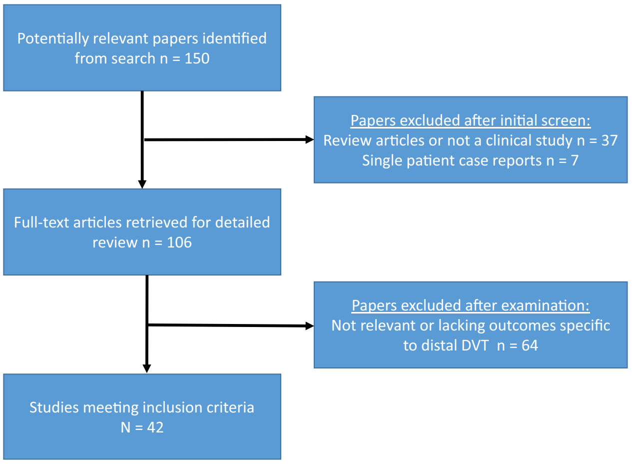

Fig 1. Flow diagram of literature search and study selection.

RESULTS

Epidemiology

Epidemiologic studies and data regarding isolated DDVT have been scarce. Although an annual DVT incidence of 80 cases per 100,000 persons has been reported, lower extremity DVT prevalence was found to be 1 in 1000.[50] Furthermore, DVT was associated with a 30-day mortality of 5.5%.[51] It has been estimated that 300,000 cases of DDVT are diagnosed in the United States annually.[52]

The incidence of isolated DDVT, however, has been reported to range from 5% to 37% in both in- and outpatient medical settings.[12] This broad range is likely the result of a higher incidence of asymptomatic and undiagnosed cases. In addition, the high rate of heterogeneity in patient populations, clinical settings, and diagnostic strategies in the observational data could have resulted in an underestimation of the DDVT prevalence. Regardless, DDVT is a prevalent disorder that can lead to significant morbidity and mortality. Existing studies have suggested that DDVT represents only 20% of all cases of DVT diagnosed in the inpatient setting. However, DDVT has been reported to comprise ≤70% of all DVT cases diagnosed in the outpatient setting, including emergency rooms.[53]

Risk Factors

Ciuti et al[12] reported that of 154 hospitalized patients with acute medical illness, 25 had been found to have DDVT on admission (Table II). Those with DDVT were significantly older than those without (82.3 vs 75.3 years; $P = .009$), and the women were more likely to have experienced silent DDVT events ($P = .014$). Furthermore, patients admitted for renal abnormality[5] or electrolyte imbalance were found to have a greater risk of developing silent DDVT (odds ratio [OR], 4.46; 95% confidence interval [CI], 3.1-21.7; $P < .001$), and a lack of mobility was found to be an independent risk factor (OR, 7.97; 95% CI, 2.42-26.27; $P = .001$). Proximal propagation occurred in 2 of the 25 patients with DDVT.[12]

Shin et al[13] enrolled 261 consecutive patients who had undergone total knee arthroplasty (TKA) to prospectively evaluate the relationship between the calf muscle volume and the prevalence of VTE. Patients with a lower vastus lateralis muscle volume were found to have a significantly greater risk of developing DDVT after TKA (subclinical DVT: adjusted OR, 2.97; symptomatic DVT: adjusted OR, 2.68). These results suggest that a low thigh muscle mass is an independent risk factor for the development of DDVT in the postoperative period after TKA.[13]

Li et al[14] performed a retrospective study of patients admitted with ischemic stroke to develop a prediction scale for DDVT. Of the 671 included patients, 148 were found to have DDVT. Multivariable logistic regression was used to identify independent risk factors for DDVT, and a scale was produced that included female gender ($P < .01$), age ≥60 years ($P < .01$), atrial fibrillation ($P < .01$), acute infection ($P < .01$), active cancer ($P < .01$), and low-density lipoprotein level of ≥2.6 mmol/L ($P < .01$). The scale was highly predictive of DDVT occurrence within 10 days (c statistic, 0.70; 95% CI, 0.63-0.78; $P < .0001$). Among these risk factors, active cancer and age >60 years carried the highest risk.[14]

Endovenous heat-induced thrombosis (EHIT) can also occur after venous thermal ablation. In a retrospective study of 642 patients who had undergone radiofrequency ablation (RFA), we reported an EHIT rate of 6.6%.[54] In addition, concurrent stab phlebectomy and sclerotherapy with RFA was associated with an increased

Table I. Studies included in present review

Investigator	Patient group	Treatment	Study design	Sample size	Follow-up	Endpoints	Results
Epidemiology							
Ueda et al,[11] 2012	Earthquake evacuees with suspected DDVT	None	Prospective	8630 (701 with DDVT)	None	DDVT prevalence	Patients in tsunami-flooded vs nonflooded shelters (March-May), $P = .0016$
Ciuti et al,[12] 2012	Asymptomatic patients hospitalized for acute medical illness	Therapeutic dose LMWH or fondaparinux + compression stockings	Prospective	154 (25 with DDVT)	None	Risk factors for DDVT	Older age: $P = .009$; female sex,: $P = .014$; renal/electrolyte abnormalities: OR, 4.46; 95% CI, 1.1-19; $P = .046$; low degree of mobility: OR, 8.25; 95% CI, 3.1-21.7; $P < .001$; low degree of mobility (multivariate): OR, 7.97; 95% CI, 2.42-26.27; $P = .001$; normal ambulation: OR, 0.14; 95% CI, 0.051-0.37; $P < .001$; low degree of mobility vs DDVT length, $P = .026$
Shin et al,[13] 2019	Patients after TKA surgery	Prophylactic dose LMWH ×5-7 days	Retrospective	261	2 years	DDVT	Unilateral TKA: muscle volume vs subclinical DDVT, OR, 2.97; muscle volume vs symptomatic DDVT, OR, 2.68; bilateral TKA: muscle volume vs subclinical DDVT, OR, 1.73-2.97; muscle volume vs symptomatic DDVT, OR, 1.76-1.86
Li et al,[14] 2017	Ischemic stroke inpatients	None	Retrospective	671	10 days	DDVT	10-day risk (validation group): OR, 0.70; 95% CI, 0.63-0.78; $P < .0001$; 10-day risk (derivation group): OR, 0.68; 95% CI, 0.63-0.74; $P < .0001$
Trinchero et al,[15] 2018	Meta-analysis: patients with acute symptomatic IDDVT or PDVT (± distal), without PE; cohort study: consecutive patients with in- or out-of-hospital first isolated acute PDVT or DDVT, without PE or previous VTE	Routine AC at a dosage and duration consistent with international guideline recommendations	Meta-analysis and cohort study	Meta-analysis: 7 studies, 20,354 patients (4886 IDDVT); cohort study, 831 (202 IDDVT)	NA	Meta-analysis: association with presentation and risk difference for DDVT for females vs males; cohort study: differences in DVT location, unprovoked vs provoked events, age >50 vs ≤50 years	Meta-analysis: DDVT proportion, women vs men (6 studies): OR, +5.4%; 95% CI, +0.7% to +9.5%; OR, 1.30; 95% CI, 1.07-1.58; first DDVT event only: OR, +6.5%; 95% CI, +2.1% to +10.9%; OR, 1.38; 95% CI, 1.11-1.72; either first or recurrent DDVT event (5 studies): OR, +5.3%; 95% CI, +0.5% to +10.0%; OR, 1.29; 95% CI, 1.03-1.61); cohort study: DDVT proportion, women vs men: OR, +5.7%; 95% CI, −0.1% to +11.5%; age, 51-70 vs 18-50 years, women vs men: OR, +9.5%; 95% CI, +2.9% to +16.1%; OR, 1.68; 95% CI, 1.17-2.42; unprovoked events, women vs men: OR, +8.5%; 95% CI, −0.9% to +17.9%; OR, 1.67; 95% CI, 0.94-2.97

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Table I. Continued.

Investigator	Patient group	Treatment	Study design	Sample size	Follow-up	Endpoints	Results
Barco et al,[16] 2017	Patients with first objectively diagnosed acute DVT, without symptomatic PE	No therapy standardization	Post hoc analysis of RIETE registry	24,911 (4266 with DDVT)	NA	Proportion of first acute IDDVT and PDVT in women and men stratified by presence and type of provoking risk factor and age to study age-dependent prevalence of VTE risk factors; evaluate association with DVT site	First DDVT, women vs men: OR, +0.3%; 95% CI, −0.6% to +1.2%; unprovoked DVT: OR, +1.2%; 95% CI, −0.3% to +2.6%; women aged 40-49 years: OR, +6.7%; 95% CI, +3.7% to +9.9%; recent surgery, women: aOR, 1.59; 95% CI, 1.30-1.94; recent surgery, men: OR, 1.58; 95% CI, 1.30-1.93; active cancer, women: aOR, 0.48; 95% CI, 0.39-0.58; active cancer, men: aOR, 0.59; 95% CI, 0.49-0.72; active cancer, pregnancy: aOR, 0.35; 95% CI, 0.20-0.60; hormonal therapy, women: aOR, 1.51; 95% CI, 1.16-1.96; hormonal therapy, men: aOR, 0.63; 95% CI, 0.25-1.59; immobilization, women: aOR, 0.69; 95% CI, 0.57-0.84; immobilization, men: aOR, 0.94; 95% CI, 0.78-1.14
Presentation							
Sartori et al,[17] 2014	Symptomatic outpatients with DDVT	LMWH ×30 days (provoked DDVT) vs VKA ×3 months (unprovoked DDVT)	Prospective	90	1 month; 3 months; 1 year; 2 years	VTE recurrence (composite of PE, PDVT, DDVT recurrence or extension), PE/PDVT recurrence	VTE, male: HR, 4.46; 95% CI, 1.46-13.6; $P = .008$; cancer: HR, 4.85; 95% CI, 1.58-14.9; $P = .006$; PE/PDVT, cancer: HR, 19.9; 95% CI, 3.95-100; $P = .001$; previous VTE: HR, 6.19; 95% CI, 1.03-37; $P = .046$; cancer (multivariate): HR, 23.8; 95% CI, 3.68 to >100; $P = .001$
Galanaud et al,[6] 2010	Patients with symptomatic DCVT and MCVT	Unspecified AC	Retrospective	725	3 months	Mortality, VTE recurrence, major bleeding	Localized pain: $P = .02$; swelling: $P < .001$; treatment with AC: $P = .003$; VTE: OR, 0.98; 95% CI, 0.24-4.11; death: OR, 0.98; 95% CI, 0.24-4.11
Diagnosis							
Sartori et al,[18] 2012	Symptomatic patients with suspected DVT and negative proximal CUS	None	Prospective	725	None	DDVT	D-dimer (DDVT vs not): $P = .0001$
Engelberger et al,[19] 2011	Consecutive inpatients and outpatients with suspicion of DVT	NA	Prospective	298 with suspected DVT (36 with DDVT)	3 months	Objectively confirmed symptomatic VTE	Original vs modified Wells score, DDVT risk: low-risk, $P > .99$; intermediate-risk, $P = .63$; high-risk, $P = .25$
Luxembourg et al,[20] 2012	Outpatients with DVT symptoms	14% Received prophylactic or therapeutic heparin or fondaparinux 48 hours before presentation	Prospective	243 (31 with DDVT)	3 months	Sensitivity, specificity, and NPV for 5 D-dimer assays for excluding DDVT	Sensitivity, 78%-93%; NPV, 92%-97%

Table I. Continued.

Investigator	Patient group	Treatment	Study design	Sample size	Follow-up	Endpoints	Results
Zhang et al,[21] 2019	Patients without symptoms of DVT who underwent testing for lower limb DVT using US and venography	None specified	Meta-analysis	3951 from 26 studies, (11 with DDVT data; total with DDVT not given)	NA	Primary outcomes: sensitivity and specificity of US to identify asymptomatic DVT using venography as reference standard	Sensitivity: 43%; 95% CI, 38%-48%); $I^2 = 93.0\%$, $P < .001$; specificity: 95%; 95% CI, 94%-96%; $I^2 = 89.5\%$; $P < .001$
Treatment and outcomes							
Garcia et al,[22] 2018	Inpatients with acute calf DVT	NA (described variation in treatment types offered)	Retrospective	159	None	NA	Administration route: in inpatient setting, most AC required parenteral administration (73.5%), but most discharged home with orally prescribed drugs (58.2%); hospitalized patients: UFH and enoxaparin preferred, followed by warfarin; discharge: enoxaparin most often (32.7%), followed by warfarin (28.1%) and DOAC drugs (28.1%); therapeutic doses prescribed to most at diagnosis (77%) and at discharge (81%); surgical patients less likely to receive AC vs nonsurgical patients: OR, 2.24; 95% CI, 1.01-4.94; $P = .46$); most surgical patients receiving AC received prophylactic doses (OR, 16.42; 95% CI, 5.75-46.88; $P < .0001$)
Anstadt et al,[23] 2014	NA (not a study of patients)	NA	Survey	99 physicians	NA	Use of AC in calf DVT, anticoagulation type used, treatment duration, IVC filter use	Anticoagulation for DDVT, 48.5% vs none, 51.5%; of anticoagulation group, 62.3% used LMWH and 11% used IV heparin; treatment duration, 3 months for 58% and 6 months for 30% of responders; of no anticoagulation group, 71.2% will reassess for clot propagation or resolution with duplex examination; IVC filters used by 46% with contraindication to AC and 13.7% when propagation noted on follow-up scan
Supporting anticoagulation for DDVT							
Horner et al,[24] 2014	Patients with symptomatic ambulatory IDDVT	Therapeutic AC vs conservative management	Randomized	70	90 days	Composite (proximal propagation, PE, death attributable to VTE, major bleeding)	Composite: aRR, 11.4%; 95% CI, −1.5 to 26.7; $P = .11$; propagation: $P = .24$; PE: $P = 1.0$; minor bleeding: $P = .31$; significant adverse event: $P = 1.00$; adverse event: $P = .08$

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Table I. Continued.

Investigator	Patient group	Treatment	Study design	Sample size	Follow-up	Endpoints	Results
Palareti et al,[25] 2010	Symptomatic outpatients with likely DDVT, without PDVT	None	Prospective	431	3 months	VTE, PE, PDVT, propagation	VTE (DDVT vs not): 4.7%; 95% CI, 1%-13%; $P =$ .049
Utter et al,[26] 2016	Patients with isolated calf DVT	AC vs no AC	Retrospective	384	180 days	Proximal DVT, PE, bleeding	PDVT/PE: OR, 0.33; 95% CI, 0.12-0.87; bleeding: OR, 4.87; 95% CI, 1.37-17.3
Franco et al,[27] 2017	Patients with DDVT	AC vs no AC; duration of AC >6 weeks vs 6 weeks	Meta-analysis	4-20 studies; 1136-2936 patients	4 weeks to 2 years	Recurrent VTE (proximal propagation, DVT, PE)	VTE recurrence (AC vs no AC): OR, 0.50; 95% CI, 0.31-0.79; major bleeding (AC vs no AC): OR, 0.64; 95% CI, 0.15-2.73; PE recurrence (AC vs control): OR, 0.48; 95% CI, 0.25-0.91; VTE recurrence (>6 weeks AC vs 6 weeks): OR, 0.39; 95% CI, 0.17-0.90
Lim et al,[28] 2017	Patients with DDVT	AC vs no AC; duration of AC	Meta-analysis	13 studies, total patients not specified	Not given	Composite endpoint (proximal extension, PE), proximal extension, recurrent DVT, PE, major bleeding	AC vs no AC: proximal extension: OR, 0.29; 95% CI, 0.13-0.67; $P <$ .004; recurrent DVT: OR, 0.16; 95% CI, 0.04-0.65; $P =$ .01; composite: OR, 0.34; 95% CI, 0.16-0.72; $P =$ .005; PE: $P =$ NS; major bleeding: $P =$ NS; duration of AC >8 vs <6 weeks: OR, 0.23; 95% CI, 0.11-0.48; $P <$ .001
Against anticoagulation for DDVT							
Righini et al,[29] 2016	Low-risk outpatients with first acute symptomatic calf DVT	Therapeutic LMWH vs placebo ×42 days	Randomized	259	6 weeks	Composite: extension to proximal veins, contralateral PDVT, PE; primary safety outcome: major or clinically relevant non−major bleeding	Composite outcome: $P =$ .54; bleeding: $P =$ .0255
Schwarz et al,[30] 2010	Symptomatic DVT in soleal and/or gastrocnemius muscle veins	Therapeutic LMWH ×10 days and compression ×3 months vs compression alone	Randomized	107	3 months	Progression to DVT, PE, major bleeding, death not due to PE, complete recanalization	Progression into deep veins: $P =$ .99; complete recanalization: $P =$ .23
Sales et al,[31] 2010	Inpatients with isolated gastrocnemius and/or soleal vein clot	AC (heparin, heparin substitute, or warfarin) vs no AC	Retrospective	141	30 days	Propagation, DVT progression	Propagation: $P =$ .83; DVT progression: $P =$ .50; DVT progression (multivariate): OR, 1.28; 95% CI, 0.55-3.01; $P =$ .57
Dose and duration of anticoagulation for DDVT							
Lautz et al,[32] 2010	Patients with IGSVT	Therapeutic AC vs prophylactic AC vs none	Retrospective	406	Mean, 7.5 ± 11 months	Recurrent VTE, resolution	VTE: $P =$ .0003; resolution: $P =$ .003

Table I. Continued.

Investigator	Patient group	Treatment	Study design	Sample size	Follow-up	Endpoints	Results
Dentali et al,[33] 2017	Patients with DDVT and active cancer	99% received AC (LMWH in 93.5%)	Retrospective	308	Mean, 13.9 months	Recurrent VTE, major bleeding, death	Prophylactic vs intermediate vs therapeutic: VTE during treatment: $P =$ .080; VTE after treatment: $P =$ .249; <6 weeks vs ≥3 months VTE after treatment: $P =$ .038; with recurrent VTE vs without: mortality: $P <$ .05
Li et al,[34] 2015	Patients with axial vein DDVT	AC duration (none vs <6 weeks vs 6 weeks vs ≥6 weeks)	Retrospective	507	3 months	Proximal propagation, VTE recurrence, major/minor bleeding, mortality	No AC vs <6 weeks vs >6 weeks: propagation: $P =$ .001; 6 weeks vs >6 weeks: VTE: $P =$ .147; <6 weeks vs >6 weeks: VTE: $P =$ .08
IVC filters							
Pan et al,[35] 2019	Trauma patients undergoing major orthopedic surgery with DDVT	IVC filter vs AC vs none	Prospective	3295	Perioperative period	PE	IVC filter vs no IVC filter: PE: $P =$ .021; IVC filter vs no IVC filter (no AC): PE: $P =$ .049
Yoon et al,[36] 2017	Patients with isolated calf DVT	IVC filter vs medical treatment (surveillance vs prophylactic AC vs therapeutic AC)	Retrospective	647	Mean, 7.7 ± 11 months	PE, VTE recurrence (propagation of DVT, PE)	PE: $P =$ .27; VTE: $P =$ .0003
Compression therapy							
Guarnera et al,[37] 2014	Patients with gastrocnemius or tibial vein thrombosis	LMWH + compression therapy (no control)	Prospective	110	7 and 28 days	Propagation, calf and ankle circumference, VAS for pain scores, adverse events	Calf circumference: significant decrease in affected leg in 4 weeks; VAS for pain scores significantly decreased at first 3 visits
DOAC agents							
Komiyama et al,[38] 2019	Patients with ovarian cancer and DDVT	Bevacizumab (chemotherapy) with DOAC (3-18 months)	Retrospective	7	3-18 months	Adverse events, resolution, propagation, recurrent VTE	None (small sample size)
VTE recurrence							
Baglin et al,[39] 2010	Patients with a first VTE	Unspecified AC	Meta-analysis	2554	5 years	Recurrence of VTE, PE, or DVT	VTE: HR, 4.76; 95% CI, 2.06-10.98; PE: HR, 4.46; 95% CI, 0.59-33.88
Risk factors for recurrence							
Galanaud et al,[40] 2017	Patients with cancer-related DVT (PDVT vs DDVT and cancer vs no cancer)	Unspecified AC	Prospective	368	3 years	Death, VTE recurrence, bleeding	Cancer-related DDVT vs cancer-related PDVT: death: HR, 1.0; cancer-related vs non −cancer-related DDVT: death: HR, 9.3
Galanaud et al,[41] 2014	Patients with DDVT vs PDVT	Unspecified AC	Prospective	749	3 years	VTE recurrence	VTE: $P =$ .02; age >50 years: HR, −3.7; 95% CI, 1.0-10.6; unprovoked: HR, −3.1; 95% CI, 1.4-6.9; multiple unilateral thromboses: HR, −2.9; 95% CI, 1.4-6.1; bilateral thromboses: HR, 4.0; 95% CI, 1.4-11.1
Donadini et al,[42] 2017	Patients with symptomatic DDVT	LMWH ×4-6 weeks	Retrospective	321	Mean, 42.3 months	Recurrent VTE	Unprovoked: HR, 2.16; 95% CI, 1.12-4.16; previous VTE: HR, 1.97; 95% CI, 1.01-3.86

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Table I. Continued.

Investigator	Patient group	Treatment	Study design	Sample size	Follow-up	Endpoints	Results
Brateanu et al,[10] 2016	Patients with symptomatic DDVT	No specific therapy tested; created a model for risk stratification	Retrospective	450	3 months	Proximal propagation, PE	VTE, inpatient status: OR, 6.38; 95% CI, 2.17-18.78; $P < .001$; VTE, age: OR, 1.02 per year; 95% CI, 0.99-1.05; $P = .19$
Cowell et al,[43] 2016	Patients with symptomatic DVT (PDVT or DDVT)	Standard LMWH	Retrospective	347	10 years	Mortality, morbidity, recurrent DVT and/or PE, PTS	5-year survival: $P = .08$; 10-year survival, $P = .11$; recurrent DVT: RR, 0.54; 95% CI, 0.32-0.93; PE: RR, 0.992; 95% CI, 0.422-2.36; PTS: RR, 0.54; 95% CI, 0.27-1.11; recurrent DDVT vs prolonged immobility: RR, 10.27; 95% CI, 1.39-75.85
Ho et al,[44] 2016	Consecutive patients with DDVT or major VTE without active malignancy	88% received therapeutic AC (131 VKA, 13 LMWH), 5 prophylactic AC, 9 aspirin, 4 no AC; median, 4 months	Retrospective	1024 VTE cases (164 DDVT)	Minimum, 24 months	VTE recurrence	Gender: $P = .65$; provoked events: $P = .10$; history of VTE: $P = .36$; anticoagulation duration: $P = .11$; age >60 years: RR, 2.69; $P = .075$
Propagation							
Olson et al,[45] 2014	Trauma patients with DVT (PDVT or DDVT)	Therapeutic AC vs IVC filter vs other	Retrospective	251	In-hospital (median LOS, 13 days)	PE, DVT progression or resolution	PE: $P = .10$; use of therapeutic AC or IVCF: $P < .0001$
Singh et al,[46] 2012	Patients with isolated calf DVT	Prophylactic dose LMWH	Prospective	156	2-3 days; 1-3 months; 6-8 months	Resolution, proximal propagation, PE	72 hours: 8.3% had complete resolution; 6-8 months: 51% resolved; 43% had persistent thrombus; 7% propagated; 6% developed PE
Recanalization							
Sartori et al,[47] 2016	Patients with symptomatic calf DVT	LMWH	Prospective	172	6 weeks	Clot diameter, recanalization	Clot diameter > 5 mm: sensitivity, 0.76; 95% CI, 0.69-0.82; clot diameter >3.5 mm: sensitivity, 0.94; 95% CI, 0.89-0.97; recanalization vs mobility, $P = .05$
Dentali et al,[48] 2018	Patients with cancer-associated isolated DDVT	Unspecified AC	Retrospective	153	Median, 94 days; 2 years	RVO, VTE recurrence, mortality	VTE recurrence: RVO: 12.9%; 95% CI, 6.9%-22.7%; recanalization: 6.0%; 95% CI, 2.6%-13.3%; mortality: RVO: 54.3%; 95% CI, 42.7%-65.4%; recanalization: 39.8%; 95% CI, 29.9%-50.5%
Mortality							
Barco et al,[16] 2017	Patients with symptomatic acute DVT (PDVT or DDVT)	Routine AC	Retrospective	831 (202 DDVT)	Median, 7.6 years	Recurrent PDVT/PE, all-cause death	PDVT/PE: aHR, 0.32; 95% CI, 0.19-0.55; death: aHR, 0.75; 95% CI, 0.55-1.02; death after unprovoked event: aHR, 0.58; 95% CI, 0.26-1.31
Salazar Adum et al,[49] 2017	Patients with cancer-associated calf DVT	No therapy tested; evaluated KRS score as predictor of poor prognosis	Retrospective	109	Median, 2.5 years	Mortality, major bleeding, recurrence of VTE	High vs not high risk KRS score: mean survival time, $P < .01$

AC, Anticoagulation; *aOR,* adjusted odds ratio; *CI,* confidence interval; *DCVT,* deep calf vein thrombosis; *DDVT,* distal deep vein thrombosis; *DOAC,* direct oral anticoagulant; *DVT,* deep vein thrombosis; *IVC,* inferior vena cava; *IDDVT,* isolated distal deep vein thrombosis; *IGSVT,* isolated gastrocnemius and soleal vein thrombosis; *KRS,* Khorana risk score; *LMWH,* low-molecular-weight heparin; *MCVT,* muscular calf vein thrombosis; *NA,* not applicable; *NPV,* negative predictive value; *NS,* not statistically significant; *OR,* odds ratio; *PDVT,* proximal deep vein thrombosis; *PE,* pulmonary embolism; *TKA,* total knee arthroplasty; *UFH,* unfractionated heparin; *US,* ultrasound; *VAS,* visual analog scale; *VKA,* vitamin K antagonist; *VTE,* venous thromboembolism.

Table II. Risk factors associated with developing DDVT

Risk factor	Investigator	Probability of DDVT	Population
Age	Ciuti et al[12]; Li et al[14]	$P = .009$ (82 vs 75 years); $P < .01$ (≥60 vs <60 years)	Inpatients (acute medical illness); inpatients (ischemic stroke)
Female sex	Ciuti et al[12]; Li et al[14]	$P = .014$ (female vs male); $P < .01$ (female vs male)	Inpatients (acute medical illness); inpatients (ischemic stroke)
Malignancy	Li et al[14]	$P < .01$ (malignancy vs no malignancy)	Inpatients (ischemic stroke)
Electrolyte imbalance/renal abnormality	Ciuti et al.[12]	$P < .001$ (admitted for electrolyte imbalance or renal abnormality vs not)	Inpatients (acute medical illness)
Lack of mobility	Ciuti et al[12]	OR, 7.97; 95% CI, 2.4-26.3; $P = .001$ (lack of mobility vs none)	Inpatients (acute medical illness)
Low thigh muscle volume	Shin et al[13]	OR, 2.97 (subclinical); OR, 2.68 (symptomatic; low thigh muscle volume vs not)	Patients status after TKA surgery
Atrial fibrillation	Li et al[14]	$P < .01$ (atrial fibrillation vs none)	Inpatients (ischemic stroke)
Acute infection	Li et al[14]	$P < .01$ (acute infection vs none)	Inpatients (ischemic stroke)
LDL level ≥2.6 mmol/L	Li et al[14]	$P < .01$ (LDL ≥2.6 vs <2.6 mmol/L)	Inpatients (ischemic stroke)

DDVT, Distal deep vein thrombosis; *LDL*, low-density lipoprotein; *OR*, odds ratio; *TKA*, total knee arthroplasty.

risk of EHIT compared with RFA alone ($P = .021$).[54] Itoga et al[55] had similarly reported an increased risk of DVT at 30 days after thermal ablation with concomitant stab phlebectomy. Furthermore, the risk was lower with laser ablation than with RFA ($P < .001$). However, in our literature search, we could not find studies specifically addressing the risk of DDVT after vein closure procedures. The American Venous Forum and the Society for Vascular Surgery guidelines have recommended individualized treatment of occlusive deep vein thrombosis (EHIT class IV) according to the risks and benefits for each patient.[56]

Presentation

Sartori et al[17] reported that in 90 symptomatic patients with DDVT confirmed by compression ultrasound findings, leg pain and edema were the most often recorded symptoms (86.7% and 62.9%, respectively), followed by skin redness or rash (14.8%) and leg warmth (12.8%). A subanalysis of the OPTIMEV study (long term assessment

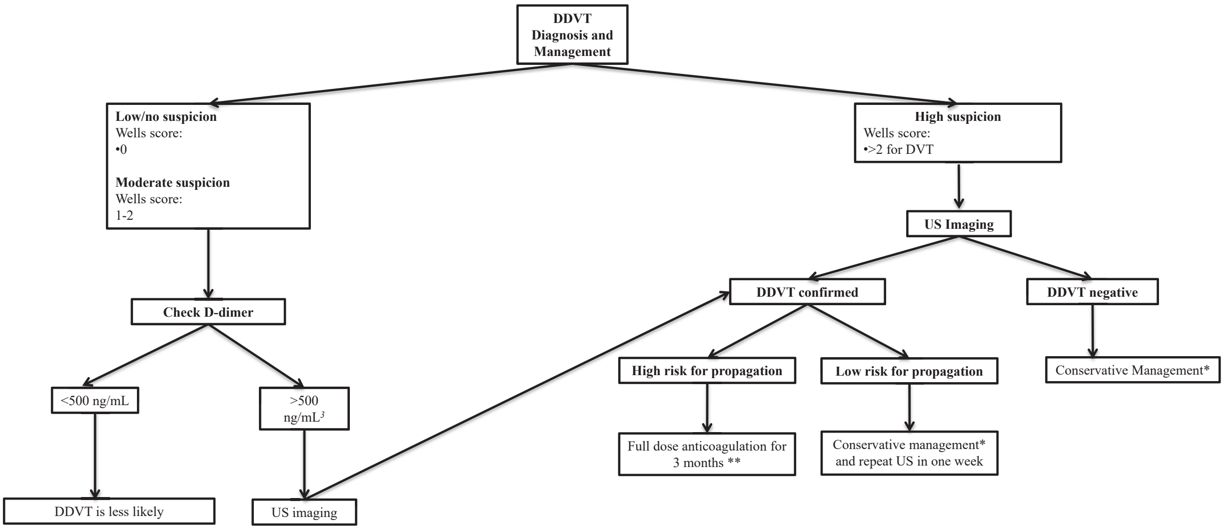

Fig 2. Flow chart showing distal deep vein thrombosis (*DDVT*) diagnosis and management. *DVT*, Deep vein thrombosis; *US*, ultrasound. *Compression, elevation, and walking exercises. **Consider inferior vena cava (IVC) filter used if patient contraindicated for anticoagulation therapy.

of post thrombotic syndrome: OPTIMEV study) that included 725 patients with symptomatic calf DVT reported a significant association between thrombus location and presentation. Localized pain was more frequently reported with muscular vs axial vein thrombosis (30.4% vs 22.4%; $P = .02$). In contrast, swelling was more commonly reported with axial than with muscular vein thrombosis (62.7% vs 47.9%; $P < .001$).[6]

Diagnosis

Clinical decision rules. The diagnosis of DVT is determined by the history, clinical presentation, physical examination, and imaging findings. The Wells criteria is one of the most commonly used risk stratification scoring systems to predict the pretest probability (PP) for DVT (low, ≤0 points; moderate, 1-2 points; or high risk, ≥3 points).

One study that had focused on the value of the Wells criteria to diagnose DDVT reported a sensitivity and specificity of 47% (95% CI, 36%-57%) and 74% (95% CI, 70%-77%), respectively. However, the scoring system was found to have a good negative predictive value (NPV) of 91% (95% CI, 88%-93%).[18] Another study compared both Wells and modified Wells criteria and found neither was especially useful in diagnosing DDVT.[19]

D-dimer. The reliability and cost-effectiveness of D-dimer as a diagnostic test for DVT has been extensively studied. D-dimer testing is generally known to be highly sensitive but not very specific for the presence of VTE and has been associated with a high NPV for DVT. Regarding the diagnosis of DDVT, Sartori et al[18] reported a D-dimer sensitivity, specificity, and NPV of 84% (95% CI, 75%-91%), 50% (95% CI, 46%-54%), and 96% (95% CI, 93%-98%), respectively.[18] In addition, patients with isolated DDVT had a significantly higher D-dimer level than those without DDVT ($P = .0001$).

D-dimer findings are best used in combination with other diagnostic strategies. A normal D-dimer value alone is not sufficient to rule out DDVT. One study reported that close to 35% of patients with calf DVT will have a normal D-dimer level.[57] However, combined with the clinical evaluation findings, the D-dimer level has been shown to safely rule out DDVT for patients with a low PP. In a study by Luxembourg et al,[20] this strategy was associated with a NPV of 96% to 100%. In contrast, an elevated D-dimer value is not enough to confirm the diagnosis of DDVT because of its low specificity. Other conditions that have been reported to cause D-dimer elevation include infection, cancer, and surgery.[58] Thus, based on the current evidence, we have used the Wells criteria to evaluate for PP and check the D-dimer level in patients with a low and moderate probability to determine the need for ultrasound imaging (Fig 2).

Ultrasound findings. Ultrasound examination has become widely accepted as the first-line imaging modality for the diagnosis of DVT. Complete compression ultrasound (CUS) scanning to examine both proximal and distal vein groups has been used more often than serial limited CUS scans focusing only on the proximal veins. However, a meta-analysis and two randomized trials have demonstrated a similar 3-month VTE risk between the two imaging strategies, although all isolated DDVT cases were confirmed.[59-61] These results suggest that detecting and treating distal DVT might actually be deleterious, because it has not been shown to reduce VTE risk and might lead to unnecessary anticoagulation treatment.[30,31,59]

Treatment and outcomes

In support of anticoagulation for DDVT. The ACT (anticoagulation of calf thrombosis) study was a randomized controlled trial that compared therapeutic anticoagulation with dalteparin, followed by warfarin, to conservative treatment (nonsteroidal anti-inflammatory drugs and/or paracetamol) in 70 patients with calf DVT. Therapeutic anticoagulation resulted in no case of clinically relevant embolization or propagation. In the conservative group, 11.4% had experienced thrombus propagation or PE. No patients in either group had experienced a major bleeding event. The absolute risk reduction for the composite outcome was 11.4% (95% CI, −1.5% to 26.7%; $P = .11$).[24]

Similarly, a study by Utter et al[26] proved the efficacy of anticoagulation in patients with DDVT. In their study, the data from 384 patients with DDVT were retrospectively analyzed. Of the 384 patients, 243 (63.3%) had received anticoagulation therapy and 141 patients (36.7%) had not. Anticoagulation was associated with a significant risk reduction of PDVT and/or PE (OR, 0.33; 95% CI, 0.12-0.87) but at the expense of an increased risk of clinically significant bleeding (OR, 4.87; 95% CI, 1.37-17.39).[26]

Franco et al[27] reported on a meta-analysis of 2936 patients with DDVT from 20 different studies. They reported found that anticoagulation significantly reduced the recurrent risk of VTE (OR, 0.50; 95% CI, 0.31-0.79) but without a significant increase in major bleeding risk (OR, 0.64; 95% CI, 0.15-2.73). Similarly, a pooled analysis of 15 DDVT studies that included 1997 patients found a lower risk of recurrent PE with anticoagulation therapy compared with no anticoagulation therapy (OR, 0.48; 95% CI, 0.25-0.91). They concluded that anticoagulation treatment for >6 weeks in duration conferred a lower overall recurrence of VTE compared with a shorter treatment course (OR, 0.39; 95% CI, 0.17-0.90).[27]

Another meta-analysis by Lim et al[28] of 13 studies of patients with DDVT showed that anticoagulation therapy had significantly reduced the rate of proximal extension (OR, 0.29; 95% CI, 0.13-0.67; $P < .004$), recurrent DVT (OR, 0.16; 95% CI, 0.04-0.65; $P = .01$), and the composite endpoint of proximal extension and/or PE (OR, 0.34; 95% CI, 0.16-0.72; $P = .005$). However, no difference was found in the incidence of PE or major bleeding. In addition, their study found that a longer duration of anticoagulation therapy (>8 vs <6 weeks) was associated with a significant reduction in proximal extension (OR, 0.23; 95% CI, 0.11-0.48; $P < .001$) but had had no effects on the rate of PE, recurrent DVT, or major bleeding.[28]

Finally, the results of the CALTHRO study suggested that although most cases of DDVT will be inconsequential, a proportion will carry significant risk and warrant treatment. This prospective study followed up 431 untreated patients with suspected DDVT for 3 months and reported a significantly higher VTE rate in patients with confirmed DDVT compared with those without DDVT (7.8% vs 0.8%; $P = .003$). However, the rate of proximal extension in those with untreated DDVT at 1 week was much lower than expected (3.1%).[25]

Against anticoagulation for DDVT. The CAcTUS (circulating tumour DNA guided switch) trial is the only randomized placebo controlled study in which 259 outpatients with non–cancer-related initial symptomatic DDVT were assigned to once daily subcutaneous injections of either the nadroparin (171 UI/kg) or placebo for 6 weeks. The composite outcome of extension to proximal veins, contralateral proximal DVT, or PE occurred in 3.3% of the nadroparin group and 5.4% of the placebo group ($P = .54$; risk difference, −2.1%; 95% CI, −7.8% to 3.5%). The primary safety outcome of major or clinically relevant non–major bleeding occurred in 4.1% of the nadroparin group and 0.0% of the placebo group ($P = .03$; risk difference, +4.1; 95% CI, 0.4%-9.2%). These findings suggest no benefit of nadroparin compared with placebo for the reduction of proximal DVT extension or VTE, with a significantly greater risk of bleeding endpoints.[29]

Similarly, a study by Schwarz et al[30] had randomized 107 patients with calf muscle DVT in the gastrocnemius and/or soleal veins to either 10 days of a therapeutic dose of nadroparin and compression therapy vs compression therapy alone. No significant difference was found in the rate of progression to the proximal veins or in recanalization at 3 months. No PE, major bleeding, or death occurred in either group.[30]

Finally, a retrospective analysis by Sales et al[31] raised doubt regarding the value of anticoagulation treatment for patients with gastrocnemius and/or soleal DVT. A total of 141 inpatients were included and divided into two groups. The first group had received a full dose of anticoagulation (ie, heparin, heparin substitutes, warfarin) and the second group had received no treatment. No differences were found in the rate of propagation between the two groups at 30 days.[31]

Dose and duration of anticoagulation therapy for DDVT. Multiple retrospective analyses have compared different doses of anticoagulation and demonstrated that a therapeutic dose is the most favorable regimen in reducing VTE risk after a DDVT event. In a retrospective analysis of patients with isolated soleal or gastrocnemius vein thrombosis, Lautz et al[32] reported significantly greater rates of VTE in those treated with prophylactic anticoagulation (27%) or no anticoagulation (30%) than in those treated with full anticoagulation (12%) therapy ($P = .0003$). Dentali et al[33] retrospectively studied 308 patients with isolated DDVT and active cancer (93.5% receiving low-molecular-weight heparin, 4.9% receiving fondaparinux, and 0.3% receiving unfractionated heparin) and found no difference in recurrent VTE (mean follow-up, 13.9 months) according to the anticoagulation dose (therapeutic, intermediate, or prophylactic) during or after treatment ($P = .080$ and $P = .249$, respectively). After withdrawal of treatment, a significantly greater rate of VTE was found for patients treated for a duration of <6 weeks compared with ≥3 months (hazard ratio [HR], 4.42; 95% CI, 1.75-11.15). Mortality was higher for the patients with DDVT who had experienced recurrent VTE compared with those who had not (93.5 vs 34.7 per 100 patient-years; $P < .05$).[33]

In addition to the previously cited meta-analyses by Franco et al[27] and Lim et al,[28] another study evaluated the effects of the duration of anticoagulation treatment on the outcomes of DDVT. The investigators concluded that a duration of anticoagulation treatment of >6 weeks was superior to that of a shorter duration or no anticoagulation therapy in reducing proximal propagation (0% vs 2.8%; $P = .001$). However, no significant difference was found in VTE recurrence with either <6 vs ≥6 weeks or 6 vs ≥6 weeks of anticoagulation. Additionally, no significant difference was found in the major or minor bleeding risk between groups.[34]

Inferior vena cava filters. Several studies that had evaluated the role of inferior vena cava (IVC) filters in the management of DDVT yielded conflicting results. Yoon et al[36] retrospectively compared the use of an IVC filter with medical treatment (prophylactic or therapeutic dose of anticoagulation or none) in 647 patients with DDVT. They reported no difference in the PE rate between the two groups (2.5% vs 3.3%; $P = .27$).[36] Of the patients who had received an IVC filter, 20% had had a contraindication for anticoagulation. Furthermore, the complication rate in the IVC filter group was 10%, including filter tilting (1%), caval perforation (7%), and migration (1%). Complications were more likely to occur in older patients (mean age, 65 vs 61 years; $P = .004$) and those with a history of VTE (56% vs 16%; $P < .0001$) and malignancy (49% vs 28%; $P < .0001$).[36] In addition, they reported a significant difference in the rate of recurrent VTE among those who had received no anticoagulation (35%), prophylactic anticoagulation (30%), and therapeutic dose anticoagulation (10%) therapy ($P = .0003$). In contrast, Pan et al[35] found that patients with DDVT who had received an IVC filter (20% of whom were receiving also anticoagulation therapy) had had a lower rate of PE compared with those who had not (63% receiving anticoagulation therapy; 0% vs 2.08%; $P = .021$). Specifically, in the subgroup that had not received anticoagulation therapy, IVC filter placement (compared with no IVC filter) was associated with a lower rate of PE (0% vs 1.94%; $P = .049$).[35]

Compression. A prospective study by Guarnera et al[37] had shown that the use of compression therapy, in addition to nadroparin (at a dosage adjusted by the patient's body weight) administered once daily, for 110 patients with DDVT was safe and associated with no propagation to the popliteal vein or adverse events. Furthermore, the calf circumference had significantly decreased in the affected leg, which had measured 38.1 cm at baseline, 37.1 cm at 1 week, and 35.7 cm at 4 weeks. In addition, the visual analog scale for pain scores had significantly decreased during the first three visits (from 58.4 cm to 30.7 cm to 12.7 cm). The proportion of patients with recanalization was significantly greater than that reported in previous studies for untreated patients who had not received such therapy (56.4% vs 20%).[37]

DOAC agents. No strong evidence supporting the use of DOACs in the management of DDVT has been reported. The results from a retrospective study of seven patients supported the safety of DOAC drugs (ie, edoxaban, apixaban, or rivaroxaban for a median of 8 months) for the treatment of patients with ovarian cancer and DDVT, with only two patients experiencing adverse events (epistaxis and hemorrhoidal bleeding).[38] Data from clinical trials of patients with symptomatic proximal DVT and/or PE showed that DOAC agents were as effective as enoxaparin for bridging therapy to warfarin with less major bleeding risk.[62,63] Because the pathophysiology of VTE is similar for PDVT and DDVT, until the findings from further investigations on a larger scale are available, it is reasonable to consider the use of a DOAC agent over warfarin to treat patients with DDVT. However, low-molecular-weight heparin and/or warfarin could also be considered for patients for whom DOAC agents are contraindicated.

VTE recurrence and recanalization. Several studies of cohorts of patients who had received an unspecified anticoagulation treatment had reported an overall rate of VTE recurrence ranging from 7% to 23% during a follow-up period of 3 months to 8 years.[10,16,39,42] The highest reported VTE recurrence rate was 12.5/100 patient-years.[17] However, after excluding recurrent DDVT and thrombus extension, the rate decreased to 7.4/100 patient-years.[17] The lowest reported annual recurrence was 2.0% (95% CI, 1.1%-3.2%).[16] A meta-analysis of 2554 patients who had received unspecified anticoagulation therapy for DDVT reported a 5-year cumulative rate of recurrent DVT and PE of 6.4%, and 1.2%, respectively.[39]

Several factors were associated with an increased risk of VTE recurrence, with cancer the most important. In a subanalysis of the OPTIMEV trial, Galanaud et al[40] had prospectively studied 368 patients and reported a greater VTE recurrence risk for patients with cancer compared with those without (11.5% vs 5.0% per patient-year; adjusted crude cause-specific HR, 2.0; 95% CI, 1.0-3.7). Cancer-related DDVT was also associated with a ninefold increased risk of major bleeding and VTE recurrence.[40] A retrospective study of 321 patients with DDVT reported a VTE recurrence rate of 5.9/100 patient-years in those with cancer compared with 4.4/100 patients-years in the overall study population. In addition, patients with unprovoked events had a recurrence rate of 7.2/100 patient-years that remained significant on multivariate analysis (HR, 2.16; 95% CI, 1.12-4.16), as did a history of previous VTE (HR, 1.97; 95% CI, 1.01-3.86). Of the recurrent VTE cases, 31% were PE, 19% PDVT, 45% DDVT, and 5% were thrombosis at an unusual site.[42] Another subanalysis of the OPTIMEV trial had prospectively followed up 749 patients with DDVT, of which 52% were in the muscular veins, 23% were in the combined muscular and deep calf veins, and 25% were in the deep calf veins. They reported that age >50 years, unprovoked events, and the involvement of more than one vein (multiple unilateral or bilateral) had independently tripled the risk of VTE recurrence. No significant difference was found in the incidence of VTE recurrence between the muscular and deep calf veins.[41] Finally, a study by Brateanu et al[10] suggested that a simple model using only inpatient status and patient age can predict the recurrence risk in patients with DDVT. In their study, inpatients aged >60 years were found to have a greater (>10%) risk of VTE recurrence compared with those aged <60 years. Furthermore, the outpatients had a uniformly low rate of PDVT and PE (<4%). Of the 500 patients with isolated DDVT, 7% had had recurrent VTE (73% PDVT, 23% PE, and 3% both PDVT and PE).[10] Another study found that prolonged immobility was significantly associated with a greater risk of recurrent DVT (relative risk, 10.27; 95% CI, 1.39-75.85).[43]

Two additional series had addressed the rate of propagation for patients with DDVT. Olson et al[45] retrospectively studied 251 trauma patients with either PDVT or DDVT to evaluate the rate of in-hospital PE and DVT propagation. The patients had received an IVC filter, therapeutic anticoagulation therapy, or pharmacologic prophylaxis (5000 U of heparin every 8 hours or enoxaparin 30 mg twice daily). Of the patients with DDVT, including any thrombus involving the peroneal, tibial, or gastrocnemius/soleus veins, 12.9% had progressed to PDVT. Of these patients, 48% had received prophylactic anticoagulation therapy, 43% had received IVC filters, and none had received therapeutic anticoagulation therapy. The rate of in-hospital resolution was 27% (median, 13 days), with no differences in the chemical prophylaxis rates between the patients with resolved or persistent events.[45] A prospective study by Singh et al,[46] in which 156 patients with isolated calf DVT involving the anterior or posterior tibial, peroneal, gastrocnemius, or soleal vein, had received a prophylactic dose of anticoagulation (40 mg of subcutaneous enoxaparin daily or 5000 of subcutaneous unfractionated heparin every 12 hours for various durations) showed a complete resolution rate of 8.3% at 72 hours and 51% at 6 to 8 months. Persistent thrombus and proximal propagation had occurred in 43% and 7% of patients at 6 to 8 months, respectively, and were found to be associated with risk factors, including orthopedic procedure, stroke, or malignancy. Although anterior tibial vein thrombosis was the least often reported (two cases), the rate of PE at 8 months was 6%.[46]

Two studies had examined the rate of recanalization after a DDVT event. A prospective study by Sartori et al[47] reported a recanalization rate of 51% at 6 weeks for 172 patients, with provoked DDVT receiving enoxaparin (1 mg/kg subcutaneously twice daily for 2 weeks, followed by 1 mg/kg subcutaneously once daily for 4 weeks) and unprovoked DDVT receiving a vitamin K antagonist for 12 weeks. Significantly reduced mobility was associated with a lower probability of recanalization (P = .05).[47] A study by Dentali et al[48] suggested that the outcomes for cancer-related DDVT might be affected by residual vein obstruction (RVO). Of the 153 studied patients, 45.8% had RVO and 54.2% had recanalization at a median of 92 days. The cumulative risk of recurrent VTE for patients with persistent RVO (12.9%) was more than double that of patients without RVO (6.0%). The significant risk factors for RVO were female gender, body mass index >30 kg/m^2, and involvement of the axial calf (eg, peroneal, posterior tibial, anterior tibial) veins.[48]

Several studies have provided insight into the mortality outcomes for patients with DDVT. In a retrospective study of 202 patients with DDVT treated with routine anticoagulation drugs, the mortality rate was 25.7% at a mean follow-up of 7.6 years.[16] Retrospectively studying 109 patients with cancer-associated calf DVT, Salazar Adum et al[49] reported a mortality of 47% at 2.5 years and a survival rate of 75%, 66%, and 64% at 6, 12, and 24 months, respectively. The factors that significantly affected mortality in their series included smoking, metastasis, and gastrointestinal and lung cancer.[49]

DISCUSSION

Epidemiology. The incidence of isolated DDVT has been reported in a broad range, which, in part, can be explained by undiagnosed asymptomatic cases and heterogeneity in reported patient populations, clinical settings, and diagnostic strategies. Therefore, the prevalence of DDVT could have also been underestimated. The reported risk factors have included older age, active malignancy, a low degree of mobility, acute infection, and atrial fibrillation (Table II). Leg pain and edema have been the most common symptoms on presentation.

Diagnosis. The diagnosis of VTE is determined by the history, presenting symptoms, and laboratory and imaging findings. Although the use of the Wells criteria can help determine the pretest probability for the diagnosis of VTE, including DDVT, the D-dimer level can provide more insight regarding the candidacy for venous ultrasound examinations of patients with a low or moderate pretest probability (Fig 2).

Treatment and outcomes. The current evidence has shown that DDVT can carry a high risk of VTE recurrence and/or DVT propagation that can be determined by a few risk factors, including cancer, advanced age, immobility, and/or hospitalization. Multiple studies included in the present review have supported the use of anticoagulation therapy for patients with DDVT. Although the cohorts differed, compared with conservative treatment, more evidence has indicated that anticoagulation therapies were associated with a reduced risk of recurrent VTE and/or thrombus propagation. In contrast, anticoagulation therapies were associated with an increased risk of bleeding in some, but not all, studies.[54]

If and when anticoagulation therapy is considered, a full dose administered for >6 weeks is the more efficacious treatment modality and duration compared with a prophylactic dose and treatment for <6 weeks. However, the final decision regarding anticoagulation therapy should be determined by balancing the benefit of reducing VTE-related outcomes with the risk of an increased rate of bleeding.

No strong evidence is available to support the use of IVC filters for patients with DDVT. Thus, their use should only be considered when anticoagulation therapy is contraindicated, if at all.

The rate of VTE recurrence ranged from 7% to 23% during a follow-up period ranging from 3 months to 8 years.[10,16,39,42] The significant risk factors for VTE recurrence included cancer, older age, an unprovoked event, and inpatient status.[10,40-42]

Guidelines. The 2016 CHEST guideline and expert report on antithrombotic therapy for VTE disease recommended serial imaging of the deep veins for 2 weeks instead of anticoagulation therapy for patients with acute isolated DDVT and no severe symptoms or risk factors (grade 2C).[9] However, they suggested using anticoagulation therapy instead of conservative therapy for those with severe symptoms or risk factors, recommending only 3 months of anticoagulation therapy (grade 1B). In patients with acute isolated DDVT who had undergone serial imaging studies, no anticoagulation therapy was recommended if the thrombus did not extend (grade 1B). However, anticoagulation was recommended if the thrombus had extended but had remained confined to the distal veins (grade 2C) or if it had extended into the proximal veins (grade 1B).[9]

Based on the current evidence reported in the present review and data from clinical randomized trials of patients with PDVT, we have created the following recommendations for the management of acute DDVT (Fig 2).

Recommendations.

1. If not contraindicated, anticoagulation therapy should be used for patients with DDVT who also have risk factors for propagation or recurrence. Patients at high risk of propagation include those with active malignancy, those with a history of stroke, and those who have undergone orthopedic procedures. We favor the use of DOAC agents instead of other anticoagulant drugs.
2. A full therapeutic dose should be used instead of a prophylactic dose of anticoagulation treatment.
3. Patients should be treated for 3 months instead of a shorter or longer period of anticoagulation therapy.
4. An IVC filter should only be used if anticoagulation therapy is contraindicated and the risk of propagation is very high.
5. Serial ultrasound studies and conservative therapy, including walking exercises, compression, and elevation are recommended for patients with a low risk of propagation.
6. The use of compression therapy should be considered for patients with symptomatic edema and intact skin.

Study limitations. Most of the data discussed in the present review originated from retrospective or prospective analyses, with only few abstracted from controlled randomized trials. Although limiting the review to studies that have been reported since January 2010 could have excluded a few relevant studies, we believe that the final outcomes and recommendations could have not been significantly affected.

CONCLUSION

Few studies have addressed the diagnosis and management of DDVT. We have provided a review of the current data in the hopes of closing this gap. Further research is needed to standardize the best approach to diagnose and treat patients with DDVT.

AUTHOR CONTRIBUTIONS

Conception and design: NS, JS, JJ, MN, JM, AM
Analysis and interpretation: NS, JS, MN
Data collection: NS, JS, MN
Writing the article: NS, JS, JJ, MN, JM, AM
Critical revision of the article: NS, JS, MN
Final approval of the article: NS, JS, JJ, MN, JM, AM
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Overall responsibility: NS

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