# Catheter-directed Thrombolysis Compared with Conventional Anticoagulation Therapy in the Management of Acute Deep Vein Thrombosis: A Systematic Review and Meta-analysis

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## Abstract

**Background:** The benefit of catheter-directed thrombolysis (CDT) in patients with acute deep vein thrombosis (DVT) remains controversial. Hence, we carried out this meta-analysis to evaluate the efficacy and safety of CDT compared with conventional anticoagulation therapy (CAT) for post-thrombotic syndrome (PTS) in patients with acute DVT.

**Methods:** We conducted this systematic review in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. Pubmed was our search engine and the key words were DVT or iliofemoral vein thrombosis or CDT. Seven studies were gathered for meta-analysis.

**Results:** The forest plot of PTS showed that pooling effect (random effect) was significant (OR=0.325, 95% CI=0.142 to 0.744, p=0.008); this finding indicated that CDT was more efficient than CAT to relieve PTS in patients with DVT. The forest plot of early complete lysis of occluded vessels within 30 days showed that pooling effect was significant (OR=74.89, 95% CI=17.732 to 316.292, p<0.001); this finding indicated that CDT was associated with a higher rate of early complete lysis of occluded vessels within 30 days, as compared with CAT. The forest plot of 6-month iliofemoral patency also showed pooling effect was significant (OR=5.682, 95% CI=1.964 to 16.439, p=0.001). This finding indicated that CDT was associated with a higher rate of 6-month iliofemoral patency, as compared with CAT. The forest plot of major bleeding showed that pooling effect was significant (OR=1.74, 95% CI=1.498 to 2.022, p<0.001); this finding indicated CDT was associated with greater major bleeding risk than CAT.

**Conclusions:** In patients with acute DVT, CDT significantly improved PTS, early complete lysis of occluded vessels within 30 days and 6-month iliofemoral patency rate compared with CAT. However, CDT was associated with greater risk of major bleeding.

**Keywords:** catheter-directed thrombolysis, anticoagulation therapy, acute deep vein thrombosis, post-thrombotic syndrome

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## Background

Deep vein thrombosis (DVT) is a common medical problem highly associated with complications such as pulmonary embolism and post-thrombotic syndrome (PTS).[1-5] Although conventional anticoagulation therapy (CAT) effectively prevents thrombus extension, pulmonary embolism, recurrence and death, many patients still develop PTS.[1-5] Systemic thrombolysis is an alternative to treat DVT and prevent PTS. However, it carries a high risk of bleeding and the thrombolytic agent does not easily reach the occluded vessels. Catheter-directed thrombolysis (CDT) is a more effective method to deliver the thrombolytic agent to the thrombus occlusion site and limit bleeding complications.[3,4,6-9] However, the majority of studies on CDT are based on single center experience with no comparative group; only few studies are available to compare CDT with CAT. Most studies have small sample size, heterogeneous baseline characteristics, and different primary outcomes. Thus, we carried out this meta-analysis to evaluate the efficacy and safety of CDT compared with CAT for PTS in patients with acute DVT.

## Methods

We conducted this systematic review in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. Pubmed was our search engine and the key words were DVT or iliofemoral vein thrombosis or CDT. The language was limited to English. Animal studies were excluded. Our inclusion criteria were 1. Any study comparing the effect of CDT with CAT 2. Any study reporting one or more efficacy or safety outcomes. In all patients, anticoagulation was initiated with either low molecular weight heparin or unfractionated heparin, and then shifted to warfarin to keep the INR 2-3. Elastic compression stockings were recommended for the patients but were not well documented in all articles. CDT was performed via percutaneous entry either through the saphenous vein or popliteal vein under ultrasound guidance. Venography was then performed and a multiple side hole infusion catheter was advanced inside the occluded segment. Thrombolytic agents were infused via the infusion catheter for 48-72 hours.

The primary efficacy outcome was PTS. PTS was assessed by Villalta scale including five symptoms (pain, cramps, heaviness, pruritus and paresthesia) and six clinical signs (edema, skin induration, hyperpigmentation, vein ectasia, redness and calf compression pain). PTS was diagnosed if the score was over 5 points. The secondary efficacy outcomes were early complete lysis within 30 days and 6-month iliofemoral patency rate. The follow-up complete lysis rate or iliofemoral patency was evaluated by color duplex ultrasonography. Mortality or pulmonary embolism were not counted as our outcome since the data were not available in most trials. The safety outcome was major bleeding. The definition of major bleeding was intracerebral hemorrhage or any clinically overt bleeding that resulted in therapy cessation, further hospitalization, severe sequela, death, or required transfusion or surgical intervention.

### Statistical Analysis

Assessment of quality of systematic review was through Cochrane risk of bias table. If any criteria failed to qualify, moderate risk of bias was considered. If 2 or more criteria failed to qualify, high risk of bias was considered. Stata 14.0 (Stata Corporation, College Station, TX, USA) was used to perform the meta-analysis. Odds ratios and 95% confidence interval (CI) were used to present binary outcomes. The Mantel-Haenszel method was used to calculate the pooling effect and random effects model was used to estimate overall odds ratio. Two-sided p-values less than 0.05 were considered statistically significant. Heterogeneity of studies was tested by Cochrane's Q test. A significance level of less than 0.05 for

the chi-square test was considered as evidence of heterogeneity. I2 statistics <50% was considered as low heterogeneity. Forest plot was used for graphical display of estimated results from a number of studies along with the overall results. Sensitivity analysis was performed by excluding studies respectively. The publication bias was checked visually by funnel plot and statistically by Egger's test.

## Results

Figure 1 is the PRISMA flow chart. Pubmed was our search engine and the initial search yielded 146 results. After reviewing the titles and abstracts, 99 articles were excluded. Another 40 articles were excluded because 26 of them were single arm CDT registry studies, 4 were systematic review articles, 4 compared CDT with mechanical thrombectomy, 4 were single arm ultrasound accelerated CDT registries, and one had overlapping population. Only 7 articles remained for meta-analysis.

Table 1 shows the summary of the 7 enrolled studies, 4 of which were randomized control trials (RCT) and the remaining three were observational studies. Table 2 shows the outcomes in the CDT group and the CAT group. Table 3 shows the result of Cochrane quality assessment. The risks of bias varied from moderate to high because most studies were not RCTs and no blinding was conducted in these studies.

### Primary Efficacy Outcome

The primary efficacy outcome, PTS, is shown in Table 2 and Figures 2A to 5A. The heterogeneity was statistically significant ($p<0.05$, I-squared=82.5%), indicating high heterogeneity among the 5 studies (Figure 2A). The forest plot of PTS showed that pooling effect (random effect) was significant (OR=0.325, 95% CI=0.142 to 0.744, p=0.008); this finding indicated CDT was more efficient to relieve PTS in patients with DVT, as compared with CAT (Figure 3A). Sensitivity analysis is shown in Figure 4A; omitting Vedantham et al.'s study changed the pooling effect significantly. The funnel plot is not symmetric, indicating the existence of publication bias (Figure 5A).

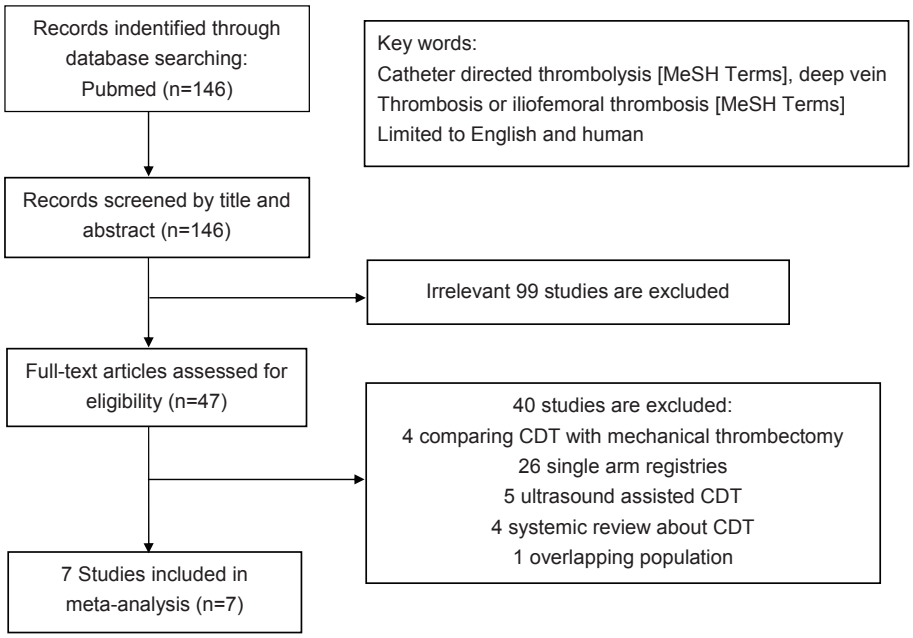


**Figure 1.** PRISMA flow chart.

**Table 1.** Literature review of previous studies

| Study (year) | Study type | Region | Patient numbers | Mean age (year) | Male (%) | Compared groups (no.) | Thrombolytic agent | Duration of Follow-up |
|---|---|---|---|---|---|---|---|---|
| AbuRahma et al. (2001) | Prospective | USA | 51 | 47 | 39 | CDT (18) vs. CAT (33) | Urokinase, rtPA | 5 years |
| Elsharawy et al. (2002) | RCT | Egypt | 35 | 46 | 31 | CDT (18) vs. CAT (17) | Streptokinase | 6 months |
| Enden et al. (2012) | RCT, multicenter | Norway | 189 | 52 | 63 | CDT (90) vs. CAT (99) | Alteplase | 2 years |
| Lee et al. (2013) | Retrospective | Taiwan | 52 | 62 | 51 | CDT (26) vs. CAT (26) | Urokinase | 15 months |
| Bashir et al. (2014) | Retrospective | USA | 7188 | 53 | 51 | CDT (3594) vs. CAT (3594) | NA | 6 years |
| Srinivas et al. (2014) | RCT | USA | 55 | 49 | 30 | CDT (27) vs. CAT (28) | Streptokinase | 6 months |
| Vedantham (2017) | RCT | USA | 692 | 53 | 429 | CDT (337) vs CAT (355) | tPA | 2 years |

CAT=conventional anticoagulation therapy; CDT=catheter-directed thrombolysis; NA=not available; PTS=post-thrombotic syndrome; RCT= randomized trial.

**Table 2.** Outcomes in CDT and CAT groups

| Study (year) | Patient numbers | | Postthrombotic syndrome | | Early complete lysis within 30 days | | 6-month iliofemoral patency rate | | Major bleeding complications | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CDT | CAT | CDT | CAT | CDT | CAT | CDT | CAT | CDT | CAT |
| AbuRahma et al. (2001) | 18 | 33 | 4 | 23 | 15 | 1 | 15 | 8 | 2 | 2 |
| Elsharawy et al. (2002) | 18 | 17 | - | - | 11 | 0 | 13 | 2 | 0 | 0 |
| Enden et al. (2012) | 90 | 99 | 37 | 55 | - | - | 58 | 45 | 8 | 0 |
| Lee et al. (2013) | 26 | 26 | 5 | 13 | 14 | 0 | 18 | 10 | 2 | 0 |
| Bashir et al. (2014) | 3594 | 3594 | - | - | - | - | - | - | 488 | 302 |
| Srinivas et al. (2014) | 25 | 26 | 5 | 19 | - | - | - | - | - | - |
| Vedantham (2017) | 337 | 355 | 157 | 171 | - | - | - | - | 6 | 1 |

CAT=conventional anticoagulation therapy; CDT=catheter-directed thrombolysis

**Table 3.** Quality assessment of the articles included

| | | Quality criteria | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Random allocation? | Definition of inclusion/ exclus ion criteria? | Blinding? | Selection of a representative population group? | Use of identical treatment between groups except for the intervention? | Detailed reporting of the follow-up? | Risk of bias |
| 1 | AbuRahma et al. (2001) | b | a | 0 | a | a | a | High |
| 2 | Elsharawy et al. (2002) | a | a | 0 | a | a | a | Moderate |
| 3 | Enden et al. (2012) | a | a | 0 | a | a | a | Moderate |
| 4 | Lee et al. (2013) | b | a | 0 | a | a | a | High |
| 5 | Bashir et al. (2014) | b | a | 0 | a | a | a | High |
| 6 | Srinivas et al. (2014) | a | a | 0 | a | a | a | Moderate |
| 7 | Vedantham (2017) | a | b | 0 | a | a | a | Moderate |

Abbreviations of the interventions: a: adequate explanation in the text; b: inadequate explanation in the text; 0: not blinded; 1: single-blinded; 2: double-blinded.

### Secondary Efficacy Outcomes

The outcome of early complete lysis rate within 30 days, is shown in Table 2 and Figures 2B to 5B. The heterogeneity among the 3 studies was low (heterogeneity chi-squared=0.44, p=0.803, I-squared=0%) (Figure 2B). The forest plot of early complete lysis of occluded vessels within 30 days showed that pooling effect (random effect) was significant (OR=74.89, 95% CI=17.732 to 316.292, p<0.001) (Figure 3B); this finding indicated that CDT was associated with a higher rate of early complete lysis of occluded vessels, when compared with CAT. Sensitivity analysis is shown in Figure 4B; omitting some studies did not affect the pooling effect. The funnel plot was symmetric and Egger's test was insignificant (p=0.088) (Figure 5B). No publication bias was noted.

The outcomes of 6-month iliofemoral patency are shown in Table 2 and Figures 2C to 5C. The heterogeneity among the 4 studies was high (heterogeneity chi-squared=10.01, p=0.018, I-squared =70%) (Figure 2C). The forest plot of 6-month iliofemoral patency showed that pooling effect (random effect) was significant (OR=5.682, 95% CI=1.964 to 16.439, p=0.001) (Figure 3C); this finding indicated that CDT was associated with a higher rate of 6-month iliofemoral patency, when compared with CAT. Sensitivity analysis is shown in Figure 4C; omitting Enden et al.'s study changed the pooling effect significantly. The funnel plot is asymmetric, so publication bias existed (Figure 5C).

### Safety Outcome

The safety outcome, major bleeding, is presented in Table 2 and Figures 2D to 5D. The heterogeneity among the 6 studies was not statistically significant (p=0.297, I-squared=18.4%) (Figure 2D). The forest plot of major bleeding showed that pooling effect (random effect) was significant (OR=1.74, 95%

CI=1.498 to 2.022, p<0.001) (Figure 3D); this finding indicated that CDT was associated with more major bleeding risk, when compared with CAT. Sensitivity analysis is shown in Figure 4D. Omitting Bashir et al.'s study changed the pooling effect significantly. The funnel plot was symmetric and Egger's test showed no publication bias (p=0.135) (Figure 5D).

## Discussion

Comparing with the meta-analysis conducted by Du et al. in 2005, our meta-analysis included 4 RCTs and the follow-up period was longer.[10] Wang et al. included only four RCT studies for meta-analysis and their study showed that CDT reduced the occurrence of PTS, recurrent DVT and venous obstruction in patients with proximal DVT.[11] Li et al. included 26 studies, 6 comparing CDT with CAT and 19 case series, and their meta-analysis showed that CDT had a lower incidence of PTS and a higher incidence of patency rate in patients with acute DVT compared with anticoagulation therapy.[12] The present study showed similar results.

### Primary Efficacy Outcomes

The results of the Catheter-directed Venous Thrombolysis (CaVenT) study have constituted the benchmark for acute DVT interventions in the past 10-15 years; the study established the concept that CDT could decrease the occurrence of PTS, compared with anticoagulation.[4,6,13] However, there has been some criticism of the study design because there were some discrepancies between the treatment group and the control group with regard to patients' baseline characteristics. The treatment group was more compliant towards the use of elastic compression stockings. More patients' INR in the treatment group were controlled between 2-3.[6,13] The present study integrated different trials and our results again showed that CDT was more efficient to relieve PTS in patients with acute DVT, compared with CAT. However, the sensitivity analysis showed that the results from Vedantham et al. neutralized the effect from other studies greatly (Figure 4A).[14] Thus, we should not overemphasize the benefits of CDT to prevent PTS because the trial conducted by Vedantham et al. was the latest, largest and best-designed RCT to study the effect of pharmacomechanical thrombolysis (PMT) plus CDT compared with CAT. PMT is a facilitated CDT and should be more effective than traditional CDT. The negative results from this trial by Vedantham et al. might inform us of the importance of selecting patients with more iliofemoral vein involvement and more acute symptoms.[14-16]

### Secondary Efficacy Outcomes

The present study showed that CDT was significantly associated not only with a higher rate of early complete lysis of occluded vessels within 30 days, but also with a higher 6-month iliofemoral venous patency rate. The biology behind these findings indicates that earlier and more complete vessel recanalization can prevent the occurrence of PTS. This finding is consistent with previous studies.[5,11,12]

### Safety Outcomes

The present study showed that CDT carried more bleeding risk than CTA in patients with DVT. However, after reviewing the articles included, most bleeding complications were puncture related hematoma. Rare intracerebral hemorrhage or mortality cases were reported.[1,2,6,14,17-19]

### Study Limitations

Several limitations in our meta-analysis should be acknowledged. First, we enrolled both RCTs and observational studies into our meta-analysis. The sample size was small in some studies and the design lacked blinding. This may have led to bias in the final results. Second, in our study, we only enrolled traditional CDT and PMT. Another facilitated CDT is ultrasound accelerated CDT which has also been shown quite beneficial in some case series. However, we did not enroll

related articles in our meta-analysis because most of them were single arm registries. Third, due to limited data, subgroup analysis for different kinds of thrombolytic agents or for the vessels involved was not performed.

## Conclusions

In patients with acute DVT, CDT significantly improved PTS, early complete lysis of occluded vessels within 30 days and 6-month iliofemoral patency rate, when compared with CAT. However, CDT was associated with greater risk of major bleeding.

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A.

| Study name | OR | 95% CI | | Weight % |
|---|---|---|---|---|
| | | Lower | Upper | |
| AbuRahma et al. (2001) | 0.124 | 0.033 | 0.473 | 8 |
| Enden et al. (2012) | 0.558 | 0.313 | 0.995 | 19.54 |
| Lee et al. (2013) | 0.238 | 0.069 | 0.824 | 6.65 |
| Srinivas et al. (2014) | 0.092 | 0.025 | 0.341 | 9.44 |
| Vedantham (2017) | 0.939 | 0.696 | 1.265 | 56.36 |
| M-H pooled | 0.673 | 0.527 | 0.858 | 100 |

Heterogeneity chi-squared = 22.88 (d.f. = 4) p = 0.000
I-squared (variation in OR attributable to heterogeneity) = 82.5%
Test of OR=1 : z = 3.19, p = 0.001

B.

| Study name | OR | 95% CI | | Weight % |
|---|---|---|---|---|
| | | Lower | Upper | |
| AbuRahma et al. (2001) | 160.00 | 15.34 | 1668.99 | 21.32 |
| Elsharawy et al. (2002) | 53.67 | 2.79 | 1033.40 | 36.73 |
| Lee et al. (2013) | 61.48 | 3.39 | 1115.45 | 41.95 |
| M-H pooled | 79.61 | 15.56 | 407.34 | 100 |

Heterogeneity chi-squared = 0.44 (d.f. = 2) p = 0.803
I-squared (variation in OR attributable to heterogeneity) = 0.0%
Test of OR=1 : z = 5.26, p = 0.000

C.

| Study name | OR | 95% CI | | Weight % |
|---|---|---|---|---|
| | | Lower | Upper | |
| AbuRahma et al. (2001) | 15.625 | 3.581 | 68.177 | 4.75 |
| Elsharawy et al. (2002) | 19.5 | 3.223 | 117.988 | 2.88 |
| Enden et al. (2012) | 2.175 | 1.211 | 3.906 | 76.85 |
| Lee et al. (2013) | 3.6 | 1.142 | 11.346 | 15.52 |
| M-H pooled | 3.534 | 2.24 | 5.575 | 100 |

Heterogeneity chi-squared = 10.01 (d.f. = 3) p = 0.018
I-squared (variation in OR attributable to heterogeneity) = 70.0%
Test of OR=1 : z = 5.43, p = 0.000

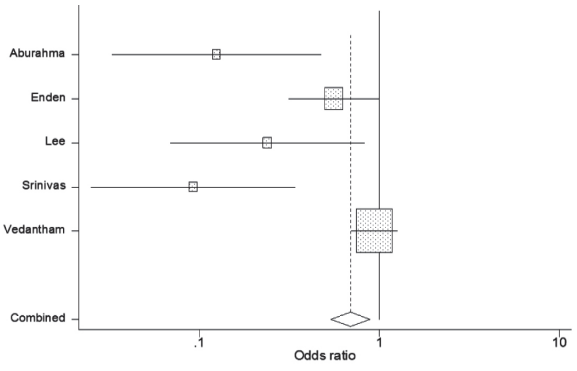
D.

| Study name | OR | 95% CI | | Weight % |
|---|---|---|---|---|
| | | Lower | Upper | |
| AbuRahma et al. (2001) | 1.938 | 0.249 | 15.061 | 0.48 |
| Elsharawy et al. (2002) | - | - | - | - |
| Enden et al. (2012) | 20.503 | 1.166 | 360.55 | 0.16 |
| Lee et al. (2013) | 5.408 | 0.247 | 118.34 | 0.17 |
| Bashir et al. (2014) | 1.713 | 1.472 | 1.993 | 98.83 |
| Vedantham et al. (2017) | 6.417 | 0.768 | 53.583 | 0.36 |
| M-H pooled | 1.768 | 1.522 | 2.054 | 100 |

Heterogeneity chi-squared = 4.90 (d.f. = 4) p = 0.297
I-squared (variation in OR attributable to heterogeneity) = 18.4%
Test of OR=1 : z = 7.46, p = 0.000

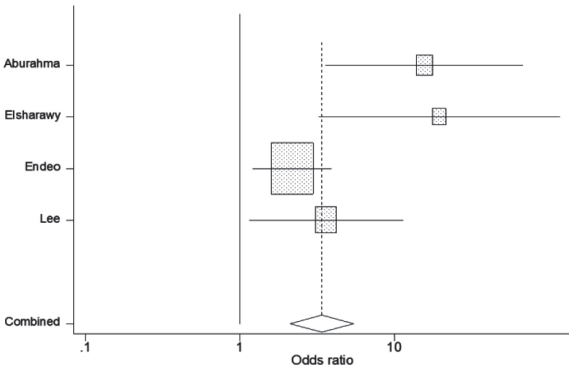
**Figure 2.** Heterogeneity of study for primary and secondary outcomes. A. Post thrombotic syndrome. B. Early complete lysis within 30 days. C. 6-month iliofemoral patency rate. D. Major bleeding.

A.



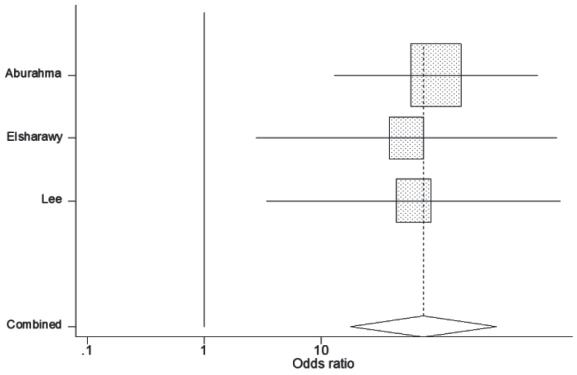

| Method | Pooled Est | 95% CI | | Asymptotic | | No. of studies |
|---|---|---|---|---|---|---|
| | | Lower | Upper | z value | p value | |
| Fixed | 0.690 | 0.537 | 0.885 | -2.915 | 0.004 | 5 |
| Random | 0.325 | 0.142 | 0.744 | -2.658 | 0.008 | |

C.



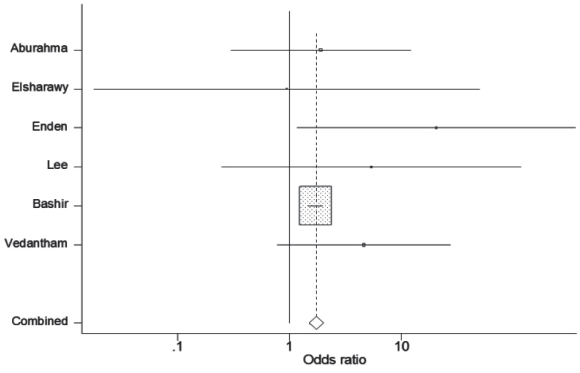

| Method | Pooled Est | 95% CI | | Asymptotic | | No. of studies |
|---|---|---|---|---|---|---|
| | | Lower | Upper | z value | p value | |
| Fixed | 3.386 | 2.107 | 5.441 | 5.040 | <0.001 | 4 |
| Random | 5.682 | 1.964 | 16.439 | 3.205 | 0.001 | |

B.




| Method | Pooled Est | 95% CI | | Asymptotic | | No. of studies |
|---|---|---|---|---|---|---|
| | | Lower | Upper | z value | p value | |
| Fixed | 74.890 | 17.732 | 316.292 | 5.872 | <0.001 | 3 |
| Random | 74.890 | 17.732 | 316.292 | 5.872 | <0.001 | |

D.




| Method | Pooled Est | 95% CI | | Asymptotic | | No. of studies |
|---|---|---|---|---|---|---|
| | | Lower | Upper | z value | p value | |
| Fixed | 1.740 | 1.498 | 2.022 | 7.237 | <0.001 | 6 |
| Random | 1.740 | 1.498 | 2.022 | 7.237 | <0.001 | |

**Figure 3.** Forest plots for primary and secondary outcomes. A. Post thrombotic syndrome. B. Early complete lysis within 30 days. C. 6-month iliofemoral patency rate. D. Major bleeding

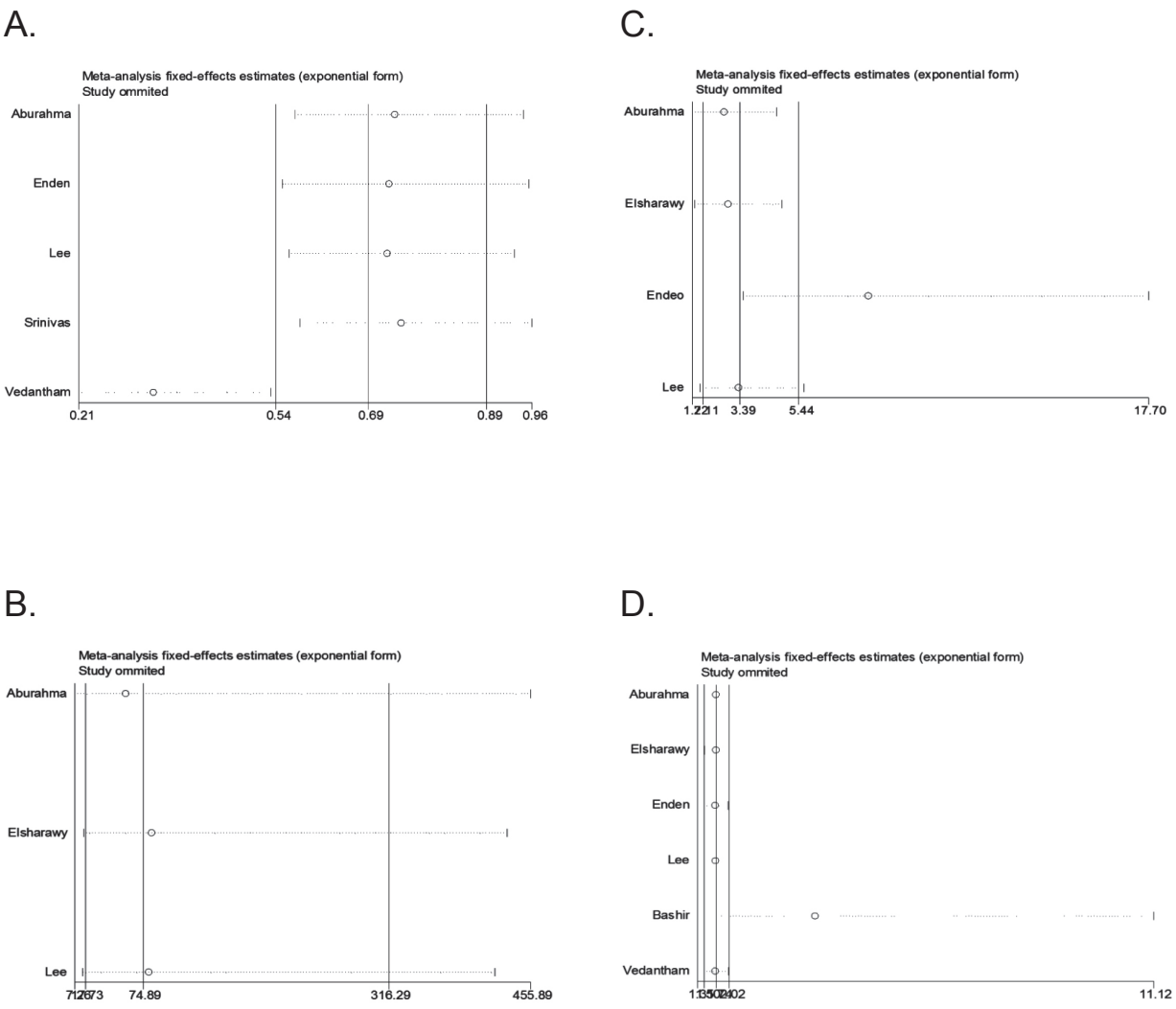
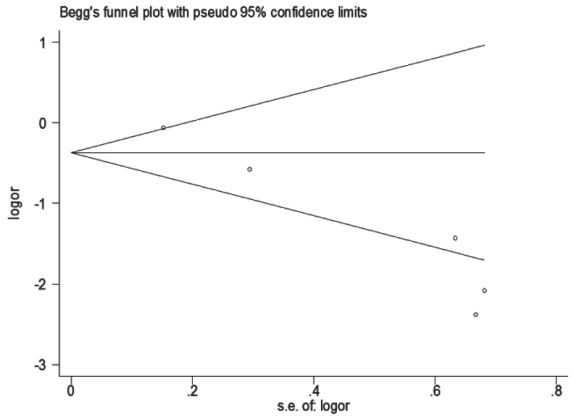



**Figure 4.** Sensitivity analysis for primary and secondary outcomes. A. Post thrombotic syndrome. B. Early complete lysis within 30 days. C. 6-month iliofemoral patency rate. D. Major bleeding.

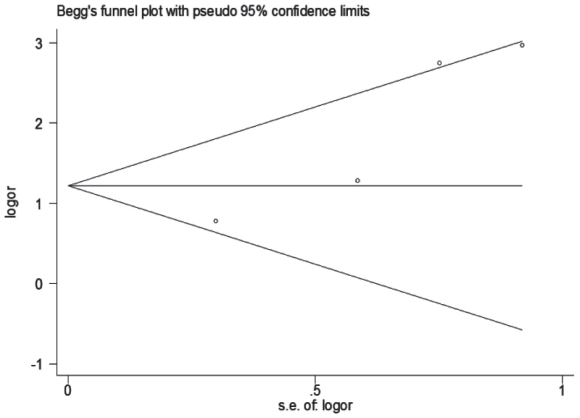
A.




Egger's test

| Std_Eff | Coef. | Std.Err. | t | p value | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| slope | 0.509 | 0.118 | 4.31 | 0.023 | 0.133 | 0.884 |
| bias | -3.733 | 0.414 | -9.02 | 0.003 | -5.050 | -2.417 |

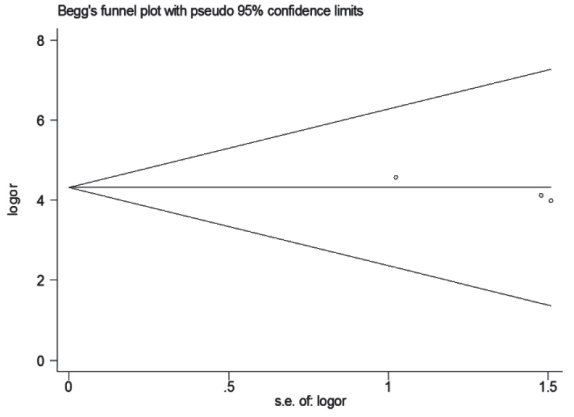
C.




Egger's test

| Std_Eff | Coef. | Std.Err. | t | p value | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| slope | -0.320 | 0.393 | -0.81 | 0.502 | -2.012 | 1.373 |
| bias | 3.517 | 0.813 | 4.33 | 0.049 | 0.021 | 7.014 |

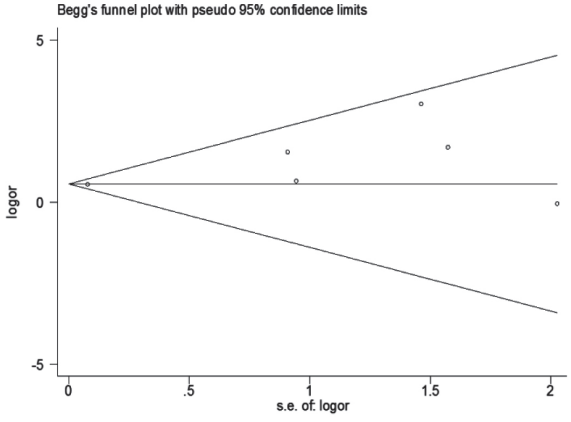
B.




Egger's test

| Std_Eff | Coef. | Std.Err. | t | p value | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| slope | 5.687 | 0.194 | 29.38 | 0.022 | 3.227 | 8.146 |
| bias | -1.095 | 0.152 | -7.21 | 0.088 | -3.027 | 0.836 |

D.




Egger's test

| Std_Eff | Coef. | Std.Err. | t | p value | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| slope | 0.484 | 0.071 | 6.80 | 0.002 | 0.286 | 0.681 |
| bias | 0.709 | 0.379 | 1.87 | 0.135 | -0.344 | 1.763 |

**Figure 5.** Funnel plots for primary and secondary outcomes. A. Post thrombotic syndrome. B. Early complete lysis within 30 days. C. 6-month iliofemoral patency rate. D. Major bleeding.