

Safety of catheter-directed thrombolysis for the treatment of acute lower extremity deep vein thrombosis

A systematic review and meta-analysis

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Abstract

Background: Despite established guidelines, catheter-directed thrombolysis (CDT) for the management of acute lower extremity deep vein thrombosis (DVT) should not be overstated because the risks of CDT are uncertain. We performed a meta-analysis to comprehensively and quantitatively evaluate the safety of CDT for patients with acute lower extremity DVT.

Methods: Relevant databases, including PubMed, Embase, Cochrane, Ovid MEDLINE, and Scopus, were searched up to January 2017. The inclusion criteria were applied to select patients with acute lower extremity DVT treated by CDT or compared CDT with anticoagulation. In case series studies, the pooled estimates of safety outcomes for complications, pulmonary embolism (PE), and mortality were calculated across studies. In studies comparing CDT with anticoagulation, summary odds ratios (ORs) were calculated.

Results: Of the 1696 citations identified, 24 studies (6 comparing CDT with anticoagulation and 18 case series) including 9157 patients met the eligibility criteria. In the case series studies, the pooled risks of major, minor, and total complications were 0.03 (95% confidence interval [CI]: 0.02–0.04), 0.07 (95% CI: 0.05–0.08), and 0.09 (95% CI: 0.08–0.11), respectively; other pooled risk results were 0.00 for PE (95% CI: 0.00–0.01) and 0.07 for mortality (95% CI: 0.03–0.11). Our meta-analysis of 6 studies comparing the risk of complications and PE related to CDT with those related to anticoagulation showed that CDT was associated with an increased risk of complications (OR=4.36; 95% CI: 2.94–6.47) and PE (OR=1.57; 95% CI: 1.37–1.79).

Conclusion: Acute lower extremity DVT patients receiving CDT are associated with a low risk of complications. However, compared with anticoagulation, CDT is associated with a higher risk of complications and PE. Rare mortality related to thrombolytic therapy was reported. More evidence should be accumulated to prove the safety of CDT.

Abbreviations: CDT = catheter-directed thrombolysis, CI = confidence interval, DVT = deep vein thrombosis, OR = odds ratio, PE = pulmonary embolism, RCT = randomized clinical trial, VTE = venous thromboembolism.

Keywords: catheter-directed thrombolysis, meta-analysis, safety, systematic review, venous thrombosis

1. Introduction

Deep vein thrombosis (DVT) is widely prevalent, and the incidence of DVT in the leg is between 48 and 182 per 100,000 in

the population each year.^[1] As the population ages, the incidence of DVT is steadily increasing.^[2] Additionally, approximately one-third of patients with primary DVT may develop asymptomatic (silent) pulmonary embolism (PE).^[3,4] Venous thromboembolism (VTE) is related to significant morbidity and mortality, not only because DVT can exert a great influence on treatment and prognosis for patients but also because it represents a significant clinical and economic disease burden on healthcare systems.^[5] Hence, the importance of treatment for DVT cannot be overemphasized. The immediate goals of the successful management of DVT is essential to minimize the risk of PE, mortality, and recurrent DVT in the short-term with acceptable complication rates, including those of bleeding.^[6]

Anticoagulation treatment is mainly aimed at the prevention of PE and recurrent DVT.^[7] Regrettably, over half of DVT patients will develop some degree of postthrombotic syndrome (PTS) in the follow-up of posttherapy.^[8] Elastic compression stockings are recommended for the prevention of PTS in DVT patients by previous guidelines^[9,10]; unfortunately, a recent meta-analysis of 6 randomized controlled trials including 1462 patients reported no use of elastic compression stockings to prevent PTS.^[5] Catheter-directed thrombolysis (CDT) uses the local delivery of plasminogen-activating agents directly into the thrombus, with an effective result to prevent PTS for acute lower extremity DVT

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patients, has been suggested by the American College of Chest Physicians antithrombotic therapy for VTE disease chest guideline; however, the recommendation based on low-quality evidence, making it weak.^[7] The safety of the patients is of great concern with measures to reduce bleeding complications and prevent PE.^[11] To address this dilemma, we performed this systematic review and meta-analysis to assess the safety of CDT including the incidence of PE, complication, and mortality after incident acute lower extremity DVT.

2. Methods

2.1. Data source and searches

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement for reporting in this meta-analysis.^[12] The literature search was performed using Ovid MEDLINE (1946 to January 2017), PubMed (January 31, 2017), Embase (1974 to January 2017), Cochrane Library (2016), and Scopus (1960 to January 2017). Boolean logic was used with search terms, including “catheter-directed thrombolysis” OR “catheter-directed therapy” OR “catheter-directed treatment” AND “deep vein thrombosis” OR “venous thromboembolism” (see example search in Table 1). Additional studies identified through the reference list from the selected articles were reviewed. Endnote software was used to manage citations obtained through the database search.

2.2. Selection standards

Two authors (WL, ZCL) independently established the study eligibility; any difference in opinion concerning eligibility was resolved by discussion or by consulting the corresponding author (MSY) and research team. All abstracts were reviewed using inclusion and exclusion criteria to narrow the selection of studies considered for the systematic review and meta-analysis. The studies had to meet the following criteria: studies about CDT to treat acute lower extremity DVT or studies compared CDT plus anticoagulation with anticoagulation alone; randomized clinical trials (RCTs), nonrandomized comparative studies, and case series studies; studies reporting the data on one or more study outcomes (PE, mortality, complication); patients ≥ 18 years old; sample size ≥ 10 patients; and articles published in peer-reviewed English studies. Studies were excluded if they were studies irrelevant to CDT; studies that reported chronic or upper DVT; studies that provided no useful data; and studies that were case reports or duplicate articles.

2.3. Data extraction

Data were extracted from all included studies by 2 independent reviewers (WL, ZCL). Disagreements about discrepancy were resolved by consulting the corresponding author. We extracted the first author, publication year, study design, region, mean age, the ratio of men to women, treatment method, thrombolytic

agent, safety outcomes (PE, mortality, and complication), the time of follow-up, and method of DVT diagnosis.

2.4. Assessment of bias risk

Assessment of the bias risk of the included studies was independently performed by 2 investigators. The quality of the included RCT studies was assessed using the Jadad scale, and the quality items scored were as follows: studies' description of randomization (2 points), blinding (2 points), and attrition information (1 point). Scores ≤ 2 were divided into low-quality literature and ≥ 3 were divided into high-quality literature.^[13] All included nonrandomized comparative and case series studies were appraised by The Newcastle–Ottawa scale.^[14] The quality of a study was judged on the selection of the study groups, comparability of the groups, and ascertainment of the outcomes. High quality was judged if studies received a star in every domain.

2.5. Definition of safety outcomes

The safety outcomes were the occurrence of PE, complication, and mortality.

- (1) PE: the occurrence of PE was based on the reports of computed tomography pulmonary angiography
- (2) Complications: the outcomes of major and minor complications were defined as follows: minor complication – if no therapy or nominal therapy was required and included overnight admission for observation; major complication – required therapy, longer hospitalization, or caused permanent adverse sequelae or death
- (3) Mortality: the rate of death related to thrombolytic treatment

2.6. Statistical analysis

We used the software Stata 12.0 (Stata Corporation, College Station, TX) to perform the meta-analysis. The data on the safety outcomes in the case series studies were pooled proportions, and the data in RCT or nonrandomized comparative studies were extracted to calculate odds ratios (ORs) and associated 95% confidence intervals (CIs). All meta-analyses were performed using both fixed- and random-effects models for combining proportions. Cochrane Q statistic and I^2 were statistics calculated to provide information about heterogeneity between studies. I^2 statistic $< 25\%$ was considered as low heterogeneity, and I^2 statistic $> 50\%$ was considered as high heterogeneity, according to the method suggested by Higgins et al.^[15] The publication bias was tested using the Egger regression asymmetry test^[16] and Begg-adjusted rank correlation test.^[17] Additionally, we performed subgroup analyses based on the thrombolytic agent and study design. Several sensitivity analyses were performed to test the robustness of our findings. All statistical tests were 2 tailed.

2.7. Ethics approval

The ethical approval was not necessary in our study because of the meta-analysis study design.

3. Results

3.1. Literature search

After the database searches, 1684 articles were retrieved and a further 12 potential articles were identified from citations. In total, 734 unique citations were identified by our electronic

Table 1

The example search in PubMed used the search terms below.

```
#1 Catheter-directed thrombolysis
#2 Catheter-directed therapy
#3 Catheter-directed treatment
#4 Deep vein thrombosis
#5 Venous thromboembolism
#6 #1 OR #2 OR #3
#7 #4 OR #5
#8 #6 AND #7
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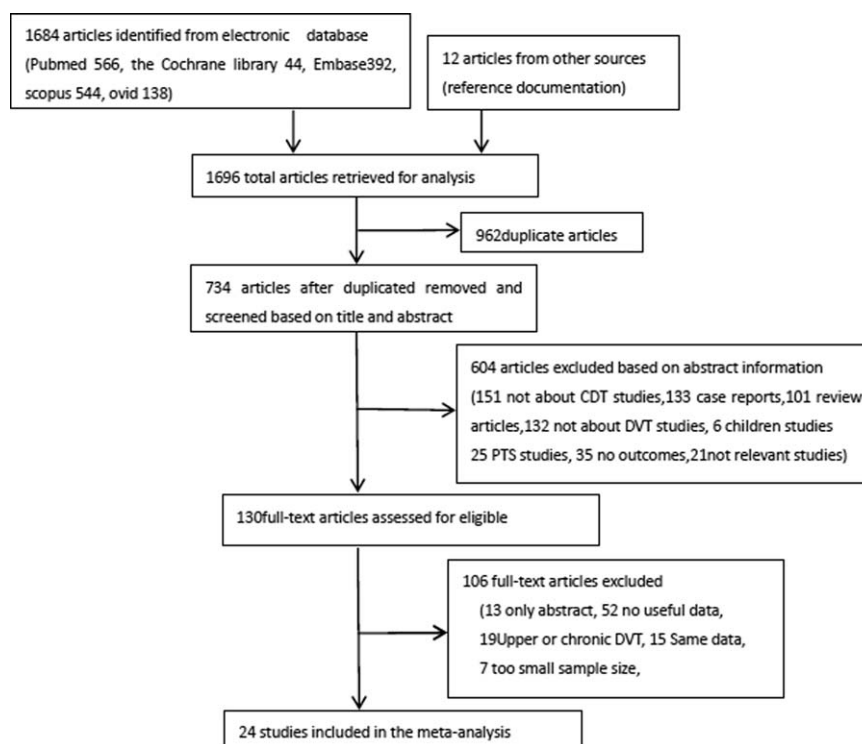


Figure 1. Flow chart of the study selection.

searches after the deletion of duplicate publications by screening the study titles and abstracts. After applying the inclusion and exclusion criteria, 24 articles were considered for our meta-analysis, among which 18 case series articles^[18–35] involving 1538 patients and another 6 were articles^[36–41] comparing CDT with anticoagulation involving 7619 patients fulfilled the eligibility criteria. The data abstraction process is shown in Fig. 1.

3.2. Study characteristics

Eighteen case series articles including 8 prospective^[18–20,23,24,26,28,31] and 10 retrospective studies^[21,22,25,27,29,30,32–35] and 6 comparison articles including 3 RCTs^[38–40] and 3 nonrandomized comparative articles^[36,37,41] were all published in peer-reviewed journals. Except for 1 study^[30] that did not describe the method of DVT diagnosis, the others confirmed the presence of DVT using Duplex ultrasound or venography. When CDT was performed, rt-PA, Urokinase, Alteplase, or Retavase was infused. The characteristics of the included studies are summarized in Table 2.

3.3. Meta-analysis of studies comparing CDT with an anticoagulation group

3.3.1. Complications. All 6 comparative studies^[36–41] reported complications posttreatment.

Compared with anticoagulation, CDT showed a significant increase in the occurrence of complications (OR=4.36; 95% CI: 2.94–6.47; $P < .001$; $I^2 = 28.7\%$) (Fig. 2); 3 studies^[36,40,41] reported minor and major bleeding, and the pooled results showed the same results that CDT had a significant increase in the occurrence of minor (OR=2.01; 95% CI: 0.87–4.66; $P = .104$; $I^2 = 0.0\%$) (Fig. 3) and major bleeding (OR=3.19; 95% CI: 0.76–13.42; $P = .113$; $I^2 = 0.0\%$) (Fig. 4) compared with anticoagulation.

3.3.2. PE. Among 6 studies,^[36–41] 3 studies^[39–41] were eliminated because there were no events in both groups. Patients treated with CDT were significantly more likely to experience PE (OR=1.57; 95% CI: 1.37–1.79; $P < .001$; $I^2 = 0.0\%$) (Fig. 5).

3.3.3. Mortality. Five studies^[36,38–41] reported no deaths in both groups; only 1 study^[37] with a large sample size recorded in-hospital mortality in the 2 groups (CDT vs anticoagulation: 1.2% vs 0.9%, respectively).

3.4. Meta-analysis of case series studies on CDT

3.4.1. Complications. Fourteen case series studies^[19–24,26–29,32–35] reported complication outcomes posttreatment, in which 3 studies^[20,24,35] and 2 studies^[22,34] reported no events for major and minor complications, respectively. The complication rate ranged from 6% to 25% after CDT. The pooled data showed that the rate of total complications, minor complications, and major complications from high to low were 0.09 (95% CI: 0.08–0.11), 0.07 (95% CI: 0.05–0.08), and 0.03 (95% CI: 0.02–0.04), respectively. Moderate heterogeneity was detected for all 3 complication analyses (Figs. 6–8).

3.4.2. PE. Twelve studies^[18,19,21,23,25–31,33] were involved for PE data. Two of them^[18,19] only reported suspected PE, and 4 studies^[25,26,29,31] were excluded due to no events; thus, 6 studies^[21,23,27,28,30,33] were eventually included. Patients treated with CDT showed a zero rate of PE (0.00, 0.01). High heterogeneity ($I^2 = 0.807$; $P = .000$) was detected among the included studies (Fig. 9).

3.4.3. Mortality. Two studies^[19,35] reported mortality not related to the thrombolytic therapy, 3 studies^[18,25,31] reported no mortality during follow-up, and 3 studies^[28–30] reported

Table 2
Characteristics of the included studies in the meta-analysis.

Study	Design	Region	Mean age, y	Male/female (no)	Treatment method (no)	Thrombolytic agent	Outcomes	Follow-up	Method of DVT diagnosis
Studies compared CDT with anticoagulation									
AbuRahma et al 2001	prospective	USA	47	21/30	CDT+AA (18) vs AA (33)	Urokinase rt-PA	Major complications, PTS, patency rate	5 y	Venous duplex imaging/ iliofemoral phlebography
Bashir et al 2014	Retrospective	USA	53	3649/3539	CDT+AA (3594) vs AA (3594)	NA	Death, PE, hematoma, length of stay, charges	6 y	Principal discharge diagnosis
Elshtarawy et al 2002	RCT	Egypt	46	11/24	CDT+AA (18) vs AA (17)	Streptokinase	PTS, complete lysis	6 mo	Color duplex ascending venography
Ernden et al 2012	RCT, multicenter	Norway	52	119/70	CDT+AA (90) vs AA (99)	Alteplase	Complications, patency rate PTS, recurrent DVT	2 y	Routine ultrasound, or by venography or CT
Ernden et al 2009	RCT, multicenter	Norway	52	64/39	CDT+AA (50) vs AA (53)	Alteplase	iliofemoral patency, venous obstruction	6 mo	Routine ultrasound, or by venography or CT
Lee et al 2013	Retrospective	USA	53	27/26	CDT+AA (27) vs AA (26)	Urokinase	Patency rate, complications, PTS, venous function	15 mo	Venography ultrasound
Case series studies without a comparison group									
Baekgaard et al 2010	Prospective	Denmark	29	23/78	CDT (101)	rt-PA	Vein reflux, PTS, rethrombosis, patency rate, mortality	6 y	Ultrasomography
Bjarnason et al 1997	Prospective	USA	47	27/50	CDT (77)	Urokinase	Complication, PE, mortality patency rate	5 y	Duplex ultrasound
Casella et al 2007	Prospective	Brazil	4/14	NR	CDT (18)	rt-PA	Complete lysis, rethrombosis, bleeding, venous reflux	1 y	Duplex-scan
Du et al 2015	Retrospective	China	59	207/220	CDT (427)	Urokinase	Complete lysis, patency rates, PTS, complication, PE	2 y	Ultrasound or digital subtraction angiography
Duan et al 2015	Retrospective	China	65	49/57	CDT (106)	Urokinase	Complication, rethrombosis, patency rate	2 y	Conventional venography
Engelberger et al 2014	Prospective	Switzerland	46	35/52	UACDT (87)	rt-PA	PTS, patency, complication, rethrombosis, PE, complete lysis	1 y	Duplex sonography
Fiengo et al 2015	Prospective	UK	35	NR	CDT (24)	Urokinase	Complete lysis, PTS, vein reflux, complication	2 y	Ultrasound Doppler
Jackson et al 2005	Retrospective	USA	NR	14/14	CDT (28)	Urokinase Retavase rt-PA	Complete lysis, patency rate, PE, mortality	15 mo	Ultrasound
Köbel et al 2007	Prospective	Sweden	31	11/26	CDT+stent (37)	Alteplase	Complication patency	27 mo	Venography color Doppler scan
Li et al 2015	Retrospective	China	46	93/173	CDT (266)	Urokinase	PE, bleeding, complication complete lysis	NR	Computed tomography venography or ultrasound Doppler
Manninen et al 2012	Prospective	Finland	48	26/30	CDT (56)	Urokinase	Complication, complete lysis, patency, PTS, PE, mortality	3.5 y	Ultrasound venography
Park et al 2008	Retrospective	Korea	55	10/24	CDT (34)	Urokinase	Complete lysis, recurrence, PTS, complication, PE mortality	16 mo	Duplex scan computed venography
Protack et al 2007	Retrospective	USA	48	27/42	CDT (69)	rt-PA	Rethrombolysis, complete lysis, PE, mortality	2.1 y	NR
Sharifi et al 2013	Prospective	USA	52	19/14	CDT (33)	rt-PA	complete lysis, PE, mortality, complication	22 mo	Venous duplex imaging.
Sliessen et al 2005	Retrospective	Denmark	31	7/38	CDT (45)	Alteplase	Complication, PE vein reflux, rethrombosis	1 y	Doppler ultrasound
Strijkers et al 2012	Retrospective	Germany	42	18/19	USGDT (37)	Urokinase rt-PA	Patency rate, complete lysis, complications, rethrombosis	1 y	Duplex sonography
Warner et al 2013	Retrospective	USA	43	9/23	CDT+stent (32)	Alteplase	Complication, patency rate	29 mo	Venous duplex ultrasonography
Xue et al 2014	Retrospective	China	64	25/36	CDT+stent (61)	Urokinase	Patency, mortality, PTS complication	5 y	duplex

AA = anticoagulation, CDT = catheter-directed thrombolysis, DVT = deep vein thrombosis, NR = not reported, PE = pulmonary embolism, PTS = postthrombotic syndrome, QOL = quality of life.

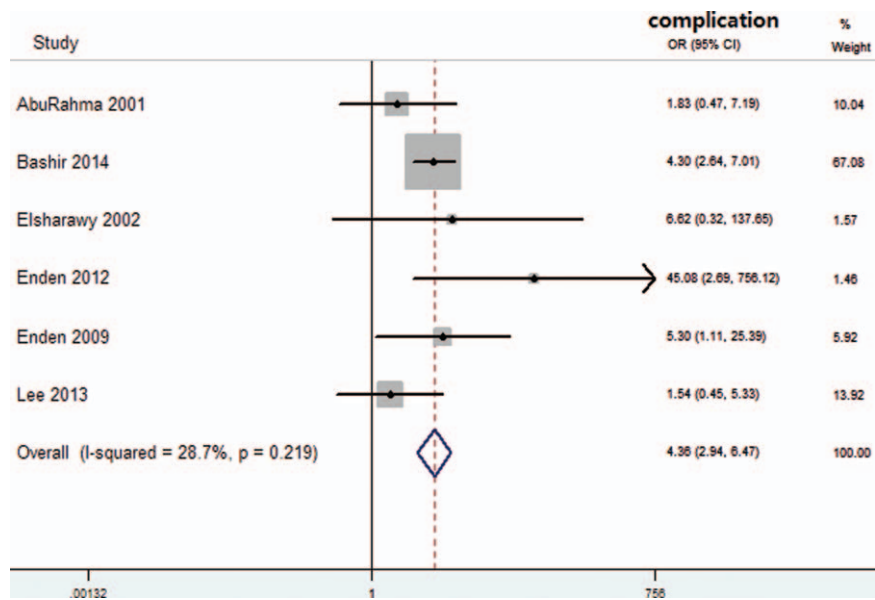


Figure 2. Forest plot showing pooled complication after CDT and CIs from CDT compared with that from anticoagulation. CDT = catheter-directed thrombolysis, CI = confidence interval.

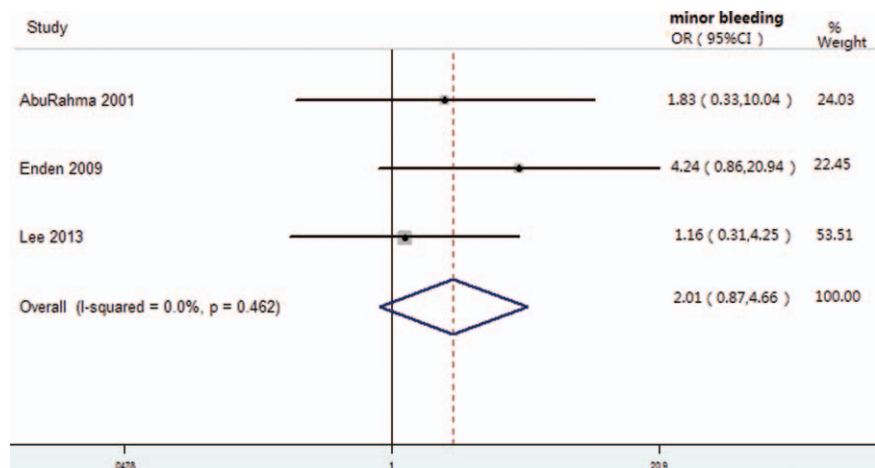


Figure 3. Forest plot showing pooled minor bleeding after CDT and CIs from CDT compared with that from anticoagulation. CDT = catheter-directed thrombolysis, CI = confidence interval.

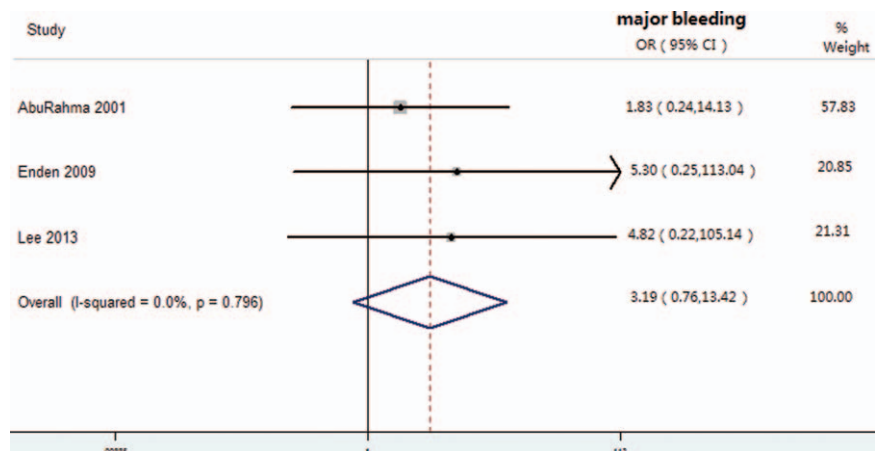


Figure 4. Forest plot showing pooled major bleeding after CDT and CIs from CDT compared with that from anticoagulation. CDT = catheter-directed thrombolysis, CI = confidence interval.

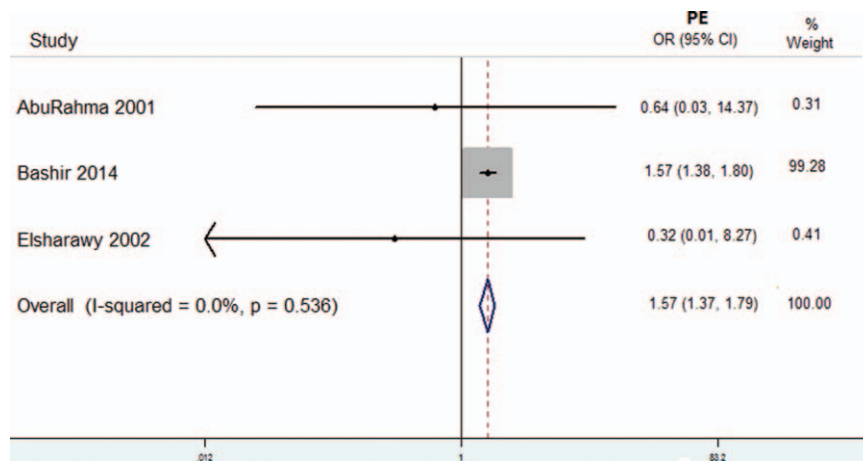


Figure 5. Forest plot showing pooled PE after CDT and CIs from CDT compared with that from anticoagulation. CDT=catheter-directed thrombolysis, CI=confidence interval, PE=pulmonary embolism.

mortality posttreatment. The pooled mortality rate was 0.07 (95% CI: 0.03–0.11); I^2 was 63.8% ($P=.063$), indicating high heterogeneity.

3.5. Subgroup analyses

Subgroup analyses were performed to assess the outcomes by study design (Table 3) and use of different thrombolytic agent (Table 4). Regarding the rate of PE, that in the prospective studies was slightly lower than that in the retrospective studies. However, the rate of complication was higher in prospective

studies than in retrospective studies (Table 3). Subgroup analyses stratified by thrombolytic agent showed that the frequency of complication was lowest in urokinase studies, and PE occurred at a slightly lower frequency in rt-PA studies.

3.6. Publication bias

No significant publication bias was conducted on complications. Publication bias evaluation on the 2 endpoints (PE and mortality) was not detected due to the limited number of studies involved^[42] (Table 5).

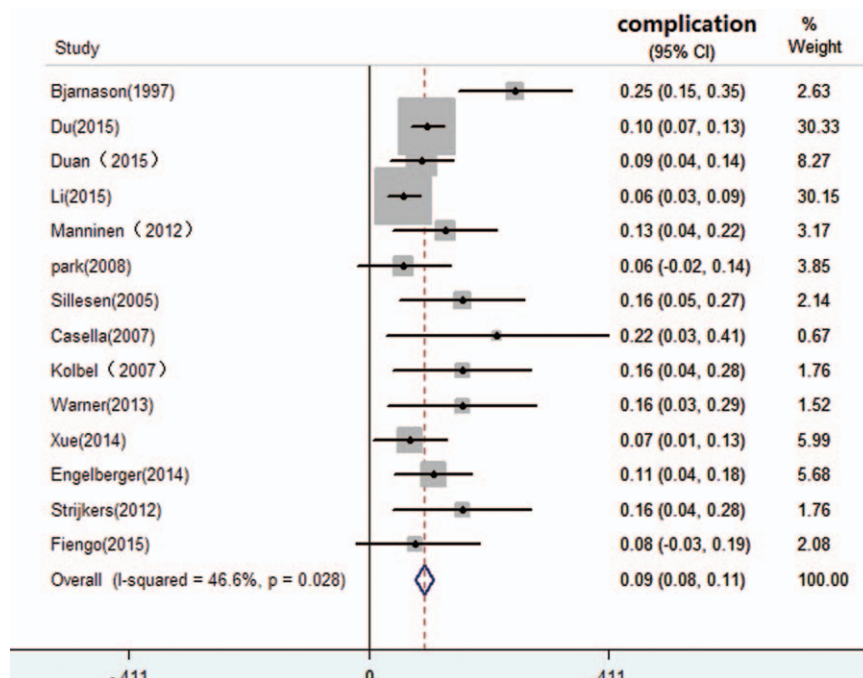


Figure 6. Forest plot showing pooled complication rates after CDT and CIs from the case series studies CDT=catheter-directed thrombolysis, CI=confidence interval.

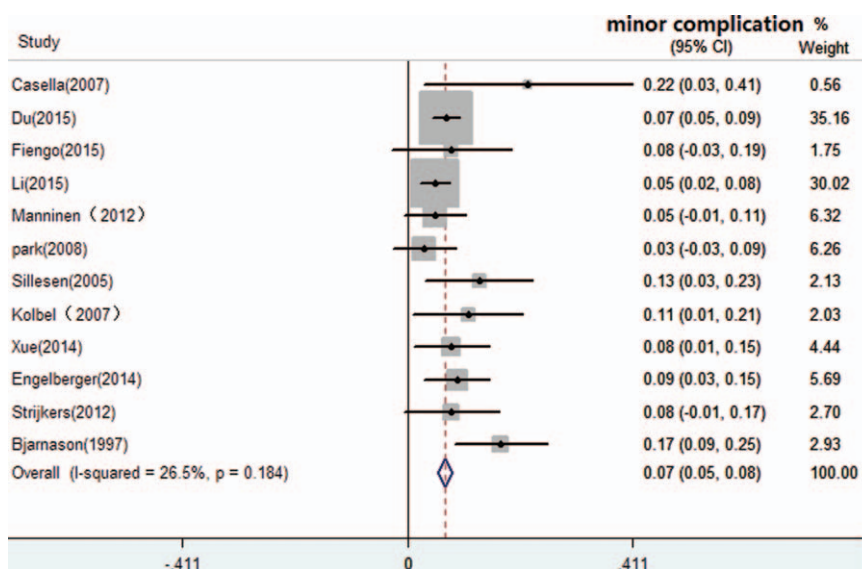


Figure 7. Forest plot showing pooled minor complication rates after CDT and CIs from the case series studies. CDT=catheter-directed thrombolysis, CI=confidence interval.

3.7. Quality assessment

When assessing RCTs by the Jadad score, all 3 RCTs^[38–40] had an adequate description for randomization and showed blinded assessment of outcomes. The information was provided in all RCTs. Therefore, the 3 RCTs were generally of high quality (Table 6). All nonrandomized comparative and case series studies were assessed by the Newcastle–Ottawa scale. Of the 11 studies^[18–21,23,26,29,30,32,33,36] that were generally of high quality, 4 studies^[24,27,35,37] had an outcome present at the start of the study, 2 studies^[24,31] had no assessment of outcome, and 5 studies^[22,25,28,34,41] had no adequate follow-up; 1 study^[27] had no report of the length of follow-up. Ten studies^[22,24,25,27,28,31,34,35,37,41] were generally of low quality (Table 7).

4. Discussion

CDT has been developed as an alternative therapy in patients with lower extremity DVT since the early 1990s^[43] because the advantages include rapid venous thrombolysis, a minimally invasive character, quicker symptomatic relief, and prevention of PTS. However, the safety of the DVT patients is of great concern with measures to reduce complications and mortality and prevent PE. The latest Antithrombotic Therapy for VTE Disease CHEST Guideline notes that the balance of the risks and benefits with CDT is uncertain.^[7] In our meta-analysis, patients with acute lower extremity DVT receiving CDT are associated with a high risk of complications and PE than those receiving anticoagulation. However, in our case series pooled results, CDT is associated with a low risk of complication.

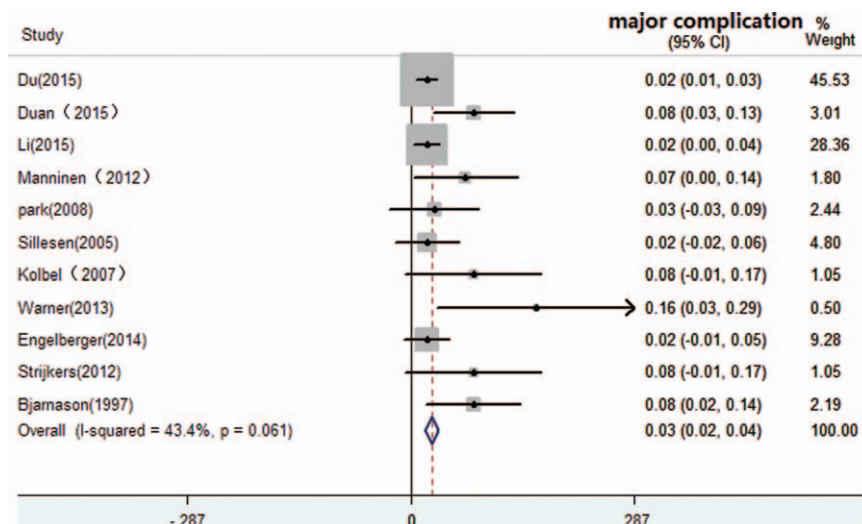


Figure 8. Forest plot showing pooled major complication rates after CDT and CIs from the case series studies. CDT=catheter-directed thrombolysis, CI=confidence interval.

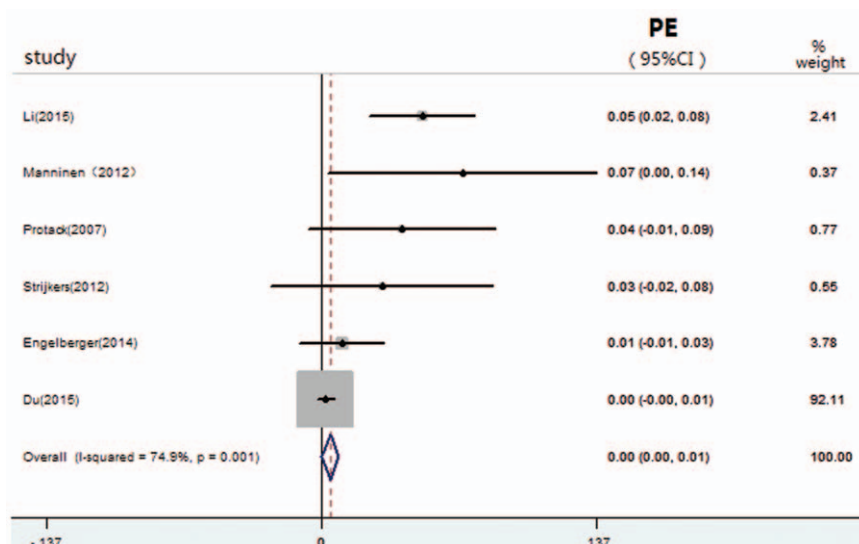


Figure 9. Forest plot showing pooled PE rates after CDT and CIs from the case series studies. CDT = catheter-directed thrombolysis, CI = confidence interval, PE = pulmonary embolism.

Table 3

Subgroup of prospective and retrospective study design.

	Prospective				Retrospective			
	N	Rate (95% CI)	I ² %	P	N	Rate (95% CI)	I ² %	P
Complication	6	0.14 (0.10,0.18)	35.5	.171	8	0.08 (0.07,0.10)	25.6	.225
PE	2	0.03 (-0.02,0.09)	64.5	.093	5	0.04 (0.00,0.08)	85.2	.000

N, the number of studies; P, P for heterogeneity. CI=confidence interval, PE=pulmonary embolism.

Table 4

Subgroup analyses of urokinase, rt-PA, alteplase, and more than or equal to 2 thrombolytic agents.

	Urokinase				rt-PA				Alteplase				≥2 Thrombolytic agents			
	N	Rate (95%)	I ² %	P	N	Rate (95%)	I ² %	P	N	Rate (95%)	I ² %	P	N	Rate (95%)	I ² %	P
Complication	8	0.09 (0.07,0.10)	58.3	.019	2	0.12 (0.06,0.18)	11.9	.287	3	0.16 (0.09,0.23)	0.0	1.000	1	0.16 (0.04,0.28)	NA	NA
PE	3	0.03 (-0.01,0.08)	87.8	.000	2	0.02 (-0.01,0.04)	25.5	.247	1	0.22 (0.09,0.35)	NA	NA	1	0.03 (-0.02,0.08)	NA	NA

N, the number of studies; P, P for heterogeneity. CI=confidence interval, NA=not applicable, PE=pulmonary embolism.

Complications include major bleeding, minor bleeding, fever, hematoma, and pain in all of the included studies. The pooled results of major complications (0.03) from case series studies were under the suggested threshold made by the Society of Interventional Radiology.^[44] No threshold value was found for the minor bleeding rates, which should be as minimal as possible.^[44] Rigorous acute lower extremity DVT inclusion criteria may explain the good safety outcome of complications. However, in our findings, compared with anticoagulation CDT, there was a nearly 3-fold increased likelihood of major bleeding. A systematic review that included 9 trials of anticoagulation and thrombolysis reported higher rates of bleeding among patients

treated with thrombolytic agents (RR, 2.23; 95% CI, 1.41–3.52).^[45] Another meta-analysis showed that, compared with anticoagulation alone, CDT was also associated with a significant increase in the occurrence of major bleeding events (OR: 2.06; 95% CI: 1.62–2.62).^[46] Several reasons could explain the raised risk of bleeding with CDT. For example, an older age of treated people in our comparative studies (the average age ranged from 46 to 53 years) (Table 1), a longer duration of thrombolysis

Table 6

Jadad scale for randomized clinical trials (RCTs) quality assessment.

Study	Description of randomization	Blinding	Attrition information	Overall quality
Elsharawy et al 2002	2	2	1	High
Enden et al 2012	2	2	1	High
Enden et al 2009	2	2	1	High

Table 5

Publication bias.

	Begg test	Egger test
Complication	0.337	0.715

Table 7**The Newcastle–Ottawa scale for non-RCTs and noncomparison studies quality assessment.**

Study	Selection of exposed and nonexposed cohorts			Outcome present at start of study	Comparability of cohorts	Outcome of interest			Overall quality
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure			Assessment of outcome	Length of follow-up	Adequate of follow-up	
Studies with a comparison group									
AbuRahma et al 2001	*	*	*	*	*	*	*	*	High
Bashir et al 2014	*	*	*	NA	*	*	*	*	Low
Lee et al 2013	*	*	*	*	*	*	*	N	Low
Studies without a comparison group									
Baekgaard et al 2010	*	NA	*	*	NA	*	*	*	High
Bjarnason et al 1997	*	NA	*	*	NA	*	*	*	High
Casella et al 2007	*	NA	*	*	NA	*	*	*	High
Du et al 2015	*	NA	*	*	NA	*	*	*	High
Duan et al 2015	*	NA	*	*	NA	*	*	NR	Low
Engelberger et al 2014	*	NA	*	*	NA	*	*	*	High
Fiengo et al 2015	*	NA	*	NA	NA	NR	*	*	Low
Jackson et al 2005	*	NA	*	*	NA	*	*	NR	Low
Kölbl et al 2007	*	NA	*	*	NA	*	*	*	High
Li et al 2015	*	NA	*	NA	NA	*	NR	*	Low
Manninen et al 2012	*	NA	*	*	NA	*	*	NR	Low
Park et al 2008	*	NA	*	*	NA	*	*	*	High
Protack et al 2007	*	NA	*	*	NA	*	*	*	High
Sharifi et al 2013	*	NA	*	*	NA	NR	*	*	Low
Sillesen et al 2005	*	NA	*	*	NA	*	*	*	High
Strijkers et al 2012	*	NA	*	*	NA	*	*	*	High
Warner et al 2013	*	NA	*	*	NA	*	*	NR	Low
Xue et al 2014	*	NA	*	NA	NA	*	*	*	Low

Only comparison studies with stars in all domains were considered high quality. In noncomparison studies, the comparability of cohort was excluded given study design. Only studies that had stars in all domains besides from comparability were considered high quality. Retrospective studies were all assumed to have adequate follow-up. NA = not applicable, NR = not reported, RCT = randomized clinical trial.

*Meet the quality assessment.

therapy (more than 24 hours).^[36,40,41] The saphenous vein or popliteal vein was the common puncture site in our included studies, and most bleeding complications were puncture-related bleeding episodes, with few distant bleeding complications. We inferred that CDT performed by experienced endovascular surgeons or interventional radiologists would be beneficial for the reduction of puncture-related bleedings.

The risk of PE was markedly increased in patients with previous asymptomatic PE and heart disease,^[11] and inferior vena cava filters are recommended in such patients to prevent the passage of the thrombus to the pulmonary arteries and have been gaining popularity.^[27] Regarding the results of the case series meta-analysis, the pooled incidence of PE (0.00) was under a suggested threshold occurrence (<2%) for symptomatic PE.^[44] Almost no PE occurred because half of the included case series studies involved the use of inferior vena cava filters during lysis. A summary review about symptomatic PE during CDT has been reported in approximately 1%, and fatal PE is also rare.^[47] However, the low incidence of PE may be effected by under-reported for drug use during CDT interventional procedure in retrospective or prospective trail, so the results are only for reference. Compared with anticoagulation therapy, CDT was associated with an increase in PE (1.5-fold)^[48]; the large sample size in our included studies may be the reason for the increased incidence.^[37] A systematic review of percutaneous mechanical thrombectomy (PMT) in the treatment of DVT that included 16 retrospective case series of 481 patients have reported a <1% incidence of symptomatic PE.^[49] Future studies comparing CDT with PMT are expected to provide more safety results.

No threshold value was found regarding mortality. However, in our paper, the pooled mortality rate was high (0.07) because

13% of patients from one of the included studies had a malignancy.^[30] Hence, the mortality outcomes should be considered cautiously when interpreting the findings from our meta-analysis. In the CaVenT study, 3 deaths occurred in the CDT group (3/90) compared with anticoagulation therapy, which was associated with a decrease in mortality (RR: 0.36; 95% CI: 0.10–1.30).^[50] No procedure-related deaths were reported from the systematic review of PMT in patients with DVT.^[49] Until now, it is very difficult to compare results from studies that report data about overall mortality with those reporting DVT-specific mortality, which need more research during interventional procedure.

Although CDT has an effective result to prevent PTS for acute lower extremity DVT patients,^[7] PTS as an efficacy outcome is not discussed in this study.

Our subgroup analyses presented a larger difference in complications between prospective (0.14) and retrospective studies (0.08). The reasons to explain the result could be that, in the original prospective studies: there was a small sample size and there was incomplete standardization of the assay procedures, increasing the study complications.^[19,20] Subgroup analyses stratified by thrombolytic agent showed that urokinase had comprehensively better safety than others to reduce the risk of complications and PE. However, urokinase has a 4-fold longer half-life than rt-PA.^[11]

Several limitations should be acknowledged when interpreting the findings from our meta-analysis. First, almost half of the studies were retrospective studies; thus, that recall bias cannot be ruled out. Second, only peer-reviewed English studies were included; non-English language journals had been neglected.

Nevertheless, our study also has strength because we comprehensively analyzed the safety results of CDT treatment, providing available evidence concerning the safety of CDT.

5. Conclusion

Our meta-analysis indicates that the use of CDT is associated with a low risk of complications. However, compared with anticoagulation, CDT shows a significant increase in complications and PE. Pharmacomechanical CDT, ultrasound-accelerated CDT, and a combination with other assistive technology are thoughtful considerations to reduce the disadvantages of CDT. Furthermore, more well-designed RCTs to clarify and improve the safety of CDT treatment are needed.

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