Thrombolysis for DVT—Everyone Should Get It
Thrombolysis for DVT—Everyone with Acute Iliofemoral DVT and No Contraindication Should Get It
I use tPa for all of my DVT patients.
OBJECTIVES

• Define post-thrombotic syndrome and its prevalence.
• Review the risk/incidence of bleeding both major and minor with thrombolysis.
• Definitively support the role of thrombolysis in iliofemoral DVT treatment.
  – Cochrane Database--1969-2011
  – CaVenT trial--2012
  – Attract trial—March 2017
DVT

- AFFECTS 2.5-5% OF GEN’L POPULATION AT SOME POINT IN THEIR LIFE

- ONLY 20% OF ILIOFEMORAL DVT CAN BE COMPLETELY RECANALIZED W/ AC ALONE

Iliofemoral venous thrombosis. Pathological considerations and surgical management

G. E. Mavor, J. M. D. Galloway

First published: January 1969  Full publication
PTS

• POST-THROMBOTIC SYNDROME AFFECTS UP TO 50% OF THOSE WHO HAVE HAD DVT--some degree of pain, swelling, skin pigmentation or venous ulceration of the affected leg

• USUALLY OCCURS W/IN 2 YRS

• EVENTUAL VENOUS ULCERATION IN 6% DESPITE COMPRESSION
VENOUS ULCERATION

• The prevalence of venous ulcers in the general population is around 1 in 1000


• Between 40% to 50% of patients with venous ulcers have evidence of post-thrombotic damage

## Villalta Scoring Scale

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<td></td>
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### Scoring

- Each sign or symptom is rated as:
  - 0 = None
  - 1 = Mild
  - 2 = Moderate
  - 3 = Severe

### Summed-up ratings

- Total score:
  - $<5 = no$ PTS
  - 5-14 = mild/moderate PTS
  - $\geq15$/venous ulcer = severe PTS

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HOW TO PREVENT PTS

• ANTICOAGULATION

• COMPRESSION THERAPY

• THROMBOLYSIS
  – PHARMA
  – MECHANICAL
Determinants and Time Course of the Postthrombotic Syndrome after Acute Deep Venous Thrombosis

Susan R. Kahn, MD, MSc; Ian Shrier, MD, PhD; Jim A. Julian, MMath; Thierry Decruet, MSc; Louise Arsenault, BA; Marie-José Miron, MD; Andree Roussin, MD; Sylvie Desmarais, MD; France Joyal, MD; Jeanline Kassis, MD; Susan Solymoss, MD; Louis Desjardins, MD*; Donna L. Lamping, PhD; Mina John, PhD; and Jeffrey S. Ginsberg, MD

Predictors of Post-Thrombotic Syndrome

- Common femoral or iliac vein thrombosis (OR 2.23 p<0.001)
- Post-thrombotic morbidity at 1 month (p<0.001)
SOX Trial
Elastic Compression Stockings vs Placebo Control

Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

Susan R Kahn, Stan Shapiro, Philip S Wells, Marc A Rodger, Michael J Kovacs, David R Anderson, Vicky Tagalakis, Adrielle H Houweling, Thierry Ducruet, Christina Holcroft, Mira Johri, Susan Solymoss, Marie-José Miron, Erik Yeo, Reginald Smith, Sam Schulman, Jeannine Kassis, Clive Kearon, Isabelle Chagnon, Turnly Wong, Christine Demers, Rajendar Hanmiah, Scott Kaatz, Rita Selby, Suman Rathbun, Sylvie Desmarais, Lucie Opatri, Thomas L. Ortel, Jeffrey S Ginsberg, for the SOX trial investigators

- **Objective**: To evaluate the effectiveness of elastic compression stockings (ECS), compared with placebo stockings to prevent post-thrombotic syndrome (PTS)

- **Design**: Multicenter, randomized, placebo-controlled trial of active (N=410) vs placebo (N=396) ECS

- **Key Inclusion Criteria**: First indicative, proximal DVT (with or without coexisting pulmonary embolism or distal DVT)

- **Primary Endpoint**: PTS diagnosed at 6 months or later using Ginsberg’s criteria (ie, leg pain and swelling of ≥1 month)

SOX Trial Results
Elastic Compression Stockings vs Placebo Control

“ECS did not prevent PTS after a first proximal DVT”

PTS incidence rate at 2 years:
14.2% for active ECS vs. 12.7% for placebo (p=0.58)\(^a\)

THROMBOLYSIS

- Drugs activate plasminogen
- Plasmin breaks links between fibrin molecules
- ROUTES OF ADMIN
  - peripheral vein
  - CDT
  - PCDT
RATIONALE FOR THROMBOLYSIS—THE OPEN VEIN THEORY

- Dissolving the thrombus in the acute phase may reduce the risk of more permanent damage to the structure and function of the vein.
- In particular venous valvular function, thus lowering the risk of post-thrombotic complications in the long term.
• RANDOMIZED TRIALS ONLY
• ACUTE DVT, defined as onset of symptoms within seven days and confirmed by objective testing
• EXCLUSION--trials including participants with
  – chronic or recurrent venous thrombosis
  – treatment after a maximum of 21 days from the onset of symptoms
TRIAL DETAILS—no standardized protocols

- 1969-2011
- The majority of trials assessed systemic thrombolysis, with streptokinase the most common agent used
- DOSAGES of thrombolytics varied
- Route of administration varied
- Heparinization varied
- Duration of anticoagulation after initial event varied
- 9 trials: <50pts
- 2 trials: >100pts (largest 250pts)
Contraindications for Lysis

- surgery or head trauma within the previous three months
- malignancy
- renal and hepatic dysfunction
- bleeding dysfunction
OUTCOME MEASURES

• EARLY--up to one month

• INTERMEDIATE--6 months to 5 yrs

• LATE-->5 yrs
PRIMARY OUTCOMES

- Any improvement in venous patency
- Complete clot lysis
- Bleeding complications (defined as bleeding causing treatment to be stopped, requiring transfusion or surgery, or causing chronic or fatal sequelae)
- Stroke and in particular haemorrhagic stroke
- PTS
- Venous Ulcer
- Mortality
SECONDARY OUTCOMES

• Recurrent DVT
• PE
• Venous function
  • assessed by duplex ultrasound or other objective means such as foot volumetry or ambulatory venous pressure measurements
• Quality of life (QoL)
• Cost
Pooling all types of thrombolysis, the results showed a reduction in the risk of PTS with use of thrombolysis by 34% at the intermediate time point (RR 0.66; NNTB 5) and a reduction in the risk of PTS of 42% at late follow-up (RR 0.58; NNTB 4).

There was no difference in ulceration beyond six months; data were limited by small numbers and the short length of follow-up, as ulcers are more likely to occur later than a year or two after the DVT.
RESULTS--BLEEDING

• Participants receiving thrombolysis were significantly more likely than control participants to experience a bleeding complication.

• 9% (62/662) of patients in the thrombolysis group experienced a bleeding complication compared to 4% (19/441) of patients in the standard anticoagulation group.

• Most bleeding complications occurred in earlier studies.
RESULTS--ICH

- Out of a total of 1103 participants 3 events occurred in the treatment group (a rate of 0.3%) and none in the control group. The pooled RR was 1.92 (95% CI 0.34 to 10.86) with wide uncertainty regarding the true effect.
RESULTS--ICH

- Three intracerebral bleeds occurred in these trials (Common 1976—streptokinase & P Vera; Goldhaber 1990—controlled HTN; Marder 1977—remote Hx of CVA). Adoption of current contra-indications may have prevented these events in more recent trials.

- Two of the early deaths in the treatment groups may also have been prevented with the use of current contra-indications to thrombolysis: a participant with metastatic carcinoma (Common 1976), and a participant with recent surgery (Kakkar 1969).
RESULTS--MORTALITY

- A total of 5 (? 2 possibly preventable) events occurred in the treatment group and 7 in the control group out of a total 529 participants. The pooled RR was 0.76 (95% CI 0.31 to 1.89)
CaVenT Trial:

Long-Term Outcome After Additional Catheter-Directed Thrombolysis versus Standard Treatment for Acute Iliofemoral Deep Vein Thrombosis (The CaVenT Study): A Randomised Controlled Trial

Enden T et al.
*Proc ASH* 2011;Abstract LBA-1.
CaVenT Trial: Study Design

Eligibility (n = 209)
- Age: 18-75 years
- First-time acute iliofemoral DVT
- Objectively verified DVT above midthigh level
- Symptom duration up to 21 days
- No increased risk of bleeding

* Initial low molecular weight heparin (LMWH) and warfarin followed by warfarin alone with target intensity international normalized ratio (INR) of 2.0-3.0

- Randomization was stratified for involvement of the pelvic veins.
- Primary outcomes:
  - Frequency of PTS at 24 months, assessed by the Villalta score
  - Iliofemoral patency after 6 months

## Villalta Scoring Scale

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**Scoring** — Each sign or symptom is rated as:

- 0 = None
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**Summed-up ratings = total score:**

- <5 = no PTS
- 5-14 = mild/moderate PTS
- ≥15/venous ulcer = severe PTS

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Exclusion criteria

- Anticoagulant treatment before trial entry for more than the past 7 days
- Contraindications to thrombolytic treatment, including bleeding diathesis
- Indications for thrombolytic treatment—eg, phlegmasia caerulea dolens or isolated vena cava thrombosis
- Severe anaemia (haemoglobin <80 g/L)
- Thrombocytopenia (platelets <80·10⁹/L)
- Severe renal failure (estimated creatinine clearance <30 mL/min)
- Severe hypertension—ie, persistent systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 100 mm Hg
- Pregnancy or thrombosis within 7 days postpartum
- Less than 14 days postsurgery or post-trauma
- History of subarachnoid or intracerebral bleeding
- Disease with life expectancy less than 24 months
- Drug misuse or mental disease that could interfere with treatment and follow-up
- Former ipsilateral proximal deep vein thrombosis
- Malignant disease needing chemotherapy
- Any thrombolytic treatment within 7 days before trial inclusion
CaVenT t-PA dosing

- 20 mg alteplase at 0.01 mg/kg per h for maximum 96 h, and the maximum dose was 20 mg/24 h.

- Unfractionated heparin adjusted to keep activated partial thromboplastin time at 1.2–1.7 times higher than the upper normal limit.

- Additional antiplatelet treatment was not given
# Outcomes: Additional CDT versus Standard Therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Additional CDT (n = 90)</th>
<th>Standard therapy only (n = 99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>PTS after 6 mo</td>
<td>27</td>
<td>30.3 (21.8-40.5)</td>
<td>32</td>
</tr>
<tr>
<td>PTS after 24 mo</td>
<td>37</td>
<td><strong>41.1</strong> (31.5-51.4)</td>
<td>55</td>
</tr>
<tr>
<td>Iliofemoral patency after 6 mo*</td>
<td>58</td>
<td><strong>65.9</strong> (55.5-75.0)</td>
<td>45</td>
</tr>
</tbody>
</table>

* Five patients had inconclusive patency assessments, and 1 was lost to follow-up. At completion of 24 months of follow-up, 189 patients were available for analysis.

- PTS is defined as a Villalta score ≥5.
- p-values stated are from an unadjusted Chi-square test.
- Absolute risk reduction of long-term endpoint PTS at 24 months of follow-up in CDT versus standard therapy: 14.4% (95% CI 4-502).


**NNT=7**
### PTS After 24 Months in Patients with Iliofemoral Patency or Insufficient Recanalization After 6 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Regained iliofemoral patency (n = 103)</th>
<th>Insufficient recanalization (n = 80)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>PTS after 24 mo</td>
<td>38</td>
<td><strong>36.9 (28.2-46.5)</strong></td>
<td>49</td>
</tr>
</tbody>
</table>

- Absolute gain in short-term endpoint iliofemoral patency after 6 months in CDT versus standard therapy group: 18.5% (95% CI 4.2–31.8).
- Absolute risk reduction in the frequency of PTS after 24 months in patency versus insufficient recanalization: 24.4% (95% CI 9.8–37.6).

## Adverse Events (AEs)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Additional CDT (n = 101)</th>
<th>Standard treatment (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding complications</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Clinically relevant bleeding complications</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Pulmonary embolisms</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Cerebral hemorrhages</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Nonbleeding complications</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Recurrent VTE at 24 mo</td>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>

NR = not reported

During follow-up, 28 patients had recurrent VTE and 11 had cancer; no significant difference between treatment groups (p > 0.05).

20 Bleeding Complications

• MAJOR—3
  – ABDOMINAL WALL HEMATOMA--XFUSION
  – POPLITEAL FOSSA HEMATOMA REQUIRING FASCIOTOMY FOR COMPARTMENT SYNDROME
  – INGUINAL PUNCTURE SITE HEMATOMA

• CLINICALLY RELEVANT—5

• NO DEATHS

• NO CEREBRAL HEMORRHAGES
• 5 year follow-up--176 patients (84% of the 209 patients originally randomised)
• 87 (CDT) and 89 (control)
• 37 CDT pts (43%; 95% CI 33–53) developed PTS
• 63 Control pts (71%; 95% CI 61–79) (p<0·0001) developed PTS

• Absolute risk reduction of 28% and NNT--4
The ATTRACT Trial

**Acute Venous Thrombosis:**
Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis

**Symptomatic Proximal DVT**

- **Stratify**
  - Iliofemoral DVT
    - **Randomize**
      - Catheter-Based Thrombus Removal + Anticoagulation
      - Anticoagulation Alone
  - Femoral-Popliteal DVT
    - **Randomize**
      - Catheter-Based Thrombus Removal + Anticoagulation
      - Anticoagulation Alone

**Post-Thrombotic Syndrome During 24 Month Follow-Up**

- Villalta Score
- CEAP Classification
- QOL Evaluation
- Venous Clinical Severity Score
- Venous Duplex
  - Patency
  - Valve Function
Study Population

- Symptomatic proximal DVT involving the iliac, common femoral, and/or femoral vein
  - stratify randomization by thrombus extent
  - actual: 60% with "iliofemoral" DVT

- EXCLUDE patients with:
  - Higher bleeding risk, CNS lesions
  - Acute limb threat or massive PE
  - Symptom duration > 2 weeks
  - Same-leg PTS or DVT < 2 yrs
  - Active cancer
Primary Measure

Villalta Scale

- The best-validated measure to diagnose incident PTS, evaluates 5 symptoms and 6 signs of PTS, highly sensitive to mild-moderate forms of PTS

- $\text{PTS} = \text{score} \geq 5$ or presence of ulcer in index leg

- 692 patients provides 80% power to detect 1/3 reduction in PTS over 2 years, alpha 0.05, 2-tailed, assuming 10% loss to follow-up of randomized pts
Secondary Outcomes

**PRESENT**

- PTS Severity (Villalta Scale, VCSS, CEAP Clinical Class)
- QOL (SF-36, VEINES-QOL)
- Relief of pain (Likert scale) & swelling (limb circumference)
- Safety (bleeding, VTE, death) & costs (dollars per QALY)
- Mechanism (obstruction and reflux by ultrasound - VSDS)

**ABSENT**

- What biomarkers of clot amplification/resolution, inflammation, vascular injury can predict which patients are best-suited?
- What are the biological effects of catheters/devices upon vein wall & blood?
- Collaborative opportunity for valuable future studies
ATTRACTION

- 692 patients with acute proximal deep vein thrombosis involving the femoral, common femoral, and/or iliac vein into the ATTRACT study at 56 centres
- Randomised 337 catheter-directed thrombolysis and 355 to anticoagulation alone
- AngioJet thrombectomy system (Boston Scientific); the Trellis-8 Peripheral Infusion System (Medtronic. This device is no longer on the market); or catheter-directed rt-PA infusion for up to 24 hours
ATTRACT

- Pharmacomechanical catheter-directed thrombolysis reduces early deep vein thrombosis symptoms and post-thrombotic syndrome severity.
- Researchers also found that DVT patients who received both blood-thinning drugs and PCDT were 25 percent less likely (18 percent with PCDT vs. 24 percent without) to develop moderate-to-severe PTS.
ATTRACT RESULTS

• The open vein hypothesis is likely relevant to post-thrombotic syndrome progression and there is a suggestion that targeting this therapy to patients with iliofemoral deep vein thrombosis based on the high risk of post-thrombotic syndrome [might be beneficial],” Vedantham added.
SUMMARY

• PTS occurs in at least 40% and up to 70% of patients after iliofemoral DVT w/ AC alone.
• Overall risk for any bleeding complication w/ lysis is 8-10% w/ ICH risk of 0-0.3%.
• Cochrane, CaVenT and Attract all support PCDT in patients w/ iliofemoral DVT and no contraindication.
THANK YOU
• Data from subgroups and secondary analyses suggest that catheter-directed thrombolysis may have a benefit in patients who have acute iliofemoral deep vein thrombosis
Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.
DUTCH-CAVA Study
NCT 00970619 (Netherlands)

- 180 patients with first-episode iliofemoral DVT
- Randomized to AC vs. AC + US-Assisted CDT
- Primary Outcome – PTS at 1 year (also – QOL, recurrent VTE, reflux)
RESULTS--ULCERATION

3--treatment group VS 2--control group

342 participants (P = 0.87)

RESULTS—COMPARISONS 2,3,4

• Comparison 2 (SYSTEMIC VS CONTROL)
• Comparison 3 (LOCO-REG VS CONTROL)
• Comparison 4 (CDT VS CONTROL)

NO STATISTICAL DIFFERENCE
RESULTS--BLEEDING

• Most bleeding episodes and deaths occurred in the earlier studies.

• It is notable that no bleeding occurred in the Elsharawy 2003 study. This may have been due to strict exclusion criteria and the close radiological monitoring and dose titration depending upon clot lysis.
RESULTS--BLEEDING

- Participants receiving thrombolysis were significantly more likely than control participants to experience a bleeding complication.

- 9% (62/662) of patients in the thrombolysis group experienced a bleeding complication compared to 4% (19/441) of patients in the standard anticoagulation group (RR 2.23; 95% CI 1.41 to 3.52, P = 0.0006; moderate quality evidence; NNT of 17.)

- Most bleeding complications occurred in earlier studies.
RESULTS--BLEEDING

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• 9% (62/662) of patients in the thrombolysis group experienced a bleeding complication compared to 4% (19/441) of patients in the standard anticoagulation group (RR 2.23; 95% CI 1.41 to 3.52, P = 0.0006; moderate quality evidence; NNT of 17.)

• Most bleeding complications occurred in earlier studies
### Thrombolysis for acute deep vein thrombosis

**Patient or population:** patients diagnosed with acute DVT  
**Setting:** hospital  
**Intervention:** any thrombolysis  
**Comparison:** control anti-coagulation

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete clot lysis (intermediate, 6 months to under 5 years after treatment)</td>
<td>Study population: RR 2.44 (1.4 to 4.27)</td>
<td>630 (7 RCTs)</td>
<td></td>
<td>MODERATE</td>
<td>78 (of 240) patients treated with standard anticoagulation had complete clot lysis compared to 198 (of 390) in the thrombolysis group</td>
</tr>
<tr>
<td>325 per 1000 793 per 1000 (455 to 1000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding (early, up to 1 month after treatment)</td>
<td>Study population: RR 2.23 (1.4 to 3.52)</td>
<td>1103 (17 RCTs)</td>
<td></td>
<td>MODERATE</td>
<td>Although 17 studies reported on bleeding, these were small studies</td>
</tr>
<tr>
<td>43 per 1000 96 per 1000 (61 to 152)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-thrombotic syndrome (intermediate, 6 months to under 5 years after treatment)</td>
<td>Study population: RR 0.66 (0.53 to 0.81)</td>
<td>306 (3 RCTs)</td>
<td></td>
<td>MODERATE</td>
<td>96 (of 146) patients treated with standard anticoagulation developed PTS compared to 72 (of 160) treated with thrombolysis</td>
</tr>
<tr>
<td>658 per 1000 434 per 1000 (348 to 533)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-thrombotic syndrome (late, 5 year follow-up after treatment)</td>
<td>Study population: RR 0.58 (0.45 to 0.77)</td>
<td>211 (2 RCTs)</td>
<td></td>
<td>MODERATE</td>
<td>72 (of 107) patients treated with standard anticoagulation developed PTS compared to 41 (of 104) treated with thrombolysis</td>
</tr>
<tr>
<td>673 per 1000 390 per 1000 (303 to 518)</td>
<td></td>
<td></td>
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*GRADE Working Group grades of evidence*  
*High quality: We are very confident that the true effect lies close to that of the estimate of the effect.*  
*Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*  
*Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*  
*Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*
Treatment with catheter directed thrombolysis for acute DVT

Patient or population: patients diagnosed with acute deep vein thrombosis
Setting: hospital
Intervention: catheter-directed thrombolysis
Comparison: control anti-coagulation

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<tr>
<td>Complete clot lysis (intermediate, 6 months to under 5 years after treatment)</td>
<td>Study population</td>
<td>RR 2.52 (0.52 to 12.17)</td>
<td>224 (2 RCTs)</td>
<td>MODERATE&lt;sup&gt;1&lt;/sup&gt;</td>
<td>None of 116 patients in the standard anticoagulation group had complete clot lysis compared to 81 (of 108) in the CDT group.</td>
</tr>
<tr>
<td>Bleeding (early, up to 1 month after treatment)</td>
<td>Study population</td>
<td>RR 7.69 (0.40 to 146.90)</td>
<td>224 (2 RCTs)</td>
<td>MODERATE&lt;sup&gt;2&lt;/sup&gt;</td>
<td>None of 116 patients in the standard anticoagulation group had bleeding complications compared to 3 (of 108) in the CDT group.</td>
</tr>
<tr>
<td>Post-thrombotic syndrome (intermediate, 6 months to under 5 years after treatment)</td>
<td>Study population, 556 per 1000</td>
<td>RR 0.74 (0.55 to 1.00)</td>
<td>189 (1 RCT)</td>
<td>MODERATE&lt;sup&gt;3&lt;/sup&gt;</td>
<td>55 (of 99) patients in the standard anticoagulation group developed PTS compared to 37 (of 90) in the CDT group.</td>
</tr>
<tr>
<td>Post-thrombotic syndrome (late, 5 year follow-up after treatment)</td>
<td>Study population, 708 per 1000</td>
<td>RR 0.60 (0.45 to 0.79)</td>
<td>176 (1 RCT)</td>
<td>MODERATE&lt;sup&gt;3&lt;/sup&gt;</td>
<td>63 (of 89) patients in the standard anticoagulation group developed PTS compared to 37 (of 87) in the CDT group.</td>
</tr>
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</table>
Emailed Kirk Freeman

- **DUTCH CAVA-trial.** Ultrasound accelerated catheter-directed thrombolysis for primary iliofemoral deep vein thrombosis (IFDVT) compared to non-invasive conventional anticoagulant therapy alone: a Dutch randomized controlled multicenter clinical trial.

INDICATIONS FOR EARLY THROMBUS REMOVAL

• Patients meeting the following criteria:
  – (a) a **first episode** of acute iliofemoral deep venous thrombosis
  – (b) symptoms **<14 days** in duration
  – (c) a **low risk** of bleeding
  – (d) ambulatory with **good functional capacity** and an acceptable life expectancy (Grade 2C)
TECHNIQUES for EARLY THROMBUS REMOVAL

• Strategy of pharmacomechanical thrombolysis be considered over CDT alone (Grade 2C)

• The use of mechanical devices alone, without the concurrent use of thrombolytic drugs, cannot be routinely recommended.
ARTICLES DOCUMENTING IMPROVED QOL
Treatment of acute iliofemoral DVT: a systematic review and meta-analysis

- Low-quality evidence suggests that surgical thrombectomy decreases the incidence of postthrombotic syndrome and venous reflux
- Catheter-directed pharmacologic thrombolysis decreases the incidence of postthrombotic syndrome and venous obstruction
REVIEW

• Catheter-directed thrombolysis for extensive iliofemoral deep vein thrombosis: review of literature and ongoing trials

• Aaron Liew Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK & James Douketis

• Pages 189-200 | Received 10 Sep 2015, Accepted 13 Nov 2015, Accepted author version posted online: 15 Nov 2015, Published online: 17 Dec 2015
TORPEDO TRIAL

PEVI + AC vs AC alone

91 pts 
92 pts

Recurrent VTE (mean f/u 30m)

4 (4.5%) of the 88 
13 (16%) of the 81

PTS

6 (6.8%) 
24 (29.6%)
17 trials/1103 participants

<table>
<thead>
<tr>
<th>Study</th>
<th>Potential levels of leg vein included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>proximal to calf</td>
</tr>
<tr>
<td>Common 1976</td>
<td>not specified</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>proximal</td>
</tr>
<tr>
<td>Elisharawy 2002</td>
<td>femoral and iliofemoral</td>
</tr>
<tr>
<td>Enden 2011</td>
<td>pelvic, iliofemoral, femoral</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>popliteal or more proximal</td>
</tr>
<tr>
<td>Goldhaber 1996</td>
<td>proximal</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>not specified</td>
</tr>
<tr>
<td>Kill 1981</td>
<td>not specified</td>
</tr>
<tr>
<td>Marder 1977</td>
<td>calf up to iliac vein</td>
</tr>
<tr>
<td>Schulman 1986</td>
<td>calf vein thrombosis only</td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>not specified</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>popliteal or more proximal</td>
</tr>
<tr>
<td>Tsapogas 1973</td>
<td>not specified</td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>proximal</td>
</tr>
<tr>
<td>Ugurlu 2002</td>
<td>popliteal up to inferior vena cava</td>
</tr>
<tr>
<td>Verhaeghe 1989</td>
<td>popliteal or more proximal</td>
</tr>
</tbody>
</table>

Cochrane Database of Systematic Reviews

Thrombolysis for acute deep vein thrombosis

Lorna Watson, Cathryn Broderick, Matthew P. Armon
First published: 10 November 2016
The ATTRACT Trial

Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis

NIH Sponsored Trial
Registration No. - NCT00790335
http://clinicaltrials.gov

The ATTRACT Trial
Almost 7 Years
Almost 700 Patients
Almost Done
...What Will We Find?

Anthony J. Comerota, MD, FACS, FACC
Director, Jobst Vascular Institute
Adjunct Professor of Surgery, University of Michigan
Figure 1. Acute femoropopliteal deep venous thrombosis before percutaneous endovenous intervention. Note the inflammatory appearance of the left lower extremity (A). Normalization of the limb 14 hours post percutaneous endovenous intervention (B).
CaVenT t-PA dosing

- 20 mg alteplase (Actilyse, Boehringer-Ingelheim, Ingelheim am Rhein, Germany) diluted in 500 mL 0.9% NaCl was given at 0.01 mg/kg per h for maximum 96 h, and the maximum dose was 20 mg/24 h. Unfractionated heparin was given simultaneously as a continuous intravenous infusion and the dose was adjusted to keep activated partial thromboplastin time (Cephotest, Axis-Shield, Oslo, Norway) at 1.2–1.7 times higher than the upper normal limit. Additional antiplatelet treatment was not given
Thrombolytic therapy

Deep vein thrombosis
1.2.6 Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:

- symptoms of less than 14 days’ duration and
- good functional status and
- a life expectancy of 1 year or more and
- a low risk of bleeding. [2012]
Post Thrombotic Syndrome

Ambulatory Venous Pressures & Symptoms

• 28 mmHg – Asymptomatic
• 36 mmHg – Varicosities
• 41 mmHg – Edema
• 47 mmHg – Hyperpigmentation
• 60 mmHg – Ulceration

Greater pressure associated with worse PTS symptoms
PTS and QOL

- CDT pts 1999 to 2008
- 109 pts completed
  - Short form 36 health assessment survey (sf-36)
  - Venous Insufficiency Epidemiological and Economic Study (VEINES)
- Mean F/U 71 months
- 18 pts developed PTS (16.5%)
- Pts with patent deep veins and sufficient valves have higher QOL scores than patients with reflux and occluded veins
Fixed low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting of residual stenosis for acute ilio-femoral deep-vein thrombosis

Prospective, non-randomized

87 pts w/ iliofemoral DVT (up to 28d)

U/S asst’d CDT w/ fixed dose (20 mg tPA) for 15 h

Routine stenting of residual venous stenosis

- Residual luminal narrowing >50%
- Static flow
- Collateral flow at site of suspected stenosis
RESULTS

• At 15h—77% pts had thrombolysis success (<50% stenosis)
• Venous stents in 80% pts
• One major bleed—RP hematoma—4 U PRBCs
• Freedom from PTS at 1 yr—94% by Villalta score

Fixed low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting of residual stenosis for acute ilio-femoral deep-vein thrombosis

Rolf P. Engelberger¹; Jennifer Fahrni¹; Torsten Willenberg¹; Frederic Baumann¹; David Spirk²; Nicolas Diehm¹; Dai-Do Do¹; Iris Baumgartner¹; Nils Kucher¹

¹Clinic for Angiology, Swiss Cardiovascular Center, Inselspital, University Hospital and University of Bern, Switzerland; ²Institute of Pharmacology, University of Bern, Switzerland
• 3 RCTs and 3 non-randomized trials
• Efficacy outcome—PTS—significant decline in CDT pts
• Safety outcome—Major Bleeding—significant increase in CDT pts
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Region</th>
<th>Mean age (year)</th>
<th>Male (%)</th>
<th>Compared groups (no.)</th>
<th>Thrombolytic agent</th>
<th>Clinical outcomes</th>
<th>Duration of follow-up</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbuRahma et al., 2001&lt;sup&gt;[23]&lt;/sup&gt;</td>
<td>Prospective</td>
<td>USA</td>
<td>47</td>
<td>39</td>
<td>CDT + AA (18) vs. Urokinase, rtPA</td>
<td>Patency rate, long-term symptom resolution, major complications</td>
<td>5 years</td>
<td>NOS: S4C2O3 = 9</td>
<td></td>
</tr>
<tr>
<td>Lee et al., 2013&lt;sup&gt;[24]&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>Taiwan</td>
<td>62</td>
<td>51</td>
<td>CDT + AA (27) vs. Urokinase AA (26)</td>
<td>Patency rate, major complications, PTS, venous function, recurrent DVT</td>
<td>15 months</td>
<td>NOS: S4C2O3 = 9</td>
<td></td>
</tr>
<tr>
<td>Bashir et al., 2014&lt;sup&gt;[11]&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>USA</td>
<td>53</td>
<td>51</td>
<td>CDT + AA (3594) vs. AA (3594) NA</td>
<td>Mortality, major complications</td>
<td>6 years</td>
<td>NOS: S4C2O3 = 9</td>
<td></td>
</tr>
</tbody>
</table>

CDT, catheter-directed thrombolysis; NA, not available; PTS, post-thrombotic syndrome; RCT, randomized controlled trial; Jadad score for RCTs: randomization (R0-2), blinding (B0-2) and attrition information (A0-1); Newcastle-Ottawa Scale (NOS) for cohort studies: selection (S0-4), comparability (C0-2), and outcome (O0-3).
PTS

• LIFELONG

• INCREASED RISK FOR RECURRENCE

• RECURRENT DVT INCREASES RISK AND SEVERITY OF PTS 6X
Thrombolysis for acute deep vein thrombosis

17 studies included in previous version of review

1654 records identified from CRS search
87 records from trials registers

1089 records after duplicates removed

1085 records screened by CRS

35 records screened by authors

1054 records assessed as not relevant for this review

16 not relevant for this review

7 additional studies (7 records) excluded, with reasons
2 additional studies (3 records) added to ongoing studies

19 full-text articles assessed for eligibility

5 NEW studies added but 9 reports added to previously included study

17 studies included

17 studies included in quantitative synthesis (meta-analysis)

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10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Random sequence generation (selection bias) - Low risk of bias
Allocation concealment (selection bias) - Low risk of bias
Blinding of participants and personnel (performance bias) - Low risk of bias
Blinding of outcome assessment (detection bias) - Low risk of bias
Incomplete outcome data (attrition bias) - Low risk of bias
Selective reporting (reporting bias) - Low risk of bias
Other bias - Low risk of bias

Low risk of bias
Unclear risk of bias
High risk of bias
Thrombolysis for acute deep vein thrombosis

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Any thrombolysis versus control
Outcome: 1 Any improvement in venous patency (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>15/21</td>
<td>5/21</td>
<td>13.4%</td>
<td></td>
<td>3.00 [1.33, 6.75]</td>
</tr>
<tr>
<td>Common 1976</td>
<td>17/21</td>
<td>15/25</td>
<td>16.4%</td>
<td></td>
<td>1.35 [0.92, 1.98]</td>
</tr>
<tr>
<td>Elsharawy 2002</td>
<td>18/18</td>
<td>0/17</td>
<td>3.9%</td>
<td></td>
<td>35.05 [2.28, 539.63]</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>29/53</td>
<td>2/12</td>
<td>9.8%</td>
<td></td>
<td>3.28 [0.90, 11.91]</td>
</tr>
<tr>
<td>Goldhaber 1996</td>
<td>6/8</td>
<td>6/9</td>
<td>14.9%</td>
<td></td>
<td>1.13 [0.61, 2.07]</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>7/9</td>
<td>4/9</td>
<td>13.4%</td>
<td></td>
<td>1.75 [0.78, 3.93]</td>
</tr>
<tr>
<td>Kiil 1981</td>
<td>1/11</td>
<td>1/8</td>
<td>4.2%</td>
<td></td>
<td>0.73 [0.05, 9.97]</td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>22/40</td>
<td>9/42</td>
<td>14.7%</td>
<td></td>
<td>2.57 [1.35, 4.88]</td>
</tr>
<tr>
<td>Ugurlu 2002</td>
<td>28/50</td>
<td>2/47</td>
<td>9.3%</td>
<td></td>
<td>13.16 [3.32, 52.21]</td>
</tr>
</tbody>
</table>

Total (95% CI) 231 190
Total events: 143 (Thrombolysis), 44 (Standard anticoagulation)
Heterogeneity: Tau² = 0.55; Chi² = 34.37, df = 8 (P = 0.00003); I² =77%
Test for overall effect: Z = 2.92 (P = 0.0035)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Any thrombolysis versus control
Outcome: 2 Complete clot lysis (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common 1975</td>
<td>6/23</td>
<td>1/26</td>
<td></td>
<td>12.7 %</td>
<td>6.78 [0.88, 52.23]</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>9/26</td>
<td>0/25</td>
<td></td>
<td>9.1 %</td>
<td>18.30 [1.12, 298.59]</td>
</tr>
<tr>
<td>Elsharawy 2002</td>
<td>11/18</td>
<td>0/17</td>
<td></td>
<td>9.3 %</td>
<td>21.79 [1.38, 343.26]</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>3/53</td>
<td>0/12</td>
<td></td>
<td>8.7 %</td>
<td>1.69 [0.09, 30.65]</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>6/5</td>
<td>2/9</td>
<td></td>
<td>17.3 %</td>
<td>3.00 [0.81, 11.08]</td>
</tr>
<tr>
<td>Schulman 1986</td>
<td>8/14</td>
<td>6/13</td>
<td></td>
<td>20.9 %</td>
<td>1.24 [0.59, 2.60]</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>57/200</td>
<td>1/50</td>
<td></td>
<td>13.2 %</td>
<td>14.25 [2.02, 100.42]</td>
</tr>
<tr>
<td>Ugrulu 2002</td>
<td>3/50</td>
<td>0/47</td>
<td></td>
<td>8.6 %</td>
<td>6.59 [0.35, 124.23]</td>
</tr>
</tbody>
</table>

Total (95% CI) 393 / 199

Total events: 103 (Thrombolysis), 10 (Standard anticoagulation)
Heterogeneity: Tau^2 = 1.32; Chi^2 = 10.56, df = 7 (P = 0.01); I^2 = 62%
Test for overall effect: Z = 2.67 (P = 0.0041)
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1. Any thrombolysis versus control
Outcome: 3. Bleeding (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>4/21</td>
<td>4/21</td>
<td>1.00 (0.29, 3.48)</td>
<td>16.6%</td>
<td>1.00 (0.29, 3.48)</td>
</tr>
<tr>
<td>Common 1976</td>
<td>7/23</td>
<td>5/25</td>
<td>1.58 (0.58, 4.31)</td>
<td>19.4%</td>
<td>1.58 (0.58, 4.31)</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>3/26</td>
<td>0/25</td>
<td>6.74 (0.37, 124.21)</td>
<td>2.1%</td>
<td>6.74 (0.37, 124.21)</td>
</tr>
<tr>
<td>Elsharawy 2002</td>
<td>0/18</td>
<td>0/17</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enden 2011</td>
<td>3/90</td>
<td>0/99</td>
<td>7.69 (0.40, 146.90)</td>
<td>2.0%</td>
<td>7.69 (0.40, 146.90)</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>2/53</td>
<td>0/12</td>
<td>1.20 (0.06, 23.59)</td>
<td>3.3%</td>
<td>1.20 (0.06, 23.59)</td>
</tr>
<tr>
<td>Goldhaber 1996</td>
<td>0/8</td>
<td>1/9</td>
<td>0.37 (0.02, 7.99)</td>
<td>5.9%</td>
<td>0.37 (0.02, 7.99)</td>
</tr>
<tr>
<td>Kaikkari 1969</td>
<td>4/10</td>
<td>2/9</td>
<td>1.80 (0.43, 7.59)</td>
<td>8.7%</td>
<td>1.80 (0.43, 7.59)</td>
</tr>
<tr>
<td>Kill 1981</td>
<td>3/11</td>
<td>3/8</td>
<td>0.73 (0.20, 2.71)</td>
<td>14.4%</td>
<td>0.73 (0.20, 2.71)</td>
</tr>
<tr>
<td>Marder 1977</td>
<td>7/15</td>
<td>1/12</td>
<td>5.60 (0.79, 39.48)</td>
<td>4.6%</td>
<td>5.60 (0.79, 39.48)</td>
</tr>
<tr>
<td>Schumock 1986</td>
<td>3/17</td>
<td>1/19</td>
<td>3.35 (0.31, 29.26)</td>
<td>3.9%</td>
<td>3.35 (0.31, 29.26)</td>
</tr>
<tr>
<td>Schweizer 1990</td>
<td>4/46</td>
<td>0/23</td>
<td>4.60 (0.26, 81.08)</td>
<td>2.7%</td>
<td>4.60 (0.26, 81.08)</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>12/200</td>
<td>0/50</td>
<td>6.34 (0.38, 105.36)</td>
<td>3.3%</td>
<td>6.34 (0.38, 105.36)</td>
</tr>
<tr>
<td>Tsapogas 1973</td>
<td>0/19</td>
<td>0/15</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>5/41</td>
<td>2/42</td>
<td>2.56 (0.51, 12.46)</td>
<td>8.2%</td>
<td>2.56 (0.51, 12.46)</td>
</tr>
<tr>
<td>Ugurlu 2002</td>
<td>2/50</td>
<td>0/47</td>
<td>4.71 (0.22, 95.53)</td>
<td>2.1%</td>
<td>4.71 (0.22, 95.53)</td>
</tr>
<tr>
<td>Verhaeghe 1989</td>
<td>3/14</td>
<td>0/7</td>
<td>3.73 (0.22, 63.66)</td>
<td>2.7%</td>
<td>3.73 (0.22, 63.66)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>662</strong></td>
<td><strong>441</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>2.23 [1.41, 3.52]</strong></td>
</tr>
</tbody>
</table>

Total events: 62 (Thrombolysis), 19 (Standard anticoagulation)
Heterogeneity: Chi² = 9.76, df = 14, P = 0.78; I² = 0.0%
Test for overall effect: Z = 3.42 (P = 0.00064)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1. Thrombolysis versus control
Outcome: 4. Stroke/intracerebral haemorrhage (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>0/21</td>
<td>0/21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common 1976</td>
<td>1/23</td>
<td>0/25</td>
<td>25.7%</td>
<td>3.38</td>
<td>0.14, 79.00</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>0/26</td>
<td>0/25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elsharawy 2002</td>
<td>0/18</td>
<td>0/17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enden 2011</td>
<td>0/90</td>
<td>0/99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>1/53</td>
<td>0/12</td>
<td>44.1%</td>
<td>0.72</td>
<td>0.00, 16.73</td>
</tr>
<tr>
<td>Goldhaber 1996</td>
<td>0/8</td>
<td>0/9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaikkari 1969</td>
<td>0/10</td>
<td>0/9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kil 1981</td>
<td>0/11</td>
<td>0/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marder 1977</td>
<td>1/15</td>
<td>0/12</td>
<td>30.2%</td>
<td>2.44</td>
<td>0.11, 54.97</td>
</tr>
<tr>
<td>Schultman 1986</td>
<td>0/17</td>
<td>0/19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schweizer 1990</td>
<td>0/46</td>
<td>0/23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>0/200</td>
<td>0/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsapogas 1973</td>
<td>0/19</td>
<td>0/15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>0/41</td>
<td>0/42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ugurlu 2002</td>
<td>0/50</td>
<td>0/47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verhaeghe 1989</td>
<td>0/14</td>
<td>0/7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 662/441 1.92 [0.34, 10.86]

Total events: 3 (Thrombolysis), 0 (Standard anticoagulation)
Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² = 0.0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Any thrombolysis versus control
Outcome: 5 Mortality (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>0/21</td>
<td>1/21</td>
<td></td>
<td>15.4%</td>
<td>0.32 [ 0.01, 7.74 ]</td>
</tr>
<tr>
<td>Common 1975</td>
<td>1/23</td>
<td>0/26</td>
<td></td>
<td>4.8%</td>
<td>3.38 [ 0.14, 79.00 ]</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>0/26</td>
<td>2/25</td>
<td></td>
<td>26.2%</td>
<td>0.19 [ 0.01, 3.82 ]</td>
</tr>
<tr>
<td>Elsharawy 2002</td>
<td>0/16</td>
<td>0/17</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>2/10</td>
<td>2/10</td>
<td></td>
<td>20.6%</td>
<td>1.00 [ 0.17, 5.77 ]</td>
</tr>
<tr>
<td>Kiil 1981</td>
<td>0/11</td>
<td>1/8</td>
<td></td>
<td>17.6%</td>
<td>0.25 [ 0.01, 5.45 ]</td>
</tr>
<tr>
<td>Marder 1977</td>
<td>1/15</td>
<td>0/12</td>
<td></td>
<td>5.7%</td>
<td>2.44 [ 0.11, 54.97 ]</td>
</tr>
<tr>
<td>Schulman 1966</td>
<td>1/17</td>
<td>1/19</td>
<td></td>
<td>9.7%</td>
<td>1.12 [ 0.08, 16.52 ]</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>0/200</td>
<td>0/50</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>341</strong></td>
<td><strong>188</strong></td>
<td></td>
<td>100.0%</td>
<td>0.76 [ 0.31, 1.89 ]</td>
</tr>
</tbody>
</table>

Total events: 5 (Thrombolysis), 7 (Standard anticoagulation)
Heterogeneity: CH² = 3.14, df = 6 (P = 0.76); I² = 0.0%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

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Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978</td>
<td>1/21</td>
<td>1/21</td>
<td>1.00 [0.07, 14.95]</td>
<td>14.7%</td>
</tr>
<tr>
<td>Elsharawy 2002</td>
<td>0/18</td>
<td>1/17</td>
<td>0.32 [0.01, 7.26]</td>
<td>22.6%</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>1/26</td>
<td>2/25</td>
<td>0.48 [0.05, 4.98]</td>
<td>30.0%</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>0/5</td>
<td>1/10</td>
<td>0.37 [0.02, 8.01]</td>
<td>21.0%</td>
</tr>
<tr>
<td>Schulman 1986</td>
<td>0/17</td>
<td>0/19</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>9/200</td>
<td>0/50</td>
<td>4.82 [0.29, 81.46]</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

Total (95% CI) 291 142 100.0% 1.00 [0.33, 3.05]

Total events: 11 (Thrombolysis), 5 (Standard anticoagulation)
Heterogeneity: Chisq = 2.50, df = 4 (P = 0.65); I² = 0.0%
Test for overall effect: Z = 0.01 (P = 0.39)
Test for subgroup differences: Not applicable
## Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliot 1979</td>
<td>10/26</td>
<td>24/25</td>
<td>24.6%</td>
<td></td>
<td>0.40 [0.24, 0.66]</td>
</tr>
<tr>
<td>Enden 2011</td>
<td>37/36</td>
<td>55/59</td>
<td>52.6%</td>
<td></td>
<td>0.74 [0.55, 1.00]</td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>25/44</td>
<td>17/22</td>
<td>22.8%</td>
<td></td>
<td>0.74 [0.52, 1.04]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>160</strong></td>
<td><strong>146</strong></td>
<td><strong>100.0 %</strong></td>
<td></td>
<td><strong>0.66 [0.53, 0.81]</strong></td>
</tr>
</tbody>
</table>

Total events: 72 (Thrombolysis), 96 (Standard anticoagulation)
Heterogeneity: Chi² = 4.88, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 3.92 (P = 0.000085)
Test for subgroup differences: Not applicable

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Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978</td>
<td>4/17</td>
<td>9/18</td>
<td>0.47 [0.18, 1.25]</td>
<td>12.3%</td>
<td></td>
</tr>
<tr>
<td>Enden 2011</td>
<td>37/87</td>
<td>63/89</td>
<td>0.60 [0.45, 0.79]</td>
<td>87.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>104</strong></td>
<td><strong>107</strong></td>
<td><strong>0.58 [0.45, 0.77]</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 411 (Thrombolysis), 72 (Standard anticoagulation)
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.90 (P = 0.00007)
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1. Any thrombolysis versus control
Outcome: 9 Leg ulceration (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliot 1979</td>
<td>0/26</td>
<td>1/25</td>
<td>0.32 (0.01, 7.53)</td>
<td>53.4%</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Enden 2011</td>
<td>0/90</td>
<td>0/99</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schulten 1986</td>
<td>0/17</td>
<td>0/19</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>3/44</td>
<td>1/22</td>
<td>1.50 (0.17, 13.60)</td>
<td>46.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>177</strong></td>
<td><strong>165</strong></td>
<td>0.87 (0.16, 4.73)</td>
<td><strong>100.0%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 3 (Thrombolysis), 2 (Standard anticoagulation)
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0.0%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable
## Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis  
Comparison: 1 Any thrombolysis versus control  
Outcome: 10 Leg ulceration date

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978</td>
<td>0/17</td>
<td>3/18</td>
<td>0.15 [0.01, 2.72]</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing comparison between thrombolysis and standard anticoagulation for leg ulceration rate.](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783)
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Any thrombolysis versus control
Outcome: 11 Complete clot lysis (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common 1975</td>
<td>6/15</td>
<td>1/12</td>
<td>6.1 %</td>
<td>4.80 [0.67, 34.63]</td>
</tr>
<tr>
<td>Elliot 1979 (1)</td>
<td>12/26</td>
<td>0/25</td>
<td>3.5 %</td>
<td>24.07 [1.50, 386.09]</td>
</tr>
<tr>
<td>Elsharawy 2002</td>
<td>13/18</td>
<td>2/17</td>
<td>10.5 %</td>
<td>6.14 [1.62, 23.28]</td>
</tr>
<tr>
<td>Enden 2011 (2)</td>
<td>68/90</td>
<td>56/99</td>
<td>25.4 %</td>
<td>1.34 [1.08, 1.65]</td>
</tr>
<tr>
<td>Schulman 1986 (3)</td>
<td>11/17</td>
<td>6/19</td>
<td>17.9 %</td>
<td>2.05 [0.97, 4.33]</td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>27/44</td>
<td>8/22</td>
<td>20.2 %</td>
<td>1.69 [0.93, 3.08]</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>61/180</td>
<td>5/46</td>
<td>16.3 %</td>
<td>3.12 [1.33, 7.21]</td>
</tr>
</tbody>
</table>

Total (95% CI)
Total events: 198 (Thrombolysis), 78 (Standard anticoagulation)
Heterogeneity: Tau^2 = 0.31; Chi^2 = 19.92, df = 6 (P = 0.003; I^2 =70%
Test for overall effect: Z = 3.13 (P = 0.0017)
Test for subgroup differences: Not applicable

---

(1) control result for Elliot, entered as 2 in previous versions, reviewed as 0
(2) 24 months
(3) 12 month data
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Thrombolysis versus control
Outcome: 1. Complete clot lysis (late)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Random 25% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H, Random 25% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978 (1)</td>
<td>7/16</td>
<td>0/18</td>
<td>16.76 [1.03, 272.11]</td>
<td>39.4%</td>
<td></td>
</tr>
<tr>
<td>Enden 2011 (2)</td>
<td>68/86</td>
<td>61/86</td>
<td>1.11 [0.94, 1.33]</td>
<td>60.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>102</strong></td>
<td><strong>104</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>3.25 [0.17, 62.63]</strong></td>
</tr>
</tbody>
</table>

Total events: 75 (Thrombolysis), 61 (Standard anticoagulation)
Heterogeneity: Tau² = 3.76, Chi² = 4.70, df = 1 (P = 0.09), I² = 79%
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable

(1) mean follow up 6.5 years
(2) Four patients had inconclusive results and not reported.
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Any thrombolysis versus control
Outcome: 1.3 Mortality (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliot 1979</td>
<td>4/26</td>
<td>4/25</td>
<td></td>
<td>100.0 %</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>0/192</td>
<td>0/46</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>218/71</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Total events: 4 (Thrombolysis), 4 (Standard anticoagulation)
Heterogeneity: not applicable
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable

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Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Any thrombolysis versus control
Outcome: 14 Mortality data

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978</td>
<td>4/21</td>
<td>3/21</td>
<td>25.8%</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Enden 2011</td>
<td>3/90</td>
<td>9/98</td>
<td>74.2%</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**
- Total events: 7 (Thrombolysis), 12 (Standard anticoagulation)
- Heterogeneity: Chi² = 1.89, df = 1 (P = 0.17); I² = 47%
- Test for overall effect: Z = 1.07 (P = 0.28)
- Test for subgroup differences: Not applicable

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Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 1 Any thrombolysis versus control
Outcome: 15 Normal venous function (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elsharawy 2002</td>
<td>13/18</td>
<td>2/17</td>
<td>23.4 %</td>
<td></td>
<td>6.14 [1.62, 23.28]</td>
</tr>
<tr>
<td>Enden 2011</td>
<td>29/36</td>
<td>13/39</td>
<td>38.0 %</td>
<td></td>
<td>2.45 [1.36, 4.42]</td>
</tr>
<tr>
<td>Schulman 1966</td>
<td>10/16</td>
<td>9/15</td>
<td>38.6 %</td>
<td></td>
<td>1.04 [0.59, 1.83]</td>
</tr>
</tbody>
</table>

Total (95% CI) 124 131

Total events: 52 (Thrombolysis), 24 (Standard anticoagulation)
Heterogeneity: Tau² = 0.50; Chi² = 9.34, df = 2 (P = 0.01); I² = 79%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable

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### Thrombolysis for acute deep vein thrombosis

#### Review: Thrombolysis for acute deep vein thrombosis

**Comparison:** 1 Any thrombolysis versus control

**Outcome:** 1.6 Recurrent DVT (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>4/17</td>
<td>3/18</td>
<td></td>
<td>1.41 [0.37, 5.40]</td>
</tr>
</tbody>
</table>

![Graph showing risk ratio](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig-00116)
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 1 Any improvement in venous patency (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio N-H, Random, 95% CI</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnason 1978</td>
<td>15/21</td>
<td>5/21</td>
<td>3.00 [1.33, 6.75]</td>
<td>13.9 %</td>
</tr>
<tr>
<td>Common 1975</td>
<td>17/21</td>
<td>15/25</td>
<td>1.35 [0.92, 1.98]</td>
<td>18.7 %</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>29/53</td>
<td>2/12</td>
<td>3.28 [0.90, 11.91]</td>
<td>9.3 %</td>
</tr>
<tr>
<td>Goldhaber 1996</td>
<td>6/8</td>
<td>5/9</td>
<td>1.13 [0.61, 2.07]</td>
<td>16.2 %</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>7/5</td>
<td>4/9</td>
<td>1.75 [0.78, 3.93]</td>
<td>14.0 %</td>
</tr>
<tr>
<td>Kiil 1981</td>
<td>1/11</td>
<td>1/8</td>
<td>0.73 [0.05, 9.97]</td>
<td>3.4 %</td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>22/40</td>
<td>9/42</td>
<td>2.57 [1.35, 4.88]</td>
<td>15.8 %</td>
</tr>
<tr>
<td>Ugurlu 2002</td>
<td>28/50</td>
<td>2/47</td>
<td>13.16 [3.32, 52.21]</td>
<td>8.6 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 213 173
Total events: 125 (Thrombolysis), 44 (Standard anticoagulant)
Heterogeneity: Tukey = 0.36, Chi² = 23.77, df = 7 (P = 0.001), I² = 71%
Test for overall effect: Z = 2.87 (P = 0.004)
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-M, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common 1975</td>
<td>6/23</td>
<td>1/26</td>
<td></td>
<td>14.0%</td>
<td>6.78 [0.88, 52.23]</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>9/26</td>
<td>0/25</td>
<td></td>
<td>10.1%</td>
<td>18.30 [1.12, 298.59]</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>3/53</td>
<td>0/12</td>
<td></td>
<td>9.6%</td>
<td>1.69 [0.09, 10.65]</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>6/5</td>
<td>2/9</td>
<td></td>
<td>19.2%</td>
<td>3.00 [0.81, 11.08]</td>
</tr>
<tr>
<td>Schulman 1966</td>
<td>8/14</td>
<td>6/13</td>
<td></td>
<td>23.1%</td>
<td>1.24 [0.59, 2.60]</td>
</tr>
<tr>
<td>Schweitzer 2000</td>
<td>37/100</td>
<td>1/50</td>
<td></td>
<td>14.6%</td>
<td>18.50 [2.61, 130.95]</td>
</tr>
<tr>
<td>Ugurlu 2002</td>
<td>3/50</td>
<td>0/47</td>
<td></td>
<td>9.5%</td>
<td>6.59 [0.35, 124.23]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>275</strong></td>
<td><strong>182</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>4.37 [1.40, 13.61]</strong></td>
</tr>
</tbody>
</table>

Total events: 72 (Thrombolysis), 10 (Standard anticoagulant)
Heterogeneity: Tau² = 1.31; Chi² = 16.57, df = 6 (P = 0.01); I² = 64%
Test for overall effect: Z = 2.54 (P = 0.011)
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 3 Bleeding (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>4/21</td>
<td>4/21</td>
<td>17.0 %</td>
<td>1.00 [0.29, 3.48]</td>
</tr>
<tr>
<td>Common 1975</td>
<td>7/23</td>
<td>5/26</td>
<td>19.9 %</td>
<td>1.58 [0.58, 4.31]</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>3/26</td>
<td>0/25</td>
<td>2.2 %</td>
<td>6.74 [0.37, 12.42]</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>2/53</td>
<td>0/12</td>
<td>3.4 %</td>
<td>1.20 [0.06, 23.59]</td>
</tr>
<tr>
<td>Goldhaber 1996</td>
<td>0/8</td>
<td>1/9</td>
<td>6.0 %</td>
<td>0.37 [0.02, 7.99]</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>4/10</td>
<td>2/9</td>
<td>8.9 %</td>
<td>1.80 [0.43, 7.59]</td>
</tr>
<tr>
<td>Kiil 1981</td>
<td>3/11</td>
<td>3/8</td>
<td>14.8 %</td>
<td>0.73 [0.20, 2.71]</td>
</tr>
<tr>
<td>Marder 1977</td>
<td>7/15</td>
<td>1/12</td>
<td>4.7 %</td>
<td>5.60 [0.79, 39.48]</td>
</tr>
<tr>
<td>Schulman 1986</td>
<td>3/17</td>
<td>1/19</td>
<td>4.0 %</td>
<td>3.35 [0.38, 23.26]</td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>4/46</td>
<td>0/23</td>
<td>2.8 %</td>
<td>4.60 [0.26, 81.88]</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>9/100</td>
<td>0/50</td>
<td>2.8 %</td>
<td>9.59 [0.57, 161.57]</td>
</tr>
<tr>
<td>Tsapogas 1973</td>
<td>0/15</td>
<td>0/15</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>5/41</td>
<td>2/42</td>
<td>8.4 %</td>
<td>2.56 [0.53, 12.46]</td>
</tr>
<tr>
<td>Ugelrud 2002</td>
<td>2/50</td>
<td>0/47</td>
<td>2.2 %</td>
<td>4.71 [0.23, 95.53]</td>
</tr>
<tr>
<td>Verhaeghe 1989</td>
<td>3/14</td>
<td>0/7</td>
<td>2.8 %</td>
<td>3.73 [0.22, 63.66]</td>
</tr>
</tbody>
</table>

Total (95% CI): 454/325 (100.0 %) 2.18 [1.37, 3.47]

Total events: 56 Thrombolysis, 19 (Standard anticoagulation)
Heterogeneity: Chi² = 9.45, df = 13 (P = 0.74); I² = 0.0%
Test for overall effect: Z = 3.30 (P = 0.00067)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 4 Stroke/intracerebral haemorrhage (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnason 1978</td>
<td>0/21</td>
<td>0/21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common 1975</td>
<td>1/23</td>
<td>0/26</td>
<td></td>
<td>25.7%</td>
<td>3.38 [0.14, 79.00]</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>0/26</td>
<td>0/25</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Goldhaber 1990</td>
<td>1/53</td>
<td>0/12</td>
<td>44.1%</td>
<td></td>
<td>0.72 [0.03, 16.73]</td>
</tr>
<tr>
<td>Goldhaber 1996</td>
<td>0/8</td>
<td>0/9</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>0/10</td>
<td>0/9</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Kiil 1981</td>
<td>0/11</td>
<td>0/8</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Marder 1977</td>
<td>1/15</td>
<td>0/12</td>
<td>30.2%</td>
<td></td>
<td>2.44 [0.11, 54.97]</td>
</tr>
<tr>
<td>Schulman 1986</td>
<td>0/17</td>
<td>0/19</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>0/46</td>
<td>0/23</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>0/100</td>
<td>0/50</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Tsapogas 1973</td>
<td>0/15</td>
<td>0/15</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Turpie 1990</td>
<td>0/41</td>
<td>0/42</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Ugurlu 2002</td>
<td>0/50</td>
<td>0/47</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Verhaeghe 1989</td>
<td>0/14</td>
<td>0/7</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total (95% CI)

Total events: 3 (Thrombolysis), 0 (Standard anticoagulant)
Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² = 0.0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 5 Mortality (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978</td>
<td>0/21</td>
<td>1/21</td>
<td>15.4%</td>
<td></td>
<td>0.33 [0.01, 7.74]</td>
</tr>
<tr>
<td>Common 1975</td>
<td>1/23</td>
<td>0/26</td>
<td>4.8%</td>
<td></td>
<td>3.38 [0.14, 79.00]</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>0/26</td>
<td>2/25</td>
<td>26.2%</td>
<td></td>
<td>0.19 [0.01, 3.82]</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>2/10</td>
<td>2/10</td>
<td>20.6%</td>
<td></td>
<td>1.00 [0.17, 5.77]</td>
</tr>
<tr>
<td>Kiil 1981</td>
<td>0/11</td>
<td>1/8</td>
<td>17.6%</td>
<td></td>
<td>0.25 [0.01, 5.45]</td>
</tr>
<tr>
<td>Marder 1977</td>
<td>1/15</td>
<td>0/12</td>
<td>5.7%</td>
<td></td>
<td>2.44 [0.11, 54.97]</td>
</tr>
<tr>
<td>Schulman 1986</td>
<td>1/17</td>
<td>1/19</td>
<td>9.7%</td>
<td></td>
<td>1.12 [0.08, 16.52]</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>0/100</td>
<td>0/50</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 223 171 100.0% 0.76 [0.31, 1.89]

Total events: 5 (Thrombolysis), 7 (Standard anticoagulant)
Heterogeneity: Chi² = 3.14, df = 6 (P = 0.79); I² = 0.0%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 6 Pulmonary embolism (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Arnesen 1978</td>
<td>1/21</td>
<td>1/21</td>
<td></td>
<td>19.5 %</td>
<td>1.00 [0.07, 14.95]</td>
</tr>
<tr>
<td>Elliot 1979</td>
<td>1/26</td>
<td>2/25</td>
<td></td>
<td>39.7 %</td>
<td>0.46 [0.05, 4.98]</td>
</tr>
<tr>
<td>Kakkar 1969</td>
<td>0/5</td>
<td>1/10</td>
<td></td>
<td>27.8 %</td>
<td>0.37 [0.02, 8.01]</td>
</tr>
<tr>
<td>Schuller 1966</td>
<td>0/17</td>
<td>0/19</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>9/100</td>
<td>0/50</td>
<td></td>
<td>12.9 %</td>
<td>9.59 [0.57, 161.57]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>173</strong></td>
<td><strong>125</strong></td>
<td><strong>100.0 %</strong></td>
<td></td>
<td><strong>1.73 [0.55, 5.40]</strong></td>
</tr>
</tbody>
</table>

Total events: 11 (Thrombolysis), 4 (Standard anticoagulant)
Heterogeneity: Ch² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.34 (P = 0.35)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 7 Post-thrombotic syndromes (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliot 1979</td>
<td>10/26</td>
<td>24/25</td>
<td>0.40 (0.24, 0.66)</td>
<td>45.8%</td>
<td></td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>25/44</td>
<td>17/22</td>
<td>0.74 (0.52, 1.04)</td>
<td>54.2%</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI)
- 70
- 47
- 100.0%
- 0.56 (0.30, 1.03)

Test for overall effect: Z = 1.88 (P = 0.060)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
## Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** 2 Systemic thrombolysis versus control  
**Outcome:** B Post-thrombotic syndrome (late)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978</td>
<td>4/17</td>
<td>9/18</td>
<td>0.47 [0.18, 1.25]</td>
<td></td>
</tr>
</tbody>
</table>

---

![Graph showing risk ratio](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig00208)
Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliot 1979</td>
<td>0/26</td>
<td>1/25</td>
<td></td>
<td>53.4%</td>
<td>0.32 [0.01, 7.53]</td>
</tr>
<tr>
<td>Schulten 1986</td>
<td>0/17</td>
<td>0/19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>3/44</td>
<td>1/22</td>
<td></td>
<td>46.6%</td>
<td>1.50 [0.17, 13.60]</td>
</tr>
</tbody>
</table>

Total (95% CI)

Total events: 3 (Thrombolysis), 2 (Standard anticoagulant)
Heterogeneity: $\chi^2 = 0.62$, df = 1 ($P = 0.43$); $I^2 = 0.0$
Test for overall effect: $z = 0.16$ ($P = 0.87$)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
### Thrombolysis for acute deep vein thrombosis

#### Review: Thrombolysis for acute deep vein thrombosis
#### Comparison: 2 Systemic thrombolysis versus control
#### Outcome: 10 Leg ulceration (late)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>0/17</td>
<td>3/18</td>
<td>0.15 [0.01, 2.72]</td>
</tr>
</tbody>
</table>

![Graph](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig00210)
## Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** 2 Systemic thrombolysis versus control  
**Outcome:** 11 Complete clot lysis (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common 1976</td>
<td>6/15</td>
<td>1/12</td>
<td></td>
<td>9.7%</td>
<td>4.80 [0.67, 34.63]</td>
</tr>
<tr>
<td>Elliot 1979 (1)</td>
<td>12/26</td>
<td>0/25</td>
<td></td>
<td>5.6%</td>
<td>24.07 [1.50, 386.09]</td>
</tr>
<tr>
<td>Schulman 1986</td>
<td>11/15</td>
<td>6/12</td>
<td></td>
<td>29.5%</td>
<td>1.47 [0.77, 2.79]</td>
</tr>
<tr>
<td>Schweizer 1998</td>
<td>27/44</td>
<td>8/22</td>
<td></td>
<td>30.4%</td>
<td>1.69 [0.93, 3.08]</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>37/83</td>
<td>5/46</td>
<td></td>
<td>24.7%</td>
<td>4.10 [1.73, 9.71]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
Total events: 93 (Thrombolysis), 20 (Standard anticoagulant)  
Heterogeneity: Tau² = 0.34; Chi² = 10.12, df = 4 (P = 0.04); I² = 60%  
Test for overall effect: Z = 2.62 (P = 0.0087)  
Test for subgroup differences: Not applicable

(1) Control events changed to 1

---

Cochrane Database of Systematic Reviews  
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4  
### Thrombolysis for acute deep vein thrombosis

#### Comparison: Systemic thrombolysis versus control

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978 (1)</td>
<td>7/16</td>
<td>0/18</td>
<td>16.75 [1.03, 272.11]</td>
</tr>
</tbody>
</table>

(1) Results reported at mean of 6.5 years.
### Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** 2 Systemic thrombolysis versus control  
**Outcome:** 13 Mortality (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliot 1979</td>
<td>4/26</td>
<td>4/25</td>
<td></td>
<td>100.0%</td>
<td>0.96 [0.27, 3.43]</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>0/92</td>
<td>0/46</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 118/71  
Total events: 4 (Thrombolysis), 4 (Standard anticoagulant)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.06 (P = 0.95)  
Test for subgroup differences: Not applicable

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Cochrane Database of Systematic Reviews  
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4  
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 14 Mortality (late)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arneson 1978</td>
<td>4/21</td>
<td>3/21</td>
<td>1.33 [0.34, 5.24]</td>
</tr>
</tbody>
</table>

favours thrombolysis

favours anticoagulation
## Thrombolysis for acute deep vein thrombosis

### Review: Thrombolysis for acute deep vein thrombosis
### Comparison: Systemic thrombolysis versus control
### Outcome: Normal venous function (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulman 1986</td>
<td>10/16</td>
<td>9/15</td>
<td>1.04 [0.59, 1.83]</td>
<td></td>
</tr>
</tbody>
</table>

![Figure](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fg-00215)
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 2 Systemic thrombolysis versus control
Outcome: 16 Recurrent DVT (late)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulation n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesen 1978</td>
<td>4/17</td>
<td>3/18</td>
<td></td>
<td>1.41 [0.37, 5.40]</td>
</tr>
</tbody>
</table>

Cochrane Database of Systematic Reviews
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Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 2000</td>
<td>10/50</td>
<td>1/50</td>
<td>10.00 [1.33, 75.23]</td>
<td>10.00 [1.33, 75.23]</td>
</tr>
</tbody>
</table>

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 3 Loco-regional thrombolysis versus control
Outcome: 1 Complete clot lysis (early)
Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 1998</td>
<td>2/23</td>
<td>0/23</td>
<td>5.00 [0.25, 98.75]</td>
<td>50.0 %</td>
<td></td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>1/50</td>
<td>0/50</td>
<td>3.00 [0.13, 71.92]</td>
<td>50.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>73</td>
<td>73</td>
<td>4.00 [0.46, 34.75]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 3 (Thrombolysis), 0 (Standard anticoagulant)
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0.0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 1998</td>
<td>0/23</td>
<td>0/23</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>0/50</td>
<td>0/50</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>73</strong></td>
<td><strong>73</strong></td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: not applicable
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
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### Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** Local-regional thrombolysis versus control  
**Outcome:** Early mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 2000</td>
<td>0/50</td>
<td>0/50</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

---

![Graph of results](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig-00304)
## Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** Loco-regional thrombolysis versus control  
**Outcome:** Pulmonary embolism (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio (M-H) Fixed 95% CI</th>
<th>Risk Ratio (M-H) Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 2000</td>
<td>0/50</td>
<td>0/50</td>
<td>1</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

![Graph showing risk ratio for Thrombolysis vs Standard anticoagulation](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig00305)
## Thrombolysis for acute deep vein thrombosis

### Table: Treatment of acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 1998</td>
<td>11/22</td>
<td>17/22</td>
<td></td>
<td>0.65 [0.40, 1.04]</td>
</tr>
</tbody>
</table>

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 3 Loco-regional thrombolysis versus control
Outcome: 7 Leg ulceration (Intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 1998</td>
<td>1/22</td>
<td>1/22</td>
<td>1.00 [0.67, 1.50]</td>
<td>1.00 [0.67, 1.50]</td>
</tr>
</tbody>
</table>

favours thrombolysis

favours anticoagulation

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
# Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis  
Comparison: 3 Loco-regional thrombolysis versus control  
Outcome: 8 Complete clot lysis (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 1998</td>
<td>17/22</td>
<td>8/22</td>
<td>2.13 [1.17, 3.86]</td>
<td>60.8%</td>
<td></td>
</tr>
<tr>
<td>Schweizer 2000</td>
<td>13/45</td>
<td>5/46</td>
<td>2.44 [0.94, 6.31]</td>
<td>39.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>71</strong></td>
<td><strong>68</strong></td>
<td>2.25 [1.33, 3.80]</td>
<td><strong>100.0%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 30 Thrombolysis, 13 (Standard anticoagulant)  
Heterogeneity: CH² = 0.06, df = 1 (P = 0.80); I² = 0.0%  
Test for overall effect: Z = 3.03 (P = 0.0025)  
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweizer 2000</td>
<td>0/50</td>
<td>0/46</td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>
# Thrombolysis for acute deep vein thrombosis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elsharawy 2002</td>
<td>18/18</td>
<td>0/17</td>
<td>35.05 [2.28, 539.63]</td>
<td>0.001 0.01 0.1 1 10 100 1000 favours anticoagulation favours thrombolysis</td>
</tr>
</tbody>
</table>

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** Catheter-directed thrombolysis versus control  
**Outcome:** Any improvement in venous patency (early)
### Thrombolysis for acute deep vein thrombosis

**Study or subgroup** | **Thrombolysis n/N** | **Standard anticoagulant n/N** | **Risk Ratio** M-H.Fixed 95% CI | **Risk Ratio** M-H.Fixed 95% CI
---|---|---|---|---
Elsharawy 2002 | 11/18 | 0/17 |  | 21.79 [1.36, 343.26]

![Plot](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig-00402)

**Review:** Thrombolysis for acute deep vein thrombosis

**Comparison:** 4 Catheter-directed thrombolysis versus control

**Outcome:** 2 Complete clot lysis (early)
Thrombolysis for acute deep vein thrombosis

- **Elsharway 2002**
  - Thrombolysis: 0/18
  - Standard anticoagulant: 0/17
  - Risk Ratio (M-H, Fixed, 95% CI): Not estimable

- **Enden 2011**
  - Thrombolysis: 3/90
  - Standard anticoagulant: 0/99
  - Weight: 100.0%
  - Risk Ratio (M-H, Fixed, 95% CI): 7.69 [0.40, 146.90]

**Total (95% CI)**
- Total events: 3 (Thrombolysis), 0 (Standard anticoagulant)
- Heterogeneity: not applicable
- Test for overall effect: Z = 1.36 (P = 0.18)
- Test for subgroup differences: Not applicable
## Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** Catheter-directed thrombolysis versus control  
**Outcome:** Stroke/intracerebral haemorrhage (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elsharawy 2002</td>
<td>0/18</td>
<td>0/17</td>
<td>0.1-10</td>
<td>0.1-10</td>
</tr>
</tbody>
</table>

- favours thrombolysis  
- favours anticoagulation
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 4 Catheter-directed thrombolysis versus control
Outcome: 5 Mortality (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elsharawy 2002</td>
<td>0/18</td>
<td>0/17</td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

 favours thrombolysis

 favours anticoagulation

Cochrane Database of Systematic Reviews
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## Thrombolysis for acute deep vein thrombosis

### Review: Thrombolysis for acute deep vein thrombosis

**Comparison:** 4 Catheter-directed thrombolysis versus control

**Outcome:** 6 Pulmonary embolism (early)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>El sharawy 2002</td>
<td>0/18</td>
<td>1/17</td>
<td>-</td>
<td>0.32 [0.01, 7.26]</td>
</tr>
</tbody>
</table>

![Risk Ratio Graph](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig-00406)
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 4 Catheter-directed thrombolysis versus control
Outcome: 7 Post-thrombotic syndrome (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden 2011</td>
<td>37/90</td>
<td>55/99</td>
<td>0.74 [0.55, 1.00]</td>
<td>0.74 [0.55, 1.00]</td>
</tr>
</tbody>
</table>

favour thrombolysis

favour anticoagulation
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: Catheter-directed thrombolysis versus control
Outcome: Post-thrombotic syndrome (late)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden 2011</td>
<td>37/87</td>
<td>63/89</td>
<td>0.60 [0.45, 0.79]</td>
<td></td>
</tr>
</tbody>
</table>
## Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** Catheter-directed thrombolysis versus control  
**Outcome:** Leg ulceration (Intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden 2011</td>
<td>0/90</td>
<td>0/99</td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

![Graph showing comparison of thrombolysis vs standard anticoagulation](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002783.pub4/full#CD002783-fig00409)
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 4 Catheter-directed thrombolysis versus control
Outcome: 10 Complete clot lysis (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Random 95% CI</th>
<th>Weight</th>
<th>Risk Ratio N-H,Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elsharawy 2002</td>
<td>13/18</td>
<td>2/17</td>
<td></td>
<td>41.5 %</td>
<td>6.14 [1.62, 23.28]</td>
</tr>
<tr>
<td>Enden 2011</td>
<td>68/90</td>
<td>56/99</td>
<td></td>
<td>58.5 %</td>
<td>1.34 [1.08, 1.65]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>108</strong></td>
<td><strong>116</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.52 [0.52, 12.17]</strong></td>
</tr>
</tbody>
</table>

Total events: 81 (Thrombolysis), 58 (Standard anticoagulant)
Heterogeneity: Tau^2 = 1.09; Chi^2 = 5.62, df = 1 (P = 0.02); P = 82%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
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### Thrombolysis for acute deep vein thrombosis

#### Review: Thrombolysis for acute deep vein thrombosis
**Comparison:** Catheter-directed thrombolysis versus control
**Outcome:** Complete clot lysis (late)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden 2011 (1)</td>
<td>68/86</td>
<td>61/86</td>
<td>1.11 [0.94, 1.33]</td>
</tr>
</tbody>
</table>

(1) Four patients had inconclusive results and not reported.

---

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: Catheter-directed thrombolysis versus control
Outcome: Normal venous function (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden 2011</td>
<td>29/90</td>
<td>13/99</td>
<td>2.45 [1.36, 4.42]</td>
<td>85.8%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>108</strong></td>
<td><strong>116</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 42 (Thrombolysis), 15 (Standard anticoagulant)
Heterogeneity: Ch^2 = 1.55, df = 1 (P = 0.21); I^2 = 0%
Test for overall effect: Z = 4.01 (P = 0.000060)
Test for subgroup differences: Not applicable
Thrombolysis for acute deep vein thrombosis

Review: Thrombolysis for acute deep vein thrombosis
Comparison: 4 Catheter-directed thrombolysis versus control
Outcome: 13 Recurrent VTE (intermediate)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden 2011</td>
<td>10/90</td>
<td>18/99</td>
<td>0.61 [0.30, 1.25]</td>
</tr>
</tbody>
</table>

Cochrane Database of Systematic Reviews
10 NOV 2016 DOI: 10.1002/14651858.CD002783.pub4
### Thrombolysis for acute deep vein thrombosis

**Review:** Thrombolysis for acute deep vein thrombosis  
**Comparison:** Catheter-directed thrombolysis versus control  
**Outcome:** Recurrent VTE (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Standard anticoagulant n/N</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
<th>Risk Ratio M-H.Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enden 2011</td>
<td>13/87</td>
<td>21/89</td>
<td>0.63 (0.34, 1.18)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: The figure represents the risk ratio for recurrent VTE (days) comparing thrombolysis to standard anticoagulant treatment.*
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CDT: catheter-directed thrombolysis; CI: Confidence Interval; DVT: deep vein thrombosis; PTS: post-thrombotic syndrome; RCT: randomised controlled trial RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded by one level as confidence intervals are wide around the estimate of the effect
2. Downgraded by one level as confidence intervals wide around the estimate of effect. Studies did not report any bleeding events in standard anticoagulation group
3. Results are from one small study with a small number of events. Downgraded by one level
• 35 pts w/ iliofemoral DVT
• CDT w/ AC vs AC alone
• Streptokinase--2-4.5 million units total w/ infusion rate of 100,000 U/HR
• NO bleeding complications
• NO mortality
At 6 months, patency rate was better in cases treated with thrombolysis [13/18 (72%) vs 2/17 (12%), \(p < 0.001\)]. Venous reflux was higher in patients treated with ONLY anticoagulant [7 patients (41%) vs 2 (11%), \(p = 0.04\) ].
• NICE 2012

• DUTCH CAVA-trial. Ultrasound accelerated catheter-directed thrombolysis for primary iliofemoral deep vein thrombosis (IFDVT) compared to non-invasive conventional anticoagulant therapy alone: a Dutch randomized controlled multicenter clinical trial.

Evidence-Based Medicine

Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD, Elie A. Akl, MD, MPH, PhD, Joseph Ornelas, PhD, Allen Blaivas, DO, FCCP, David Jimenez, MD, PhD, FCCP, Henri Bounaumeaux, MD, Menno Huisman, MD, PhD,
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Thrombolysis for acute deep vein thrombosis
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