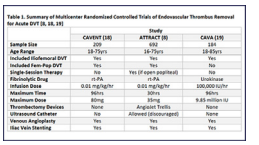

Society of Interventional Radiology Position Statement on the Endovascular Management of Acute Iliofemoral Deep Vein Thrombosis

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ABSTRACT

Purpose: To establish the updated position of the Society of Interventional Radiology (SIR) on the endovascular management of acute iliofemoral deep vein thrombosis (DVT).

Materials and Methods: A multidisciplinary writing group with expertise in treating venous diseases was convened by SIR. A comprehensive literature search was conducted to identify studies on the topic of interest. Recommendations were drafted and graded according to the updated SIR evidence grading system. A modified Delphi technique was used to achieve consensus agreement on the recommendation statements.

Results: A total of 84 studies, including randomized trials, systematic reviews and meta-analyses, prospective single-arm studies, and retrospective studies were identified and included in the review. The expert writing group developed 17 recommendations that pertain to the care of patients with acute iliofemoral DVT with the use of endovascular venous interventions.

Conclusions: SIR considers endovascular thrombus removal to be an acceptable treatment option in selected patients with acute iliofemoral DVT. Careful individualized risk assessment, high-quality general DVT care, and close monitoring during and after procedures should be provided.

ABBREVIATIONS

ASH = American Society of Hematology, ATTRACT = Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis, CAVA = Catheter-Directed Thrombolysis Versus Anticoagulation, CAVENT = Catheter-Directed Venous Thrombolysis, CDT = catheter-directed thrombolysis, CI = confidence interval, DVT = deep vein thrombosis, ETR = endovascular thrombus removal, IVUS = intravascular US, LMWH = low molecular weight heparin, MT = mechanical thrombectomy, NICE = National Institute of Healthcare Excellence, PCDT = pharmacomechanical catheter-directed thrombolysis, PE = pulmonary embolism, PTS = postthrombotic syndrome, QALY = quality-adjusted life year, QoL = quality of life, RR = relative risk, rt-PA = recombinant tissue plasminogen activator, SIR = Society of Interventional Radiology, UFH = unfractionated heparin, US = ultrasound, VTE = venous thromboembolism

INTRODUCTION

Patients with acute iliofemoral deep vein thrombosis (DVT) often experience pulmonary embolism (PE), severe presenting limb symptoms, and poor long-term clinical outcomes (1). Although the risk of PE is markedly reduced with timely anticoagulant therapy, many patients develop late limb sequelae from postthrombotic syndrome (PTS). PTS can produce varying clinical manifestations, but many patients experience limb pain, heaviness, swelling, and fatigue, with some progressing to develop venous stasis skin changes such as skin ulceration. In 2001, a large (N = 1,149) prospective cohort study (2) found that patients with acute iliofemoral DVT experience a 2.4 times increased risk of recurrent DVT compared with patients with less-extensive DVT. Another study (3) documented in detail the frequent venous claudication, severe venous physiologic abnormalities, and impaired health-related quality of life

Appendices A–C can be found by accessing the online version of this article on www.jvir.org and clicking on the Supplemental Material tab.

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(QoL) that often manifest in patients after an iliofemoral DVT episode. Moreover, in the prospective multicenter Venous Thrombosis Outcomes registry that followed 387 patients with acute DVT for 2 years, patients with iliofemoral DVT were more likely to develop PTS and to experience greater PTS severity than patients with less-extensive DVT (4,5). Data from the nonlysed control arm patients in the National Institutes of Health sponsored Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial support these observations (6–8). Over 24 months' follow-up, patients with iliofemoral DVT developed PTS more frequently (51% vs 44%) and with greater severity (mean Villalta scale scores 2 points higher) than patients with femoral-popliteal DVT (6–8). At all time points, the mean venous disease-specific QoL was substantially worse in patients with iliofemoral DVT than in patients with femoral-popliteal DVT (9).

Despite these observations, there is substantial heterogeneity within this population, and most patients with acute iliofemoral DVT do not develop disabling PTS or venous ulceration. In the nonlysed control arm of the ATTRACT trial's iliofemoral DVT subgroup, 28% of patients developed moderate-or-severe PTS and 6% developed venous ulceration during 24 months of follow-up. Although it is clear that patients with iliofemoral DVT deserve special consideration as a high-risk population, careful individualized consideration of the risk-to-benefit ratio of different treatment strategies continues to be important in selecting an optimal approach for specific patients.

Endovascular management strategies have been applied to select patients with acute iliofemoral DVT for >25 years (10). Although early referrals to interventional radiology and other endovascular specialists largely comprised patients with severe DVT manifestations that had progressed despite initial anticoagulation, many clinical practices evolved to consider front-line endovascular therapy earlier in the course of DVT care. This change can be seen in a recent claims analysis in the Centers for Medicare and Medicaid Services beneficiaries, in which the volume of thrombolysis or thrombectomy procedures for DVT was shown to have grown at a 12% yearly rate between 2007 and 2017 (from 4.27 to 13.40 service counts per 100,000 beneficiaries) (11).

In 2006, the Society of Interventional Radiology (SIR) published research reporting guidelines, quality improvement guidelines (subsequently updated in 2014), and a position statement addressing the use of endovascular thrombus removal (ETR) for acute DVT (12–15). Since then, the field has evolved substantially due to the accrual of more clinical experience, introduction of new technology for venous imaging and treatment, and evidence from new studies including pivotal randomized controlled trials. This article provides an updated review of the published literature and documents SIR's current position on the endovascular management of acute iliofemoral DVT.

METHODS

Panel Formation

Under the direction of the SIR, a multidisciplinary group of experts from interventional radiology (n = 6), vascular medicine (n = 1), and vascular surgery (n = 1) who manage venous disease was convened to review the current literature on the endovascular management of acute iliofemoral DVT. The group members were identified by the SIR-appointed work group leader and approved by the SIR Guidelines and Statements Division Councilor after review of potential conflicts of interest.

Literature Review

A comprehensive literature search was conducted in MEDLINE via PubMed in November 2020 using a combination of the following search terms: "venous thrombosis," "deep vein thrombosis," "DVT," "post-thrombotic syndrome," "post-phlebitic syndrome," "iliofemoral," "iliocaval," "pelvic," "pharmacomechanical," "thrombolysis," "fibrinolysis," "fibrinolytic," "thrombolytic," "thrombectomy," "tissue plasminogen activator," "tPA," "urokinase," "streptokinase," "reteplase," "tenecteplase," "rheolytic," "AngioJet," "Trellis," "EKOS," "ultrasound-assisted," "EkoWave," "Indigo," "ClotTriever," "CAT-8," "aspiration," "JETi," "Cleaner," "anticoagulation," "compression," "thrombectomy," "ambulation," and "thrombus removal." Full details of the search can be found in **Appendix A** (available online on the article's Supplemental Material page at *www.jvir.org*). Searches were limited to the English language from 2013 to present, with 2013 representing the last search date from the previous version of the SIR quality improvement guidelines. In December 2021, the search was updated to identify additional articles of relevance using the abovementioned terms with the addition of "Zelante," "Lightning," "Intelligent," "Flowtriever," "Aspirex," "intravascular ultrasound," and "IVUS."

Recommendation Development and Consensus

Recommendations were drafted and graded according to the updated SIR evidence grading system (**Appendix B**, available online at *www.jvir.org*). A modified Delphi technique was used to achieve consensus agreement on the recommendation statements. Consensus was defined as when 80% of the panelists were in agreement with a statement. All recommendations statements in this document achieved this 80% agreement threshold.

DEFINITIONS

Acute DVT is DVT with symptom duration of ≤14 days (16). Proximal DVT involves the popliteal vein and/or more cephalad deep veins. Proximal DVT can be subcategorized

into iliofemoral DVT (involves the iliac and/or common femoral vein, with or without other veins) and femoral-popliteal DVT (limited to veins below the common femoral vein) (16,17).

It is recognized that in clinical practice and in the published literature, endovascular DVT therapy is a multimodality treatment in which the different components of therapy are used in a highly variable and sometimes operator-specific manner. This heterogeneity cannot be fully addressed in a summary analysis, but because the basic elements of endovascular care have remained stable over time, this guidance document continues to use SIR's previous categorizations of treatment modalities (16):

> Endovascular thrombus removal encompasses any modality in which thrombus is eliminated or reduced using endovascular means.
>
> Mechanical thrombectomy (MT) refers to an ETR that uses a catheter-based mechanical device to fragment, macerate, and/or aspirate thrombus.
>
> Catheter-directed thrombolysis (CDT) refers to intrathrombus delivery of a fibrinolytic drug through an infusion catheter or wire embedded within the thrombosed vein.
>
> Ultrasound (US)-assisted CDT is CDT with an US-emitting catheter system.
>
> Pharmacomechanical CDT (PCDT) refers to any combination of CDT and MT.

RESULTS

The best available evidence on the endovascular management of acute iliofemoral DVT is summarized below according to the study design type. The search retrieved a number of studies, of varying methodological quality, on the use of ETR strategies (Appendix C). Since the last version of this document was published, the evidence base for CDT/PCDT has improved, providing a foundation for stronger recommendations. In contrast, despite its widespread use in clinical practice, few well-designed studies have objectively assessed the effects of MT strategies, specific MT devices, or adjunctive therapies. Although studies on the use of medical and surgical therapies in patients with acute iliofemoral DVT were searched, rigorous prospective studies that reported outcomes specific to this subpopulation were not identified.

CDT and PCDT

Randomized Controlled Trials. Three multicenter randomized trials (8,18,19) have rigorously compared the use of CDT or PCDT with standard therapy against standard therapy alone for acute DVT. Each trial enrolled patients initially presenting with symptomatic acute DVT, who were prescribed anticoagulation and compression stockings. Patients were randomized 1:1 to receive or not receive CDT or PCDT using recombinant tissue plasminogen activator (rt-PA) or urokinase and were allowed subsequent use of adjunctive balloon angioplasty and stent placement. The primary outcome for these studies was the occurrence of PTS by the Villalta scale (total score of ≥5) (20,21). Differences among these trials are summarized in the accompanying text below and in Table 1 (8,18,19).

Table 1. Summary of Multicenter Randomized Controlled Trials of Endovascular Thrombus Removal for Acute DVT

	Study		
	CAVENT (18)	ATTRACT (8)	CAVA (19)
Sample size	209	692	184
Age range (y)	18–75	16–75	18–85
Included iliofemoral DVT	Yes	Yes	Yes
Included femoral-popliteal DVT	Yes	Yes	No
Single-session therapy	No	Yes (if open popliteal)	No
Fibrinolytic drug	rt-PA	rt-PA	Urokinase
Infusion dose	0.01 mg/kg/h	0.01 mg/kg/h	100,000 IU/h
Maximum time (h)	96	30	96
Maximum dose	80 mg	35 mg	9.85 million IU
Thrombectomy devices	None	AngioJet, Trellis	None
Ultrasound catheter	No	Allowed (discouraged)	Yes
Venous angioplasty	Yes	Yes	Yes
Iliac vein stent placement	Yes	Yes	Yes

DVT = deep vein thrombosis; rt-PA = recombinant tissue plasminogen activator.

Two of the trials (8,18) evaluated patients with acute proximal DVT as their primary population. In the Catheter-Directed Venous Thrombolysis (CAVENT) trial, 209 patients with acute DVT extending above the midthigh were randomized to receive (n = 101) or not receive (n = 108) CDT with rt-PA (18,22,23). In this study, rt-PA infusions could be continued for up to 4 days, but thrombectomy devices were not used. The study found that CDT reduced PTS occurrence over 2 years (41% CDT vs 56% no-CDT; $P = .047$) and 5 years (42% CDT vs 70% no-CDT; $P < .01$). Most PTS cases were mild, and no effect on long-term health-related QoL was seen. In the ATTRACT trial, 692 patients with acute proximal DVT extending above the popliteal vein were randomized to receive (n = 337) or not receive (n = 355) PCDT with rt-PA delivery using one of the several methods. Single-session PCDT was permitted for patients with good popliteal vein inflow, rt-PA infusions were limited to no more than 30 hours, and the total rt-PA dose was not permitted to exceed 35 mg. In this study, PCDT did not prevent PTS over 2 years (47% PCDT vs 48% no-PCDT; relative risk [RR], 0.96; 95% confidence interval [CI], 0.82–1.11; $P = .56$) (8).

Two trials (6,19) provided evidence focused specifically on patients with iliofemoral DVT. In the iliofemoral DVT

subgroup (n = 391) of the ATTRACT trial, PCDT did not reduce the occurrence of PTS over 2 years (49% PCDT vs 51% no-PCDT; RR, 0.95; 95% CI, 0.78–1.15, $P = .59$) but did lead to greater improvement in early leg pain and swelling ($P < .01$) within 30 days, reduced occurrence of moderate-or-severe PTS over 2 years (18% vs 28%; RR, 0.65; 95% CI, 0.45–0.94, $P = .02$), and reduced PTS severity (mean differences of approximately 1.6 Villalta scale points and 1.2 Venous Clinical Severity Scale (VCSS) scale points at the 6-, 12-, 18-, and 24-month follow-ups; $P < .01$ for nearly all comparisons), compared with no-PCDT (6). PCDT led to a sizable QoL benefit within the first 6 months (approximately 9 points on the Venous Insufficiency Epidemiological and Economic Study Quality of Life [VEINES-QoL] scale, $P < .0001$) and to a smaller QoL benefit between 12 and 24 months (approximately 5 points on VEINES-QoL scale, $P = .02$) (9). In contrast, PCDT did not produce clinical benefits in femoral-popliteal DVT (n = 300) (7,9).

In the other trial focusing on iliofemoral DVT, the Dutch Catheter-Directed Thrombolysis Versus Anticoagulation (CAVA) Trial (19) randomized patients (N = 184) with acute iliofemoral DVT to receive (n = 91), or not receive (n = 93), US-assisted CDT with urokinase given through the Ekosonic MACH 4 Endovascular System (EKOS, Bothell, Washington; now Boston Scientific, Marlborough, Massachusetts). In this study, urokinase infusions could be continued for up to 4 days; use of thrombectomy devices was not noted. US-assisted CDT had no effect on PTS occurrence (29% US-assisted CDT vs 35% no–US-assisted CDT; OR, 0.75; 95% CI, 0.38–1.50; $P = .42$) or QoL at 1 year. At a median follow-up of 39 months, PTS was less frequent in the US-assisted CDT group; however, this difference was not statistically significant (31% US-assisted CDT vs 45% no–US-assisted CDT; OR, 0.54; 95% CI, 0.26–1.15; $P = .11$). A secondary analysis using the International Society of Haemostasis and Thrombosis definition of PTS observed a significant reduction in PTS (29% US-assisted CDT vs 47% no–US-assisted CDT; OR, 0.40; 95% CI, 0.19–0.84; $P = .01$) (21,24). However, similar to CAVENT, most PTS cases were mild and no long-term QoL benefit was seen.

These randomized trials did not find evidence that CDT/PCDT reduces the occurrence of symptomatic recurrent venous thromboembolism (VTE). In CDT/PCDT recipients within the CAVENT and ATTRACT trials, the volume of residual thrombus on the final procedure-day venogram did not correlate with the 2-year occurrence of PTS; however, in the ATTRACT trial's iliofemoral DVT subgroup only, residual thrombus volume correlated with PTS severity (25). In both studies (26,27), many CDT/PCDT-treated patients had venous thrombus visualized on follow-up imaging, and this finding predicted poorer 2-year clinical outcomes. In the ATTRACT trial, noncompressibility of the common femoral vein on the 1-month US predicted more PTS, more moderate-or-severe PTS, and worse QoL (27). In the CAVENT trial, venous patency at 6 and 24 months was statistically associated with reduced 24-month PTS (26). In the CAVA trial, recurrent DVT was more frequent in the US-assisted CDT group, with many events occurring within stented vein segments (19). Taken together, these findings suggest that efforts to prevent rethrombosis after ETR may be especially important in optimizing patient outcomes.

Modest limitations of these trials included statistical imprecision, potential for reporting bias attributable to the patient unblinded design, heterogeneity of ETR treatment methods, losses to follow-up (ATTRACT trial), and the limited long-term follow-up duration (ATTRACT trial, 2 years; CAVA trial, median 3 years). Each trial allowed adjunctive use of balloon angioplasty and/or stent placement during CDT/PCDT procedures; although this enabled the studies to better reflect the real-world use of CDT/PCDT, the degree to which the observed outcomes can be attributed to each element of therapy is not clear. On the contrary, these trials had strong methodologic design, multidisciplinary participation, rigorous monitoring of data, and systematic precautions against bias. Their findings apply most directly to the first-line use of CDT/PCDT in initially presenting DVT. Randomized trials have not evaluated CDT/PCDT in more selected populations (eg, symptom progression after initial anticoagulation) to date.

Randomized trials have not been designed to enable definitive assessment of individual PCDT methods for DVT treatment. In a subanalysis of the ATTRACT trial, a PCDT strategy that included the 6-F Solent Proxi and DVX AngioJet Rheolytic Thrombectomy System catheters (Possis/Boston Scientific) along with adjunctive balloon angioplasty and/or stent placement led to 80% thrombus clearance and flow restoration in the iliofemoral (100%) and femoral-popliteal (95%) venous segments (28). AngioJet-PCDT recipients experienced greater improvement in leg swelling, venous symptoms, and venous QoL within 30 days and reduced PTS within 6 months, compared with patients with nonlysed thrombosis. However, clinical benefits beyond 6 months were not observed, and recurrent DVT may have been more frequent over 24 months (13.9% AngioJet-PCDT vs 6.8% no-PCDT; $P = .03$). Outcomes were similar for the patients (n = 75) receiving single-session AngioJet-PCDT (short-term benefit, no long-term benefit). The applicability of the AngioJet-PCDT findings to other PCDT strategies is not clear, as randomized controlled trials have not evaluated other PCDT methods for DVT treatment. Although the feasibility of removing thrombus has been reported in case series for PCDT methods that used various MT devices, rigorous studies have not been completed to compare strategies head-to-head or to delineate the specific effects of MT versus other procedure elements. The addition of MT to CDT procedures seems to reduce the needed fibrinolytic drug dose and treatment time, but clear differences in safety or efficacy have not been established (29,30).

In addition to the aforementioned trials, 1 single-center randomized trial (31) was performed to compare 2 methods of performing CDT. In the BERNUTIFUL trial,

US-assisted CDT with rt-PA delivery using the Ekosonic MACH 4 Endovascular System was successful in removing thrombus in 48 patients with acute iliofemoral DVT; however, no differences in thrombus removal, safety, or 1-year PTS were seen between patients randomized to have the ultrasound energy given, versus not given (31,32). Beyond this trial, specific CDT/PCDT methods have not been compared head-to-head in prospective studies.

Systematic Reviews and Meta-Analyses. Several systematic reviews and meta-analyses have recently been published on CDT; however, most have substantial limitations (ie, significant heterogeneity in the pooling of patient populations) for the purpose of this review. One systematic review (33), however, included patients with acute iliofemoral DVT only and compared the effectiveness of MT and thrombolysis alone. The review included 17 studies (N = 1,417 patients) and found that the pooled proportions of patients having >50% clot lysis did not differ statistically between CDT and MT/PCDT but patients with CDT experienced more major bleeds (6.0% vs 1.0%, $P < .001$). A significant limitation to this study is that the authors included both observational studies and randomized trials and pooled the data from PCDT and MT procedures into 1 treatment group, reducing the insight that could be gained from its subsequent comparisons with CDT.

A recent Cochrane systematic review (34) assessed the effects of thrombolytic therapy and anticoagulation compared with anticoagulation alone in patients with acute DVT. Nineteen randomized trials were included (systemic thrombolysis, CDT, and PCDT) comprising 1,943 patients with acute DVT. The frequency of complete clot lysis was higher in the thrombolysis-treated patients at the early-stage (RR, 4.75; 95% CI, 1.83–12.33; n = 592; 8 studies) and the intermediate-stage (RR, 2.42; 95% CI, 1.42–4.12; n = 654; 7 studies) follow-up. Subgroup analyses did not identify statistically significant differences between thrombolytic strategies (ie, systemic, locoregional, and CDT/PCDT). Overall, between 6 months and 5 years, PTS was slightly less frequent in thrombolytic therapy recipients (50% thrombolysis vs 53% no-thrombolysis; RR, 0.78; 95% CI, 0.66–0.93; n = 1,393, 6 studies). Considering only the CAVENT, ATTRACT, and CAVA trials, CDT/PCDT did not reduce the occurrence of PTS (RR, 0.89; 95% CI: 0.74–1.05, n = 1,032). A similar systematic review (35) by a committee of the American Society of Hematology (ASH) found thrombolytic therapy (pooling systemic thrombolysis and CDT/PCDT) to yield a possible modest reduction in the occurrence of PTS (RR, 0.70; 95% CI, 0.59–0.83).

MT (No Fibrinolytic Drug)

Randomized Controlled Trials. In a single-center trial (36), 42 patients with acute proximal DVT receiving anticoagulants were randomized to receive or not receive percutaneous thrombus aspiration through a 9-F catheter plus balloon venoplasty and/or stent placement. Through 1 year, the MT recipients were found to have higher venous patency ($P < .001$) and fewer venous symptoms (MT 0.81 ± 0.92 points vs no-MT 2.43 ± 0.67 points on a homemade 6-point scale; $P < .001$). Study limitations included imprecision because of the small sample size, performance in a single center, lack of assessor blinding, and use of a nonvalidated scale rather than a validated PTS measure.

Besides this study, no published randomized trials or prospective studies have provided rigorous independent verification of the thrombus removal efficacy or clinical utility of MT devices (used without fibrinolytic drug) for acute iliofemoral DVT.

Observational Studies. The feasibility of removing thrombus without a fibrinolytic drug has been reported for multiple MT devices in case reports and small case series of patients with DVT, who, in most cases, presented with symptomatic nonthreatened limbs. True success rates are difficult to discern because fibrinolytic therapy, balloon angioplasty, and/or stent placement was used in many patients who had residual thrombus after MT, and treatment failures may be reported less frequently. Overall, given the small samples, retrospective design, frequent cointerventions, lack of controls, and lack of independent clinical and imaging assessments, these reports constitute low-quality evidence that does not permit reliable estimation of efficacy or safety. For MT devices that are used without fibrinolytic drugs in current practice, some information is included in this report to convey the limited nature of the evidence that is available to guide recommendations.

Rheolytic thrombectomy with the AngioJet device has been used for DVT treatment for many years, but cases in whom fibrinolytic drug therapy was not concomitantly given constitute only a small minority of the reported experience, and outcome reporting has been variable. Published reports (29,37) in which early AngioJet models were used to treat DVT suggested a limited capacity to remove large volumes of thrombus without concomitant or subsequent fibrinolytic drug administration. Within a large prospective single-arm multicenter registry of patients with DVT who were treated with AngioJet rheolytic thrombectomy (38), thrombus removal efficacy exceeded 50% in all 13 patients who did not receive fibrinolytic drug therapy. However, this may represent an overestimate of the device's actual efficacy because patients with limited thrombus removal with MT alone may have subsequently received fibrinolytic drug therapy and would have been removed from the analysis of MT alone (ie, recategorized as PCDT). No studies were identified documenting the use of newer AngioJet models for MT without fibrinolytic drugs.

The feasibility of successfully removing thrombus without a fibrinolytic drug has been reported for the Aspirex S (Straub Medical, Vilters-Wangs, Switzerland) (2 reports, n = 86) (39,40), Clottriever and Flowtriever (Inari Medical, Irvine, California) (10 reports, n = 35, including 4 patients

with phlegmasia cerulea dolens) (41–50), and Indigo System (Penumbra, Alameda, California) CAT-8 (1 report, n = 10) (51) and Lightning 12 (1 report, n = 15) (52) devices. Associated symptom improvement and limb salvage were reported in many of these cases. However, the methodologic limitations noted above also applied to these reports.

Use of the AngioVac thrombectomy device (Angiodynamics, Latham, New York) has been reported in case series and a prospective multicenter single-arm registry of 234 patients (53–59). However, most patients were treated for PE or intracardiac lesions, not DVT. In the 91 RAPID registry patients with caval or iliocaval thrombosis, Angiovac MT resulted in the removal of ≥50% of the thrombus in 86% of the treated patients; ≥70% thrombus removal was achieved in 74% of the treated patients (59). However, in the overall cohort (all indications), complications included major bleeding (2.6%), need for blood transfusion (25%), and embolic complications (3%). Most outcomes were not reported separately for patients with iliocaval thrombus, and key limb outcomes (eg, symptoms and PTS) were not quantified. Small case series (53–58) of Angiovac-treated patients with iliocaval DVT (6 reports, 37 patients) were similar. Based on the available information on its risk-to-benefit ratio and complexity, the suitability of AngioVac MT for typical cases of acute iliofemoral DVT remains unclear.

Adjunctive Elements of Endovascular Care

Because the number of prospective studies evaluating ETR procedure variations and adjunctive diagnostic or therapeutic interventions is relatively small, the design of these studies is summarized in the paragraphs below that correspond to each respective element of care.

Venous Access Site. In a single-center study (60), 106 patients undergoing CDT were randomized to have venous access obtained via the small saphenous (Group A), great saphenous (Group B), or popliteal (Group C) vein. This study found no differences in the efficacy of thrombus removal (Group A: 63.5% ± 7.7; Group B: 66.9% ± 8.4; Group C: 66.1% ± 2.7) or limb edema (measured thigh circumference) reduction (Group A: 82.3% ± 7.6; Group B: 81.6% ± 6.0; Group C: 83.9% ± 6.1) between the 3 groups ($P > .05$ for all intergroup comparisons). This study was limited by imprecision because of its small sample size. In the multicenter randomized CAVENT trial (61), PTS and venous patency were not found to differ among CDT recipients in whom venous access for CDT was obtained in the popliteal, tibial, or common femoral vein. However, bleeding was significantly more frequent with tibial or common femoral access compared with popliteal vein access ($P < .001$).

Balloon Angioplasty. In a single-center study (62), 386 patients undergoing CDT for acute or subacute iliofemoral DVT were randomized to receive CDT alone or CDT with adjunctive balloon angioplasty of residual venous stenosis or thrombus. Patients in both arms received stents for residual stenosis. PTS severity at 2 years (Villalta scores assessed by a blinded examiner) was similar in the 2 groups (balloon angioplasty 4.20 ± 3.05 vs no balloon angioplasty 4.89 ± 3.45; $P = .08$), with no difference in QoL. In subgroup analyses, balloon angioplasty did not benefit patients with acute iliofemoral DVT but was associated with reduced PTS severity and improved QoL in patients with subacute (symptom duration, 15–28 days) iliofemoral DVT.

Stent Placement. A single-center trial (63) randomized 74 patients with acute iliofemoral DVT with residual iliac vein stenosis (>50% diameter narrowing) after CDT to receive CDT plus stent placement (n = 45) or CDT alone (n = 29). The stented patients were found to have superior 1-year patency (74% stent vs 47% no stent, $P = .019$), reduced venous clinical severity ($P = .05$), and improved venous QoL ($P = .009$) compared with the nonstented patients. A systematic review and meta-analysis of studies reporting on outcomes after iliac vein stent placement (64) included a subanalysis of 629 patients (19 studies) who received stents after ETR for acute DVT. In the 13 studies with adequate data, technical success was reported in 94% of patients, with early thrombosis in 6.5% of patients and a 1-year primary patency rate of 87%. These findings are consistent with those of an early multicenter prospective single-arm CDT registry (65) in which stented patients had a better 1-year patency than nonstented patients (74% vs 53%; $P < .001$). However, this nonrandomized comparison should be viewed with caution because the 2 populations were likely dissimilar.

Anticoagulant Therapy. Before ETR: Anticoagulant therapy reduces symptomatic PE, thrombus extension, and mortality in patients with proximal DVT, and delayed achievement of fully therapeutic anticoagulant effect has been shown to correlate with poorer clinical outcomes (66–71). Therefore, anticoagulation must be instituted without delay in patients in whom acute iliofemoral DVT is diagnosed or suspected, irrespective of whether ETR is being considered. Compared with intravenous unfractionated heparin (UFH), use of subcutaneous low molecular weight heparin (LMWH) has been shown to result in faster achievement of therapeutic-level anticoagulation, a lower risk of recurrent VTE, and a trend toward reduced mortality (69,70).

During ETR: Randomized trials have not been performed to identify the optimal strategy for anticoagulation during ETR. In clinical practice and in published studies, most patients have received UFH or LMWH during ETR. Based on early clinical experiences with CDT for arterial and venous occlusions, UFH is often targeted to subtherapeutic levels during fibrinolytic drug infusions (14). In the

ATTRACT trial, major bleeds occurred in 2.2% of patients who received twice-daily injections of weight-based LMWH and in 1.7% of patients who received UFH (targeted to subtherapeutic range) during PCDT (8). In the CAVENT trial, patients received UFH targeted to subtherapeutic levels (PTT, 1.2–1.7 times control) (18). These trials are helpful in directly linking safety outcomes to specific anticoagulation protocols; however, the impact of anticoagulant choice and intensity on the clinical efficacy of CDT/PCDT in these studies remains unclear. Studies in which direct-acting oral anticoagulants were used during CDT/PCDT were not identified in the search.

After ETR: Large randomized trials have not been conducted to identify the optimal antithrombotic strategy after ETR. Only 1 small randomized study (72) (N = 72) found rivaroxaban to be as effective as warfarin in preventing DVT recurrence over 6 months after CDT.

Intravascular US. The available imaging modalities each possess strengths and limitations for the evaluation of the iliac venous system (73). This summary focuses on aspects that are directly relevant to the use of intravascular IV (IVUS) during ETR procedures for acute DVT. Multiplanar venography enables venous lumen assessment and visual estimation of dynamic flow but is poorly suited to evaluate vein wall architecture and identify internal defects (eg, webs) that are not orthogonal to the incident beam. In contrast, IVUS provides high-resolution cross-sectional imaging of vascular structures with the depiction of greater internal details (74). Because IVUS provides information that is complementary to venography, its use during venous interventions has increased in recent years, with studies of varying design suggesting that IVUS improves the diagnosis and characterization of iliac vein abnormalities. However, discrete clinical benefits have not yet been conclusively demonstrated through controlled trials.

One retrospective review (75) described 33 patients who had undergone both venography and IVUS during PCDT treatment of acute iliofemoral DVT. The analysis of thrombus volume found that multiplanar venography significantly underestimated the amount of residual thrombus after PCDT, resulting in a significant difference in the assessment of clot lysis (mean clot lysis of 80% per intravascular US was perceived as >90% clot lysis on venography, $P < .05$) and identified fewer obstructive lesions (stenosis, residual thrombus, or May-Thurner anatomy, not defined further) than IVUS (48% vs 100%, $P < .01$).

Comparative studies in patients with chronic venous disease provide further support for the notion that IVUS enhances the assessment of iliac venous stenosis. The Venogram vs. IVUS for Diagnosing Iliac Vein Obstruction (VIDIO) study, a prospective multicenter study that evaluated the addition of IVUS to multiplanar venography in 100 patients with severe chronic venous disease and suspected iliac vein obstruction (76,77). In this study, IVUS identified significant (defined as ≥50% stenosis) lesions not detected by venography in 26% of the patients, the IVUS findings changed treatment plans in 57% of the patients, and IVUS area measurements were more predictive of clinical improvement with stent placement than the degree of stenosis on venography. In another retrospective study (78) of 155 limbs with chronic venous disease, multiplanar venography often underestimated the degree of stenosis on intravascular US and was often unable to localize the IVUS–determined point of maximal stenosis, the iliac vein confluence, and the optimal distal stent landing zone.

Limitations of these studies included the modest sample sizes, the lack of a true gold standard against which to compare imaging assessments for many parameters (including what constitutes a "significant" iliac vein stenosis), and nonassessment of whether IVUS truly led to improved long-term patient outcomes in a cost-effective manner. It should also be noted that in 1 study of 41 patients with pelvic venous disorders (79), the IVUS–measured cross-sectional area of the iliac vein was significantly lower with the patients in the supine position than when they were lying on their left side; the supine position resulted in characterization of many more patients as having significant iliac vein stenosis. Although IVUS measurements were better than venography in predicting symptom response with stent placement in the VIDIO study, the investigators observed that their predictive value (area under the curve, 0.64–0.70) was not high enough to be classified as providing "excellent" diagnostic efficacy (76). Although IVUS clearly adds complementary information and enhances overall insight, care should be exercised in relying on supine IVUS assessments as a sole method of evaluating iliac vein lesions.

Safety Considerations

CDT/ PCDT. Rates of additional major bleeding with CDT/PCDT in contemporary randomized trials (8,18,19) range from 1% to 5%. In the ATTRACT trial, the use of PCDT was associated with a small but significant increase in major bleeding (1.7% PCDT vs 0.3% no-PCDT; $P = .049$) (8). Although there were no reported CDT/PCDT-related deaths or intracranial bleeds in these studies, 2 patients with retroperitoneal bleeds in the ATTRACT trial required urgent catheter embolization and 1 patient with major bleed in the CAVENT trial required surgical therapy to prevent an adverse outcome (18).

In a Cochrane review of 19 randomized controlled trials (34) (N = 1,943 patients), thrombolytic agent recipients had increased bleeding complications (6.7% vs 2.2%; RR, 2.45; 95% CI, 1.58–3.78), although most bleeds occurred in older studies with fewer exclusion criteria. Moreover, in a systematic review by Izcovich et al (35), thrombolysis led to increased major bleeding (RR, 1.89; 95% CI, 1.46–2.46) and intracranial bleeding (RR, 3.17; 95% CI, 1.19–8.41).

Real-world populations are expected to experience more bleeding than trial populations with narrow eligibility criteria and standardized procedures. In 2014, the safety of

CDT as used in real-world practice was estimated using propensity-matched comparison of administrative data from the National Inpatient Sample database (80). Among 90,618 patients who were hospitalized for DVT, in-hospital mortality did not differ between the 3,649 CDT recipients and matched patients who did not have CDT (1.2% CDT vs 0.9% no-CDT; $P = .15$). However, rates of blood transfusion (11.1% CDT vs 6.5% no-CDT; $P < .001$) and intracranial hemorrhage (0.9% vs 0.3%, $P = .03$) were significantly higher in the CDT group. The limitations of this study were the likely presence of selection bias that propensity matching could not entirely eliminate, reliance on administratively coded data, and the absence of any assessment of treatment efficacy. These findings were generally consistent with an early urokinase CDT registry (65), in which 11.4% of patients developed major bleeding and 0.4% of patients experienced an intracranial bleed.

Overall, the published literature and robust clinical experience support the existence of a nontrivial additional bleeding risk with any fibrinolytic drug therapy and argue for rigorous individualized assessment of bleeding risks, judicious patient selection, and close monitoring. When such precautions are taken, studies suggest that the risk of major bleeding may be reduced to levels that enable safe use of CDT/PCDT in patients with strong potential to benefit.

Although symptomatic PE can occur in patients with iliofemoral DVT with any treatment approach, periprocedural PE has been rare with CDT/PCDT in randomized trials and other studies (8,18,19,65). In the ATTRACT trial, symptomatic PE within 10 days postrandomization occurred in 3 patients each (<1%) in the PCDT and no-PCDT treatment groups, with no fatal PE events (8). No periprocedural symptomatic PE events were reported in the CAVENT or CAVA trials.

MT. Given the paucity of prospective studies of MT, reliable estimates of procedure risks are not available at present. Local (venous access site) and distant bleeding are likely to occur less frequently when fibrinolytic drugs are avoided; however, local bleeding risk may also depend on the sheath size, anticoagulation strategy, and other factors. Procedure-associated PE has been reported with MT, but its incidence is uncertain and may vary by device type and mode of use. Case series (50,81,82) suggest that if MT devices are used without fibrinolytic drugs, PE can occur and may be more frequent, perhaps especially with nonaspirating devices. However, the extent to which these observations apply to contemporary MT devices/strategies is uncertain.

Because of its long history of use, more information is available for the AngioJet than for other devices. Beyond the abovementioned risks, device-specific issues may include bradycardia and renal failure. Of note, these events occurred at a very low frequency in the ATTRACT trial and in the Peripheral Use of AngioJet Rheolytic Thrombectomy with a Variety of Catheter Lengths (PEARL) registry; however, these studies did not routinely assess post-procedural renal function (28,38).

Stent Placement. In the only randomized trial that evaluated stent placement after ETR of acute DVT, stent-related safety outcomes were not reported. In a meta-analysis of venous stent placement (63) that included 19 acute DVT studies with 629 patients, complications within 30 days included major bleeding (1.1% in 11 studies), PE (0.9% in 11 studies), periprocedural mortality (0.7% in 13 studies), and early thrombosis (6.5% in 13 studies). Many of these events were likely attributable not to the stents themselves but to other components of the procedures. Local postimplantation pain after stent placement has been reported to occur with moderate frequency but has usually subsided within days-to-weeks. Stent fractures, malpositions, and migrations have also been reported as infrequent occurrences that may relate to patient-specific factors, device-specific design issues, operator errors, or a combination. For some dedicated venous stent brands, despite not being seen in the original pivotal trials, such events have prompted temporary recalls, modifications to instructions for use, or permanent withdrawal from the marketplace (83–88). Stent fractures have been reported to occur after 0%–3% of placements, mainly with extension across the inguinal ligament into the common femoral vein. Most have not been associated with clinical sequelae beyond local stenosis or thrombosis. Prospective studies have not been performed to compare safety outcomes among different stent types/brands.

Cost and Cost-Effectiveness

In the CAVENT trial, the use of CDT for acute proximal DVT was estimated to cost an additional $20,429 per quality-adjusted life year (QALY) gained (89). Cost-effectiveness was not evaluated for iliofemoral DVT specifically. In the ATTRACT trial, the use of PCDT for acute proximal DVT was estimated to cost $220,041 per QALY gained, constituting low-value care by the current U.S. cost-effectiveness thresholds (<$50,000 per QALY gained is considered high-value care; $50,000–$150,000 per QALY gained is considered intermediate-value care; >$150,000 per QALY gained is considered low-value care) (90,91). In its iliofemoral DVT subgroup, the incremental cost-effectiveness of PCDT was estimated to be $137,526 per QALY gained, suggesting that PCDT represents intermediate-value care in that population. In contrast, PCDT was not cost-effective for patients with isolated femoral-popliteal DVT. Differences between the CAVENT and ATTRACT trials likely derive from the different countries in which the trials were conducted (Norway vs United States), greater use of MT devices and stents in the PCDT protocol in ATTRACT, and most importantly the observed differences in CDT/PCDT efficacy on PTS (to which the cost-effectiveness estimates were very sensitive) in the 2 trials. Using the U.S. National Inpatient Sample study, Bashir et al (80) found that the addition of CDT was associated with longer length of stay (mean, 2.2 days extra, $P < .001$) and greater hospital charges (mean difference, $56,903; $P < .001$).

Special Populations

Children, pregnant women, and many older patients (aged >75–85 years) were excluded from the randomized trials of ETR. In a prespecified subgroup analysis of the ATTRACT trial, patients aged ≥65 years fared poorly (developed more PTS) with PCDT, compared with younger patients ($P = .04$) (8). In PCDT recipients, major bleeding occurred in 8.6% of patients aged ≥65 years, versus 0.003% in patients aged <65 years. In a multivariate analysis (92), increasing continuous age and age of ≥65 years were significant predictors of major or minor bleeding ($P = .0007$).

Pregnant Women. In pregnant women with acute iliofemoral DVT, the feasibility of performing ETR and achieving initial technical success has been reported sporadically for over 20 years, including a few recent case reports and small case series (93–96). Although it can be possible to perform CDT without the use of radiation or iodinated contrast in pregnant patients with DVT, procedural radiation exposure and the risk of bleeding to the fetus and mother are still significant limiting factors (96). Sousa Gomes et al (97) summarized 65 articles describing 141 pregnant women who were treated with any form of thrombolytic therapy for any condition. Complications included maternal death (2.8%); death of embryo, fetus, or child (8.5%); and preterm delivery (9.9%). Among 20 patients who received ETR for DVT, there was 1 major bleed, 4 access site hematomas, 1 popliteal artery pseudoaneurysm, 2 fetal deaths, 1 preterm delivery, and 2 rethromboses. Hence, although there are no controlled trials, based on limited data, the risks and uncertainties of ETR argue against routine use for DVT in pregnant women but should not be considered prohibitive for patients with particularly severe DVT manifestations. If ETR is performed, an "as low as reasonably achievable" approach to radiation exposure should be used along with careful fetal monitoring (98).

Children and Adolescents. Older children and adolescents are at risk of developing PTS that impacts QoL, especially when there are severe presenting limb symptoms, completely occlusive DVT, thrombus involving multiple vessel segments, multiple recurrent DVT episodes, or adverse prognostic biomarkers (99). However, there are important differences in the physiology of hemostasis and thrombolysis between children and adults. For example, levels of clotting factors IX, X, and XII and endogenous tPA are substantially lower and levels of plasminogen activator inhibitors are substantially higher in children aged 11–16 years compared with those of adults (100). For younger children with high-risk phenotypes, limited data suggest that systemic thrombolysis may offer clinical benefits in some clinical scenarios, but well-designed studies have not been conducted to confirm these findings or assess the optimal method of thrombolytic therapy (101). Data on the use of ETR in children and adolescents are limited to case series (102–104). Although these studies support the feasibility of achieving initial technical success, the potential for catheter manipulation to cause endothelial damage is important to consider, especially for younger children with small vessel size. After ETR, untreated iliac vein obstruction can lead to rethrombosis but may not be amenable to effective treatment because the outcomes of stent placement in vessels that would normally be expected to grow over time have not been well-characterized. In a systematic review and individual patient data meta-analysis of studies including 109 patients with pediatric proximal DVT related to May-Thurner syndrome (103), the use of ETR was associated with increased vessel patency, and lack of vessel patency after treatment correlated with DVT recurrence. The use of ETR, however, was not found to influence the likelihood of developing PTS. Major bleeding occurred in 4% of the ETR-treated patients. A single-center prospective pilot study (N = 16) showed the feasibility and safety of performing MT and PCDT in adolescents, achieving initial technical success in 94% of the patients (104). There were no major bleeds but 1 case of symptomatic PE. However, MT/PCDT was associated with a 40% rate of early rethrombosis. This study had limitations, particularly imprecision because of the very small sample size and heterogeneity of treatment methods.

Phlegmasia Cerulea Dolens. The use of ETR for phlegmasia cerulea dolens has been reported in many small case series (105–109). Recent reports are similar to historical reports in demonstrating that this subgroup of patients is at a very high risk of limb amputation and death, justifying strategies beyond anticoagulation alone. Although ETR and surgical thrombectomy can clearly enable thrombus removal, clinical improvement, and limb salvage in many cases, some patients will have poor outcomes even after aggressive therapy is provided. The available reports have profound limitations because of small patient samples, retrospective design, and likely publication bias; however, this patient subpopulation cannot be randomized into clinical trials for ethical reasons; thus, treatment recommendations are obliged to rely on low-quality evidence.

Recent Societal Guidelines

Several national health organizations and medical specialty societies have developed evidence-based recommendations on endovascular management for patients with acute iliofemoral DVT (**Table 2**) (66,69,110–112). Specifically, in its 2020 guidelines on VTE management, the UK National Institute of Healthcare Excellence (NICE) recommends consideration of CDT in patients with symptomatic iliofemoral DVT who have symptoms lasting <14 days, good functional status, a life expectancy of ≥1 year, and a low risk of bleeding (110). A separate 2019 NICE guideline considers the use of MT and PCDT to be acceptable for patients with iliofemoral DVT only with special institutional precautions for oversight (111). NICE considers the use of

Table 2. Current Society Clinical Practice Guidelines on Endovascular Management of Patients with Acute Iliofemoral DVT

Society	Recommendation
National Institute of Healthcare Excellence, 2020 (110)	Consider catheter-directed thrombolytic therapy for people with symptomatic iliofemoral DVT who present with the following: symptoms lasting <14 d; good functional status; a life expectancy of ≥1 y; and a low risk of bleeding
National Institute of Healthcare Excellence, 2019 (111)	Current evidence on the safety of percutaneous mechanical thrombectomy for acute DVT of the leg shows that there are well-recognized but infrequent complications For acute iliofemoral DVT, the evidence on efficacy is limited in quality and quantity; therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. For distal DVT that does not extend into the common femoral vein, the evidence on efficacy is inconclusive; therefore, this procedure should only be used in the context of research
American Society of Hematology, 2020 (66)	In most patients with proximal DVT, the American Society of Hematology guideline panel suggests anticoagulation therapy alone over thrombolytic therapy in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects) Remarks: Thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk of bleeding with symptomatic DVT involving the iliac and common femoral veins (higher risk of more severe PTS). Patients in these categories, who value rapid resolution of symptoms, are averse to the possibility of PTS and accept that the added risk of major bleeding may prefer thrombolysis. The use of thrombolysis should be rare for patients with DVT limited to veins below the common femoral vein For patients with extensive DVT in whom thrombolysis is considered appropriate, the American Society of Hematology guideline panel suggests using catheter-directed thrombolysis over systemic thrombolysis (conditional recommendation based on very low certainty in the evidence of effects)
European Society of Vascular Surgery, 2021 (112)	In selected patients with symptomatic iliofemoral DVT, early thrombus removal strategies should be considered(Class IIa, Level A) For patients with DVT limited to femoral, popliteal, or calf veins, early thrombus removal is not recommended (Class III, Level B) For patients with DVT treated by early thrombus removal, with or without stent placement, it is recommended that the duration of anticoagulation should be at least as long as if the patients were treated by anticoagulation alone and at the discretion of the treating physician (Class I, Level C)
American College of Chest Physicians, 2021 (69)	In patients with acute DVT of the leg, anticoagulant therapy alone is suggested over interventional (thrombolytic, mechanical, or pharmacomechanical) therapy (weak recommendation, moderate certainty evidence) Comments: In patients with very severe, limb-threatening DVT (such as those with phlegmasia or threatened venous gangrene), the benefits of more rapid thrombus resolution may outweigh the risk of harm

DVT = deep vein thrombosis.

MT and PCDT to be investigational for patients with DVT that does not extend up to the common femoral vein.

The 2020 ASH guidelines for the management of VTE suggest the use of anticoagulation alone (over thrombolysis plus anticoagulation) for most patients with DVT (66). The ASH panel commented that thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk for bleeding with symptomatic iliofemoral DVT but that its use should be rare for femoral-popliteal DVT. The ASH panel also suggested that when DVT thrombolysis is performed, CDT/PCDT should be used instead of systemic thrombolysis.

The 2021 European Society of Vascular Surgery guidelines recommend that early thrombus removal strategies be considered for selected patients with acute iliofemoral DVT but not for patients with DVT limited to the femoral, popliteal, or calf veins (112). Per the European Society of Vascular Surgery panel, patients who have undergone early thrombus removal interventions, with or without stent placement, should be anticoagulated for at least as long as comparable with patients without interventions.

In its 2021 update to the Antithrombotic Therapy for VTE Disease Guideline, the American College of Chest Physicians recommends against the use of ETR for patients with acute DVT except for those with very severe, limb-threatening DVT (phlegmasia or threatened venous gangrene) (69).

CONCLUSION

Updated evidence suggests that ETR can favorably influence some clinical outcomes when used for acute DVT but does not produce sufficiently large long-term benefits to justify routine first-line use in broad populations of initially presenting patients. However, many patients with acute iliofemoral DVT are likely to be safely and effectively treated. As further research proceeds, SIR believes that adherence to the following recommendations will enable judicious use of endovascular therapy in a manner that optimizes benefit and minimizes harm.

RECOMMENDATIONS

Except where indicated, the recommendations below apply to adults and to older adolescents because their coagulation systems are biologically similar to adults, their veins are nearly adult sized, and patients aged ≥16 years were included in a relevant randomized trial (8).

1. Patients with iliofemoral DVT should be identified at the time of DVT diagnosis and followed up closely to ensure prompt and adequate anticoagulation, symptom control, and functional recovery (**Level of Evidence B, Strength of Recommendation Strong**).

Comment: Acute iliofemoral DVT should be viewed as a high-risk condition, with attention not only to the risk of PE but also to the patient's presenting symptoms and long-term risk of PTS that can limit activity and QoL. Systematic identification of most patients with iliofemoral DVT should be feasible in most centers because most cases involve the common femoral vein that is visible on lower extremity duplex US. Pelvic imaging is not routinely needed but can be obtained if there is clinical suspicion for iliac DVT and the limb US is negative, if there is concern for pelvic malignancy or other condition, or for pretreatment planning if catheter intervention is planned.

2. Prompt achievement and maintenance of fully therapeutic anticoagulation are essential for patients presenting with acute iliofemoral DVT, unless there are major contraindications (ie, active bleeding or high risk of bleeding) (**Level of Evidence A, Strength of Recommendation Strong**).

Comment: Consideration of ETR should not be permitted to delay the rapid achievement of fully therapeutic anticoagulation. A number of anticoagulant drugs can be appropriate to use. The use of weight-based, twice-daily, subcutaneously injected LMWH for most candidates with ETR is suggested because (a) compared with intravenous UFH, LMWH results in faster achievement of therapeutic-level anticoagulation; (b) the use of LMWH before, during, and after ETR can enable consistent anticoagulation without transitions that result in periods of subtherapeutic or supratherapeutic anticoagulation; and (c) the safety of concomitantly using direct-acting oral anticoagulants with fibrinolytic drugs is uncertain. Alternately, UFH is reasonable for periprocedural use provided therapeutic levels are reached quickly. Because this typically takes hours to achieve, active monitoring and timely dose adjustments are important. In most cases, it is reasonable to maintain UFH at fully therapeutic levels during the on-table component(s) of the procedure and reduce the UFH to subtherapeutic levels during fibrinolytic drug infusions. The patient's individualized risk of bleeding should also be carefully considered in calibrating UFH levels.

3. Adjunctive CDT or PCDT (along with anticoagulation) is reasonable to use in carefully selected patients with acute iliofemoral DVT after consideration of presenting clinical severity, bleeding risks, symptom duration, pre-DVT functional capacity, comorbidities, and patient preferences (**Level of Evidence B, Strength of Recommendation Moderate**).

Comment: The use of CDT/PCDT in specific clinical scenarios is summarized in the following recommendations:

a. In patients with acute limb-threatening circulatory compromise (eg, phlegmasia cerulea dolens) from acute iliofemoral DVT, urgent CDT/PCDT is recommended to promote limb salvage, unless the patient has clinical factors that confer a high risk of bleeding or other complications (**Level of Evidence D, Strength of Recommendation Moderate**).

Comment: A recommendation of moderate strength normally requires prospective studies but is provided in this document because of the high rates of amputation and mortality that are observed with use of anticoagulation alone in this morbid clinical scenario. CDT/PCDT is suggested over MT for most patients with phlegmasia cerulea dolens because experience with the former has been more robustly documented in case series and fibrinolytic drug may help to restore inflow from occluded peripheral veins. Surgical thrombectomy or MT can be used instead of CDT/PCDT in patients with elevated bleeding risk. Overall, treatment modality selection may vary based on comorbidities (surgical risk), bleeding risks, and local physician expertise and preferences. In these severely affected patients, it is particularly important to ensure that consideration of ETR does not delay anticoagulation.

b. For nonelderly patients with initially presenting acute iliofemoral DVT, nonthreatened limbs, good pre-DVT functional status, moderate-to-severe symptoms, and low risk of bleeding, adjunctive CDT/PCDT should be strongly considered for use as part of the first-line treatment approach (along with anticoagulant therapy) to enhance relief of presenting symptoms, reduce PTS severity, and improve health-related QoL (**Level of Evidence B, Strength of Recommendation Moderate).**

Comment: The recommendation is based primarily on the overall results and iliofemoral DVT subgroup outcomes in the ATTRACT trial, along with data from other comparative studies (113–115). *Decisions on the initial use of CDT/PCDT in individual patients are expected to vary based on the abovementioned factors and patient preferences; for many patients, a 3- to 7-day trial of anticoagulation may be reasonable before determining whether to perform CDT/PCDT. Discussions with patients should reflect a reasonable degree of confidence in the likelihood of seeing short-term (≤6 months) symptom/QoL benefits, and moderate uncertainty around whether long-term QoL benefits will be realized given their modest size in the ATTRACT trial and absence in other trials. Younger patients with severe presenting symptoms may be most likely to obtain benefits with CDT/PCDT that outweigh risks. Patients aged ≥65 years are less likely to benefit and more likely to be harmed by CDT/PCDT compared with younger patients.*

c. For patients with acute iliofemoral DVT who continue to have moderate-to-severe symptoms or impaired ambulation despite initial

anticoagulation, who are at low risk of bleeding, and whose thrombus is believed to have formed within the past 14 days, adjunctive CDT/PCDT should be considered to alleviate symptoms and improve ambulatory capacity (**Level of Evidence C, Strength of Recommendation Moderate).**

Comment: The recommendation is derived from characterization of the outcomes of first-line use of CDT/PCDT in randomized trials (indirect evidence), the reported outcomes of second-line CDT/PCDT use in many nonrandomized studies, and expert consensus. The severity of symptoms, their duration relative to the end of the 14-day time window, and the option of switching anticoagulant agents are all reasonable to consider in judging how long to continue with anticoagulation alone. Although ETR can recanalize the venous system beyond 14 days, complete lysis is unlikely with CDT/PCDT alone, necessitating adjunctive procedures; quality studies have not evaluated whether this practice offers benefits that outweigh risks.

d. For pregnant women with acute iliofemoral DVT, ETR should not be routinely performed but should be limited to patients with compelling clinical indications such as acute limb threat or unacceptably high PE risk from rapid DVT progression on anticoagulation (**Level of Evidence D, Strength of Recommendation Weak**).

Comment: This recommendation places substantial value on the well-being of both the mother and fetus. Strong consideration should be given to using anticoagulation alone during the pregnancy and peripartum period, with clinical reassessment postpartum to determine whether severe symptoms and anatomical obstruction persist that might justify intervention in the chronic phase. When ETR is performed in a pregnant patient, attention should be paid to minimizing the radiation dose, and close coordination with obstetricians and experts in other maternal-fetal medicine domains is recommended to optimize outcomes for mother and child.

e. For children and younger adolescents with acute iliofemoral DVT, ETR should not be routinely performed but should be limited to patients with compelling clinical indications such as acute limb threat or unacceptably high PE risk from rapid DVT progression on anticoagulation (**Level of Evidence D, Strength of Recommendation Weak**).

Comment: In children and adolescents with DVT, close collaboration with a pediatrician to define optimal care is suggested, with strong consideration for pediatric hematology consultation. In considering aggressive therapies, the availability of suitable monitoring facilities/experience and local expertise with systemic thrombolysis and pediatric catheter interventions should be weighed. If ETR is performed in children who are of less than adult size, efforts to minimize trauma to the venous system should be made and stent placement should usually be avoided. Continued clinical follow-up of these patients is important to reduce the risk of recurrent DVT and to evaluate for PTS in early adulthood.

4. The use of CDT/PCDT is not recommended for most patients with DVT that is limited to the tibial, popliteal, and femoral veins; for patients with clinical factors that confer a moderate or high risk for bleeding (including advanced age); and for patients with only mild lower extremity symptoms (**Level of Evidence B, Strength of Recommendation Strong).**

Comment: The recommendation is based primarily on the overall results and femoral-popliteal DVT subgroup outcomes in the ATTRACT trial and the established risks of CDT/PCDT.

5. When intrathrombus fibrinolytic drug infusion is performed, the use of traditional infusion CDT instead of US-assisted CDT is suggested (**Level of Evidence B, Strength of Recommendation Weak).**

Comment: The recommendation is based on the absence of long-term clinical benefits with US-assisted CDT in relevant randomized trials (BERNUTIFUL and CAVA) and other studies (116,117). *The recommendation is weak because of imprecision in the randomized trials and because it reflects a desire to reduce unnecessary procedure costs rather than concerns about safety.*

6. When PCDT is performed for the purpose of achieving a long-term reduction in PTS severity and enhancement of long-term QoL, the optimal PCDT strategy to use has not been determined (**Level of Evidence E, Strength of Recommendation Weak).**

Comment: Although long-term benefits have been documented for infusion CDT (CAVENT) and for a combination of PCDT methods (ATTRACT), no specific PCDT method has been shown to prevent PTS, reduce PTS severity, or improve QoL beyond 6 months' follow-up. Within PCDT, different drugs, devices, and methods of use could produce varying outcomes.

7. When PCDT is performed for the purpose of achieving early symptom relief, incorporation of rheolytic thrombectomy (either after an initial fibrinolytic drug infusion or as single-session PCDT for patients with good inflow) is appropriate (**Level of Evidence B, Strength of Recommendation Moderate**).

Comment: The recommendation reflects moderate confidence in the understanding of the short-term effects of PCDT that incorporates rheolytic thrombectomy. Patient selection and periprocedural care should consider the potential for increased recurrent DVT (especially when optimizing long-term function is a major goal), bradycardia, and renal

dysfunction. The use of different rheolytic thrombectomy devices and methods could produce varying outcomes.

8. The use of MT (with no fibrinolytic drug) cannot be recommended for most patients with acute iliofemoral DVT (**Level of Evidence D, Strength of Recommendation Weak**).

Comment: This recommendation reflects strong uncertainty about MT's short-term and long-term safety and efficacy, weighed alongside the availability of established therapies that have been evaluated in randomized trials: (a) anticoagulation alone may be sufficient for patients with mild symptoms—advantages are its established safety, tolerability, and modest costs; and (b) for patients with moderate-to-severe symptoms and low bleeding risk, CDT and PCDT have shown some degree of efficacy for reducing early symptoms and/or late PTS, with a modest increase in bleeding risk. Similar to CDT and PCDT, MT entails risks, inconveniences and costs, but the hypothesized thrombus removal efficacy and clinical benefits of MT have not been documented in published prospective studies with control groups and independent outcome assessments. Because different MT devices and treatment strategies may variably influence thrombus clearance, vein wall injury, valve function, inflammation, and the risks of access site bleeding, periprocedural PE, and future thrombosis, the clinical outcomes of MT cannot be assumed to resemble those observed with CDT/PCDT. In selected patients with severe symptoms in whom initial anticoagulation has failed to produce relief and in whom CDT/PCDT is contraindicated (eg, because of bleeding risk), the use of MT may enable thrombus removal and improvement in presenting symptoms.

9. In most patients undergoing ETR for acute iliofemoral DVT, the use of IVUS along with venography is suggested to improve assessment of the veins after thrombus removal (**Level of Evidence C, Strength of Recommendation Weak**).

Comment: The recommendation reflects demonstration of the ability of IVUS to improve the visualization of iliac vein lesions in a prospective study of patients with chronic venous disease (indirect evidence) and in a retrospective study of patients with acute iliofemoral DVT. The recommendation is weak because randomized studies have not been completed to establish whether the routine use of IVUS in patients with acute DVT is clinically beneficial or cost-effective.

10. If a flow-limiting obstructive lesion is identified in the iliac vein after thrombus debulking and there is a good inflow from the leg veins, stent placement is recommended to reduce symptom severity and the risk of rethrombosis (**Level of Evidence C, Strength of Recommendation Moderate**).

Comment: The recommendation is based on published studies and clinical experience that suggest that rethrombosis is frequent in patients with untreated iliac vein lesions after ETR, supplemented by data from 1 small randomized trial that found stents to be beneficial. However, the morphologic lesion criteria and degree of flow limitation that predict future rethrombosis and residual symptoms are poorly defined. The risks and uncertainties of long-term stent implantation should be discussed with patients before the initiation of ETR. The optimal stent brand to use is not clear; whichever device is chosen, care should be exercised to ensure optimal stent sizing (diameter and length) and positioning to promote stent stability and optimize long-term patency. Operators should be aware that undersized stents may be more likely to migrate, especially with shorter lesions.

11. During fibrinolytic drug infusions, patients should be closely monitored in a clinical setting that enables diligent attention to appropriate dosing of medications (eg, fibrinolytic drugs and anticoagulants), timely blood draws for laboratory monitoring assessments, evaluation for clinical changes that can signify bleeding, and rapid communication with the treating physician (**Level of Evidence B, Strength of Recommendation Strong**).

Comment: In the 3 pivotal randomized trials, the CDT/PCDT interventions were delivered under the aforementioned rigorous conditions for patient monitoring. Hence, their observed safety outcomes are believed to be applicable only when similar precautions are taken.

12. In patients with acute iliofemoral DVT who undergo ETR, a close clinical follow-up should occur to ensure that anticoagulation is fully therapeutic, to monitor for bleeding, to ensure good symptom control, and to enable timely reintervention to restore patency in patients who develop recurrent symptoms (**Level of Evidence B, Strength of Recommendation Strong**).

Comment: Randomized trials and other studies have shown that thrombus reformation is frequent after ETR and that long-term benefits are most likely to be realized when patency is maintained. Although no large prospective studies have compared antithrombotic therapy strategies after ETR, anticoagulation should be given for at least as long as comparable patients (similar DVT risk factors and bleeding risk) who did not undergo ETR. If feasible, strong consideration should be given to the use of LMWH during the weeks immediately following the procedure.

In addition to the aforementioned recommendations, ongoing adherence to published SIR guidelines that delineate best practices to enhance safety during and around ETR procedures and that summarize guidance on periprocedural utilization of inferior vena cava filters (14,118) is recommended.

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APPENDIX A. LITERATURE SEARCHES

Catheter-directed therapies

1 thromboembolism.mp.
2 exp Thromboembolism/ or exp Venous Thromboembolism/
3 thrombosis.mp.
4 venous thrombosis.mp.
5 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
6 (PE or DVT or VTE).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
7 postthrombo* syndrom*.mp.
8 post-thrombo* syndrom*.mp.
9 exp postthrombotic syndrome/
10 exp Thrombophlebitis/
11 exp postphlebitic syndrome.mp
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 (thromboly* or fibrinoly*).mp.
14 exp Thrombectomy/
15 exp Urokinase-Type Plasminogen Activator/
16 exp Streptokinase/
17 (urokinase or streptokinase or reteplase or tenecteplase).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
18 (tPA or t-PA or rtPA or rt-PA).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
19 exp Tissue Plasminogen Activator/
20 rheolytic.mp.
21 angiojet.mp.
22 Trellis.mp.
23 EKOS.mp.
24 Eko Wave.mp.
25 EkoWave.mp.
26 Indigo.mp.
27 clottriever.mp.
28 CAT-8.mp.
29 Jeti.mp.
30 Cleaner.mp.
31 (ultrasound* adj2 (thromboly* or fibrinoly* or thrombect*)).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
32 (aspiration adj2 (thromboly* or fibrinoly* or thrombect*)).mp.
33 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 12 and 33

continued

(continued)

Stent placement

1 thrombosis.mp.
2 postthrombo* syndrom*.mp.
3 post-thrombo* syndrom*.mp.
4 exp postthrombotic syndrome/
5 exp Venous Insufficiency/
6 (venous adj1 obstruction).mp.
7 venous thrombosis.mp.
8 (venous adj1 occlusi*).mp.
9 Chronic venous insufficiency.mp.
10 Postphlebitic syndrome/
11 femoral vein.mp.
12 iliac vein.mp.
13 exp Vena Cava, Inferior/
14 iliofemoral.mp.
15 endovascular.mp.
16 stent*.mp.
17 exp Angioplasty/
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
19 11 or 12 or 13 or 14
20 15 or 16 or 17
21 18 and 19 and 20

Medical and surgical therapies

1 thromboembolism.mp.
2 exp Thromboembolism/ or exp Venous Thromboembolism/
3 thrombosis.mp.
4 venous thrombosis.mp.
5 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
6 (PE or DVT or VTE).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
7 postthrombo* syndrom*.mp.
8 post-thrombo* syndrom*.mp.
9 exp postthrombotic syndrome/
10 exp Thrombophlebitis/
11 iliofemoral.mp.
12 iliocaval.mp.
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
14 11 or 12
15 13 and 14
16 exp Anticoagulants/
17 dabigatran.mp.
18 pradaxa.mp.
19 rivaroxaban.mp.
20 xarelto.mp.
21 apixaban.mp.
22 Eliquis.mp.
23 edoxaban.mp.
24 betrixaban.mp.
25 Factor Xa Inhibitors.mp.
26 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 compression stocking*.mp.

continued

(continued)

28 elastic stocking*.mp.
29 exp Stockings, Compression/
30 27 or 28 or 29
31 ambulat*.mp.
32 (surgical adj1 thrombectomy).mp. (mp = title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
33 26 or 30 or 31 or 32
34 15 and 33

DVT = deep vein thrombosis; PE = pulmonary embolism; rt-PA = recombinant tissue plasminogen activator; VTE = venous thromboembolism.

APPENDIX B. LEVEL OF EVIDENCE AND RECOMMENDATION CLASSIFICATION SYSTEM (1–3)

LEVEL OF EVIDENCE

A HIGH QUALITY EVIDENCE

Types of Evidence	Characteristics of Evidence
Multiple RCTs	Homogeneity of RCT study population
Systematic reviews or meta-analyses of high-quality RCTs	Intention-to-treat principle maintained
RCT data supported by high-quality registry studies	Appropriate blinding
	Precision of data (narrow CIs)
	Appropriate follow-up (consider duration and patients lost to follow-up)
	Appropriate statistical design

B MODERATE QUALITY EVIDENCE—Randomized Study Design

Types of Evidence	Characteristics of Evidence
≥ 1 RCTs	RCTs with limitations (eg, < 80% follow-up, heterogeneity of patient population, bias, etc)
Systematic reviews or meta-analyses of moderate-quality RCTs	Imprecision of data (small sample size, wide CIs)

C MODERATE QUALITY EVIDENCE—Nonrandomized Study Design

Types of Evidence	Characteristics of Evidence
Nonrandomized trials	Nonrandomized controlled cohort study
Observational or registry studies	Observational study with dramatic effect
Systematic reviews or meta-analyses of moderate quality studies	Outcomes research
	Ecological study

D LIMITED QUALITY EVIDENCE

Types of Evidence	Characteristics of Evidence
Observational or registry studies with limited design and execution	Case series
	Case-control studies
Systematic reviews or meta-analyses of studies limited by design and execution	Historically controlled studies

E EXPERT OPINION

Types of Evidence	Characteristics of Evidence
Expert consensus based on clinical practice	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"

STRENGTH OF RECOMMENDATION

Strong Recommendation	Moderate Recommendation	Weak Recommendation	No Recommendation
Supported by high quality evidence for or against recommendation	Supported by moderate quality evidence for or against recommendation; new research may be able to provide additional context	Supported by weak quality evidence for or against recommendation; new research likely to provide additional context	Insufficient evidence in the literature to support or refute recommendation

CI = confidence interval; RCT = randomized controlled trial.

SUPPLEMENTAL REFERENCES (APPENDIX B)

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3. Guyatt GH, Oxman AD, Vist GF, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendation. BMJ 2008; 336:924–926.

APPENDIX C

Reference	Study design	N	Objective	Key results	Level of evidence
Vedantham et al (1)	Randomized controlled trial	692	To determine whether pharmacomechanical thrombolysis prevents the PTS in patients with proximal deep vein thrombosis	No significant difference in the percentage of patients with postthrombotic syndrome (47% in the pharmacomechanical thrombolysis group and 48% in the control group)	B
Enden et al (2)	Randomized controlled trial	209	To examine whether additional treatment with CDT using alteplase reduced the development of PTS	CDT reduced PTS occurrence over 2 y (41% CDT vs 56% no-CDT; $P = .047$) and 5 y (42% CDT vs 70% no-CDT; $P < .01$)	B
Notten et al (3)	Randomized controlled trial	184	To assess the benefit of additional US-accelerated CDT for the prevention of PTS compared with that of standard therapy in patients with IFDVT	US-assisted CDT had no effect on PTS occurrence (29% US-assisted CDT vs 35% no–US-assisted CDT; OR, 0.75; 95% CI, 0.38–1.50; $P = .42$)	B
Comerota et al (4)	Randomized controlled trial	391	To examine the effect of PCDT in ATTRACT patients with IFDVT	PCDT did not reduce the occurrence of PTS over 2 y (49% PCDT vs 51% no-PCDT, RR 0.95; 95% CI 0.78–1.15, $P = .59$) but did lead to greater improvement in early leg pain and swelling ($P < .01$) within 30 d, reduced occurrence of moderate-or-severe PTS over 2 y (18% vs 28%; RR, 0.65; 95% CI, 0.45–0.94; $P = .02$), and reduced PTS severity	B
Haig et al (5)	Randomized controlled trial	176	To assess whether findings for PTS and QoL have persisted at the 5-y follow-up	37 patients (43%; 95% CI, 33%–53%) allocated to the CDT group developed PTS, compared with 63 patients (71%; 95% CI, 61%–79%) allocated to the control group ($P < .0001$). QoL scores did not differ between the treatment groups	B
Enden et al (6)	Randomized controlled trial	189	To investigate whether additional CDT improves long-term QoL compared with standard treatment with anticoagulation and compression stockings alone in patients with proximal DVT	QoL did not differ between patients treated with additional CDT and those with standard treatment alone. Patients who developed PTS reported poorer QoL and more symptoms than patients without PTS	B
Notten et al (7)	Randomized controlled trial	120	To determine the impact of additional thrombolysis on the outcomes of PTS at long-term follow-up	PTS developed in 19 patients in UA-CDT group (30.6%) vs 26 patients in No UA-CDT group (44.8%) (OR, 0.54; 95% CI, 0.26–1.15; $P = .11$)	B
Razavi et al (8)	Observational study (retrospective cohort)	317	To evaluate the relationship between immediate venographic results and clinical outcomes of PCDT	Residual thrombus burden at procedure end does not correlate with the occurrence of PTS during the subsequent 24 mos. In IFDVT, lower residual thrombus burden correlates with reduced PTS severity and possibly with improved venous QoL and fewer early symptoms	D
Haig et al (9)	Randomized controlled trial	209	To assess the effect of CDT on venous reflux and patency and to identify the possible predictors for the development of PTS	Reflux and lack of patency at 6 mos were found to be independent predictors of PTS development in patients treated with CDT (OR, 8.3; 95% CI, 2.6–26.8 for patients with reflux; OR, 0.17; 95% CI, 0.06–0.49 for patients with patency)	B
Weinberg et al (10)	Randomized controlled trial	126	To assess the relationships between endovascular therapy, duplex ultrasonography, PTS, and QoL	PCDT results in less residual thrombus but does not reduce the venous valvular reflux. CFV noncompressibility at 1 mo is associated with more PTS, more severe PTS, and worse	B

continued

(continued)

Reference	Study design	N	Objective	Key results	Level of evidence
				QoL at 24 mos. Valvular reflux may predispose to moderate-or-severe PTS	
Vedantham et al (11)	Randomized controlled trial	364	To describe the clinical outcomes of a PCDT strategy that included Angiojet rheolytic thrombectomy	Angiojet-PCDT led to a greater improvement in leg swelling (MD calf circumference, 0.55 cm; P = .009), venous QoL (MD, 6.5 VEINES-QoL points, P = .0073), and venous symptoms (MD, 5.6 VEINES-symptoms points, P = .0134) than the control group	B
Engelberger et al (12)	Randomized controlled trial	48	To assess whether the addition of intravascular high-frequency, low-power US energy facilitates the resolution of thrombosis during CDT	Found no difference in the severity of the PTS (mean Villalta score: 3.0 ± 3.9 [range, 0–15] vs 1.9 ±1.9 [range, 0–7]; P = .21), in the US-assisted CDT group compared with the conventional CDT group	B
Engelberger et al (13)	Randomized controlled trial	45	To assess whether the addition of intravascular high-frequency, low-power US energy facilitates the resolution of thrombosis during CDT	At the 1-y follow-up, there was no difference in PTS between the US-assisted CDT group and the conventional CDT group	B
Lichtenberg et al (14)	Systematic review/meta-analysis	1,417 (17 studies)	To compare the effectiveness and safety of percutaneous MT and thrombolysis alone in patients with acute or subacute IFDVT	Pooled proportion of successful lysis was similar between the groups (thrombolysis: 95% [I^2 = 68.4%]; MT: 96% [I^2 = 0%])	
Broderick et al (15)	Systematic review/meta-analysis	1,943 (19 studies)	To assess the effects of thrombolytic clot removal strategies and anticoagulation compared with anticoagulation alone for the management of people with acute DVT of the lower limb	Complete clot lysis occurred more frequently in the thrombolysis group at early (RR, 4.75; 95% CI, 1.83–12.33) and intermediate (RR, 2.42; 95% CI, 1.42–4.12) follow-up. No differences between strategies (eg, systemic, locoregional, and CDT) were detected using subgroup analysis at any follow-up time points. Up to 5 y after treatment, slightly fewer cases of PTS occurred in those receiving thrombolysis, 50% compared with 53% in the standard anticoagulation group	A
Izcovich et al (16)	Systematic review/meta-analysis	4,740 (45 studies)	To evaluate the effectiveness and safety of thrombolytic agents in patients with PE and/or DVT	A reduction in PTS with thrombolytic agents (RR, 0.70; 95% CI, 0.59–0.83)	A
Cakir et al (17)	Randomized controlled trial	42	To compare the efficacy of percutaneous aspiration thrombectomy, followed by standard anticoagulant therapy, with anticoagulation therapy alone, for the treatment of acute proximal lower extremity DVT	The venous patency rates in month 12 were 57.1% and 4.76% in the interventional and medical treatment groups, respectively	B
Kasirajan et al (18)	Observational study (case series)	17	To evaluate the efficacy of a percutaneous MT device for rapid thrombus removal after DVT	4 of 17 (24%) patients showed venographic evidence of >90% thrombus removal, 6 of 17 (35%) patients showed 50%–90% thrombus removal, and 7 of 17 (41%) patients showed <50% thrombus extraction	D
Garcia et al (19)	Observational study (registry)	329	To report procedural and patient outcomes of endovascular treatment for lower extremity DVT with rheolytic thrombectomy	Rheolytic PCDT treatment of DVT is safe and effective and can potentially reduce the need for concomitant CDT	C
Moriarty et al (20)	Observational study (registry)	91	To assess device and procedural safety and technical success associated with the use of the Angiovac System to remove vascular thrombi and cardiac masses	Angiovac MT resulted in removal of >50% of the thrombus in 86% of the treated patients; >70% thrombus removal was achieved in 74% of the treated patients	D
Duan and Ni (21)	Randomized controlled trial	106	To investigate the feasibility, effectiveness, and complications of CDT using 3 different approaches for acute lower extremity DVT	No differences in the efficacy of thrombus removal (small saphenous: 63.5% ± 7.7; great saphenous: 66.9% ± 8.4; popliteal vein: 66.1% ± 2.7) or limb edema (measured thigh circumference) reduction between the 3 groups	B
Haig et al (22)	Randomized controlled trial	92	To identify potential markers for early- and long-term efficacy of CDT,	A mean clot resolution of 82% + 25 was achieved in 92 patients. Successful lysis (>50%) was obtained in 83 patients. Early	B

continued

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Reference	Study design	N	Objective	Key results	Level of evidence
			adverse events, and their interrelationship	efficacy was equal for femoral and iliofemoral thrombus and not related to thrombus load before CDT, symptom duration, or predisposing risk factors	
Zhang et al (23)	Randomized controlled trial	386	To compare CDT alone with CDT with additional balloon dilatation for the treatment of IFDVT	No significant difference in the mean total Villalta score was observed between the CDT + balloon dilatation group (4.20 ± 3.05) and the CDT alone group (4.89 ± 3.45)	B
Jiang et al (24)	Randomized controlled trial	74	To evaluate the benefit of stent placement in the iliac vein in patients with residual iliac vein stenosis treated with CDT for acute IFDVT	Stented patients were found to have superior 1-y patency (74% stent vs 47% no stent, P = .019), reduced venous clinical severity (P = .05), and improved venous QoL (P = .009) compared with the nonstented patients	B
Razavi et al (25)	Systematic review/meta-analysis	629 (19 studies)	To determine the safety and effectiveness of venous stent placement in patients with iliofemoral venous outflow obstruction	Technical success rates were comparable among the groups, ranging from 94% to 96%. Complication rates ranged from 0.3% to 1.1% among groups for major bleeding, from 0.2% to 0.9% for PE, from 0.1% to 0.7% for periprocedural mortality, and from 1.0% to 6.8% for early thrombosis	B
Mewissen et al (26)	Observational study (registry study)	473	To evaluate CDT for the treatment of symptomatic lower vein DVT	Grade III (complete) lysis was achieved in 96 (31%) infusions; Grade II (50%–99%) lysis in 162 (52%); and Grade I (<50%) lysis in 54 (17%). For acute thrombosis, Grade III lysis occurred in 34% of cases of acute and in 19% of cases of chronic DVT (P < .01); Major bleeding occurred in 11% of patients. At 1 y, the primary patency rate was 60%	D
Kang et al (27)	Randomized controlled trial	72	To compare the safety and efficacy of rivaroxaban vs warfarin after CDT of an IFDVT	The rates of recurrent VTE were similar in both groups (11.4% vs 12.5%; P = .94). Major bleeding was less in the rivaroxaban group but without significance (2.9% vs 9.4%; HR, 0.31; 95% CI, 0.03–2.96; P = .31)	B
Murphy et al (28)	Observational study (case series)	33	To determine the most accurate method of assessing clot lysis after percutaneous MT for IFDVT and to evaluate the effectiveness of 2 different pharmacomechanical thrombectomy devices	Intravascular US was able to delineate significant residual thrombus, stenosis, or May-Thurner anatomy requiring ancillary interventions in 100% of patients vs 48% (16/33) on the venograms (P < .01)	D
Gagne et al (29)	Observational study (cohort)	100	To compare the diagnostic efficacy of intravascular US with multiplanar venography for iliofemoral vein obstruction	Clinical improvement after stent placement was best predicted by intravascular US baseline measurement of area stenosis (area under the curve, 0.64; P = .04), with >54% estimated as the optimal threshold of stenosis, indicating interventional treatment	D
Gagne et al (30)	Observational study (cohort)	100	To compare the diagnostic efficacy of intravascular US with that of multiplanar venography for iliofemoral vein obstruction	Venography identified stenotic lesions in 51 of the 100 subjects, whereas intravascular US identified lesions in 81 of the 100 subjects. Compared with intravascular US, the diameter reduction was on average 11% less for venography (P < .001). Intravascular US identified significant (defined as >50% stenosis) lesions not detected by venography in 26% of the patients	D
Montminy et al (31)	Observational study (cohort)	152	To assess the accuracy of venography compared with intravascular US in determining key parameters essential for iliac vein stent placement	The median maximal area stenosis was significantly higher with intravascular US than with venography (69% vs 52%; P < .0001). Furthermore, venographic correlation with intravascular US for the anatomic location of maximal stenosis was present in only 32% of the limbs; venography missed the location of maximal stenosis in more than two-thirds of limbs	D
Bashir et al (32)	Observational (registry study)	90,618	To compare the in-hospital outcomes of CDT plus anticoagulation with those of anticoagulation alone. The secondary objective was to evaluate the temporal trends in the utilization	In-hospital mortality was not significantly different between the CDT and the anticoagulation groups (1.2% vs 0.9%) (OR, 1.40 [95% CI, 0.88–2.25]) (P = .15). Rates of blood transfusion, PE, intracranial	C

continued

(continued)

Reference	Study design	N	Objective	Key results	Level of evidence
			and outcomes of CDT in the treatment of proximal DVT	hemorrhage, and vena cava filter placement were significantly higher in the CDT group	
Enden et al (33)	Modeling study		To estimate the cost-effectiveness of additional CDT compared with that of the standard treatment alone	Additional CDT accumulated 32.31 QALYs compared with 31.68 QALYs after standard treatment alone. The direct medical costs were $64,709 for the additional CDT group and $51,866 for the standard treatment group	C
Magnuson et al (34)	Randomized controlled trial	692	To compare the long-term costs and cost-effectiveness of CDT with anticoagulation therapy from the perspective of the US health care system	For the CDT group, the mean costs of the initial procedure were $13,600; the per-patient costs associated with the index hospitalization were $21,509 for PCDT and $3,877 for standard care (difference = $17,632; 95% CI, $16,117–$19,243). The 24-mo difference in costs was $20,045 (95% CI, $16,093–$24,120). For IFDVT, QALY gains with PCDT were greater, yielding an incremental cost-effectiveness ratio of $137,526/QALY	B
Herrera et al (35)	Observational study (case series)	13	To review the short- and long-term outcomes of 13 patients with extensive DVT of pregnancy treated with a strategy of thrombus removal	Extensive DVT of pregnancy can be effectively and safely treated with a strategy of thrombus removal, resulting in a patent venous system, normal valve function in many, prevention of PTS, and reduction in recurrence	D
Bloom et al (36)	Observational study (case series)	11	To evaluate the outcomes of CDT in pregnant and postpartum patients	>90% clot lysis was achieved in 9 of 11 (82%) patients. Metal stents were placed in 8 of 11 (73%) patients. No patient developed PTS	D
Sousa Gomes et al (37)	Review	141 (65 studies)	To summarize the available data regarding the use of thrombolytic agents in pregnancy	Among 20 patients who received ETR for DVT, there was 1 major bleed, 4 access site hematomas, 1 popliteal artery pseudoaneurysm, 2 fetal deaths, 1 preterm delivery, and 2 rethromboses	D
Goldenberg et al (38)	Observational study (retrospective cohort)	22	To compare a thrombolytic regimen vs standard anticoagulation for acute, occlusive DVT	The thrombolytic regimen was associated with a decreased odds of PTS at 18–24 mos compared with standard anticoagulation alone (adjusted OR, 0.018, 95% CI, <0.001–0.483; *P* = .02)	D
Avila et al (39)	Systematic review/meta-analysis	109 (28 studies)	To describe the outcomes of children with MTS presenting with DVT	PTS was seen in 61% of the patients, DVT recurrence in 38%, and complete vessel patency posttreatment in 65%. Recurrent thrombosis predicted PTS (OR, 3.36; 95% CI, 1.28–8.82)	C
Said et al (40)	Observational study (retrospective case series)	22	To report on an institution's experience in the management of phlegmasia cerulea dolens	Limb amputation was required in a third of patients who underwent CDT or percutaneous thrombectomy alone. Death was highest after percutaneous thrombectomy alone (66%), followed by PCDT alone (50%)	D
Comerota et al (41)	Observational study (cross-sectional)	98	To evaluate whether CDT for IFDVT is associated with improved health-related QoL, compared with standard anticoagulation and whether health-related QoL outcome in the thrombolysis group is related to lytic success	Patients treated with CDT reported better overall physical functioning (*P* = .046), less stigma (*P* = .033), less health distress (*P* = .022), and fewer postthrombotic symptoms (*P* = .006), compared with the patients treated with anticoagulation alone. Within the CDT group, phlebographically successful lysis correlated with improved health-related QoL (*P* =.038)	D

CDT = catheter-directed thrombolysis; CFV = common femoral vein; CI = confidence interval; DVT, deep vein thrombosis; ETR, endovascular thrombus removal; HR = hazard ratio; IFDVT = iliofemoral deep vein thrombosis; MD = mean difference; MT = mechanical thrombectomy; MTS = May-Thurner Syndrome; OR, odds ratio; PTS = postthrombotic syndrome; PCDT = pharmacomechanical CDT; QALY = quality-adjusted life year; QoL = quality of life; RR = relative risk; US = ultrasound.

SUPPLEMENTAL REFERENCES (APPENDIX C)

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