The Evidence Base for Treating Acute DVT

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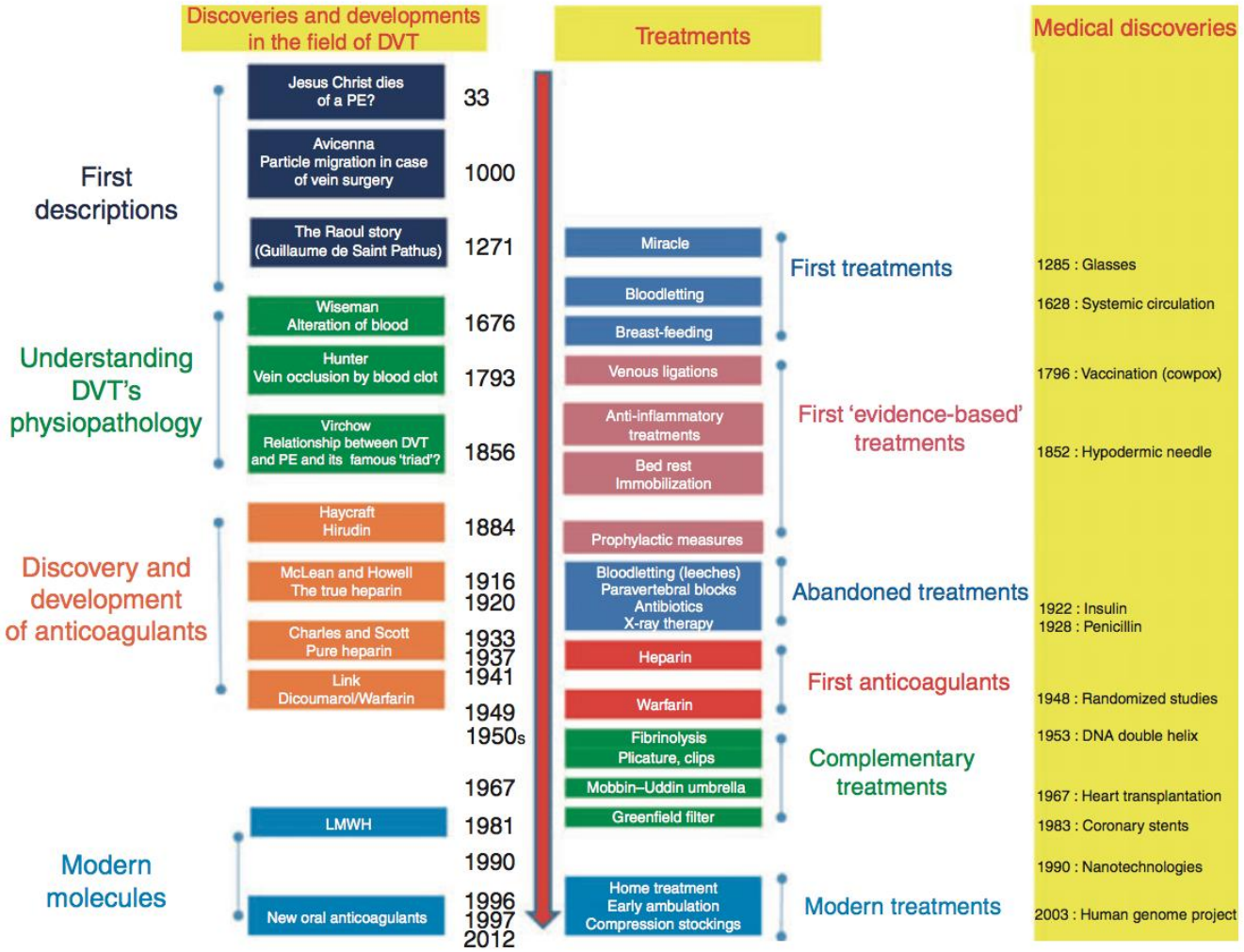
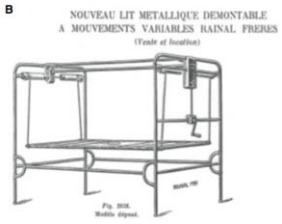
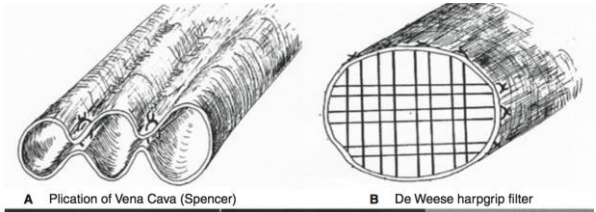
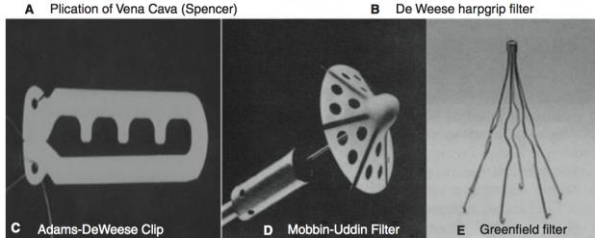
NIHR UCLH Biomedical Research Centre

A brief summary of history of DVT









Galanaud J-P et al. J Thromb Haemost 2013

Treatment aims for acute DVT

Early and accurate diagnosis (+ early treatment)

Symptomatic relief

Prevention of propagation of thrombus and pulmonary embolism (PE)

Prevention of recurrence of venous thromboembolism

Safe, and minimal bleeding and other risks / side effects

Prevention of post thrombotic syndrome (PTS)

Choice of anticoagulant

Prevention of thrombus propagation, PE and recurrent VTE

Many guidelines recommend the following

1. DOAC
2. Vitamin K antagonist, VKA (warfarin)
3. Low molecular weight heparin (LMWH)

GRADE 2B and 2C recommendations (CHEST Guideline and Expert Panel Report)[1]

1. *Kearon C et al. CHEST 2016*
2. *Konstantinides SV et al. Eur Heart J 2014*
3. *Mazzolai L et al. Eur Heart J 2017*

DOAC versus LMWH/VKA

Compared with LMWH followed by VKA, DOACs are[1]:

- Non-inferior for recurrent VTE
- Lower risk of major bleeding (absolute risk 1.1% vs 1.8%; risk ratio 0.62; 95% CI 0.45-0.85) in the first month of VTE[2, 3, 4]

DOAC therapy is more expensive than VKA

- Monthly cost for DOAC US$333-$419; VKA US$8[4]

1. *Tritschler T et al. JAMA 2018*
2. *Schulman S et al. J Thromb Haemost 2005*
3. *Gomez-Outes A et al. Thromb Res 2014*
4. *Gomez-Outes A et al. J Cardiovasc Pharmacol Ther 2015*
5. *Med Lett Drugs Ther 2018*

Duration of anticoagulation

VTE “provoked” by a transient risk factor

- Provoked by surgery - low risk of recurrence after treatment (<1% after 1 year and 3% after 5 years)
- Provoked by non-surgical transient risk factor, such as immobilisation, pregnancy, or oestrogen therapy - intermediate risk of recurrent VTE (5% after 1 year and 15% after 5 years)
- Only 3 months of anti-coagulation; RCTs demonstrated risk of bleeding outweighed recurrent VTE for >3 months

1. *Kearon C et al. CHEST 2016*
2. *Tritschler T et al. JAMA 2018*
3. *NICE CG144*
4. *Konstantinides SV et al. Eur Heart J 2014*

Duration of anticoagulation

VTE “provoked” by a persistent risk factor

- E.g. cancer-associated VTE have a high risk of recurrence (15% annualised), and therapy may be given until the cancer is cured (limited evidence)

“Unprovoked” VTE; no identifiable risk factor

- Patients with a first unprovoked VTE have a high risk of recurrence of VTE (10% after 1 year and 30% at 5 years)
- Indefinite therapy unless bleeding risk is high
- The risk in men is at least double that in women

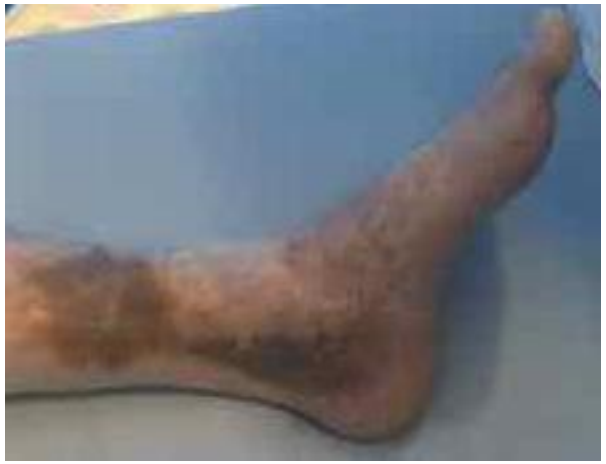
1. *Kearon C et al. CHEST 2016*
2. *Tritschler T et al. JAMA 2018*
3. *NICE CG144*
4. *Konstantinides SV et al. Eur Heart J 2014*
5. *Mazzolai L et al. Eur Heart J 2017*

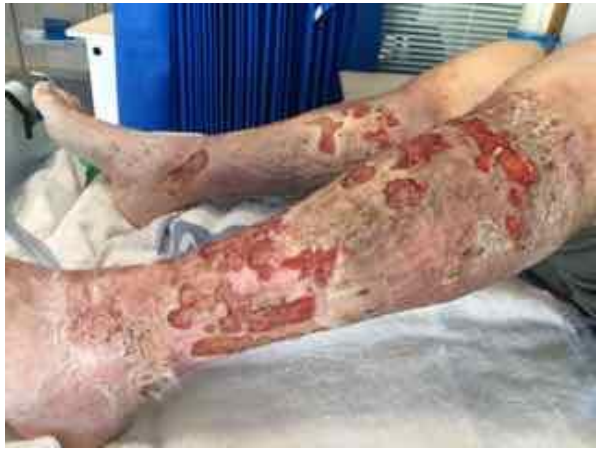
Post thrombotic syndrome (PTS)

Risk of 20-50% following DVT particularly iliofemoral (up to 80%)

Significant morbidity and reduces quality-of-life

Significant socioeconomic implications

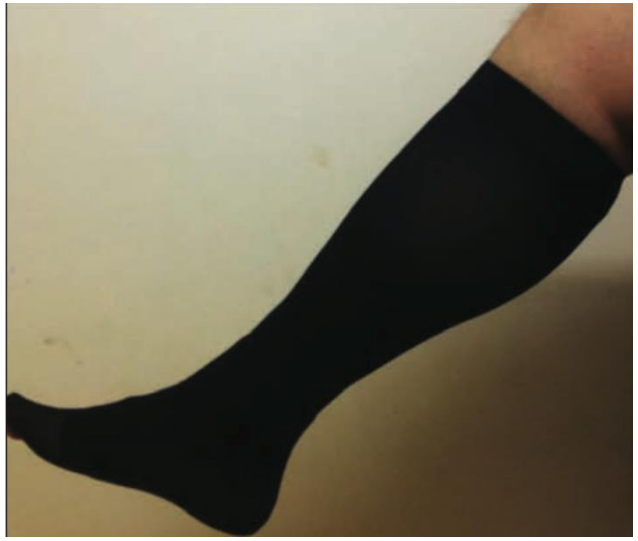




1. *Vasquez SR and Kahn SR. Circulation 2010*
2. *O'Donnell T et al. J Surg Res 1977*
3. *Busuttil A et al. Adv Exp Med Biol 2017*

Post thrombotic syndrome (PTS)

Compression therapy has been removed from many guidelines including NICE and CHEST due to insufficient evidence that it prevents PTS (GRADE 2B recommendation in CHEST guideline[1]). However, it should still be offered / considered for symptomatic relief



1. *Kearon C et al. CHEST 2016*
2. *Tritschler T et al. JAMA 2018*
3. *NICE*

Early removal of thrombus

Thrombosis causes

- acute and chronic inflammation leading to scarring of vessels, leading to obstructive venous disease

- Valvular damage leading to venous incompetence (reflux)

Early removal of thrombus (thrombolysis/thrombectomy) may reduce such risk

Systemic thrombolysis

Routine use for acute DVT is discouraged by high rates of incomplete thrombolysis and bleeding complications

Pooled analysis of 6 RCTs (streptokinase)[2]:

- 3.7 times more likely than heparin to produce “greater than minimal” thrombolysis
- Expense of 2.9-fold increase in major bleeding complications

A German multicentre study (tpa)[2]:

- Complete thrombolysis in only 8.9%
- No thrombus reduction in 33.8%

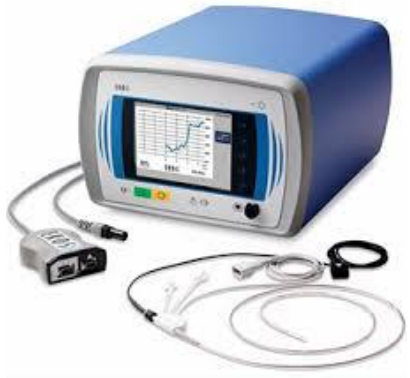
1. *Goldhaber SZ et al. Am J Med 1984*
2. *Schwieder G et al. Thromb Haemost 1995*

Catheter-directed (CDT) / pharmacomechanical (PMT) thrombolysis

CDT

PMT

- Potential benefits:
  - Shorter procedural time
  - Lower thrombolytic agent dose
  - Lower associated systemic effects
  - Lower cost
  - More complete thrombus resolution



Iliofemoral DVT

Compared to femoropopliteal DVT, iliofemoral DVT is associated with higher risk of PTS

Early non randomised studies demonstrated thrombolysis is safe and efficiently removing thrombus in iliofemoral DVT

1. *Mewissen MW et al. Radiology 1999*
2. *Meissner MH et al. J Vasc Surg 2012*

Isolated femoropopliteal DVT

Data from multicentre registries has suggested less favourable outcome for femoropopliteal than iliofemoral DVT treated with thrombolytic therapy

- 1-year patency 47% in limbs with isolated femoropopliteal DVT, compared with 64% in iliofemoral DVT
- Complete lysis was not achieved in any patient with isolated femoropopliteal DVT presented >10 days

1. *Mewissen MW et al. Radiology 1999*

J ENDOVASC THER
2012;19:273–280

273

◆ CLINICAL INVESTIGATION ◆

Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) Trial: Midterm Results

Mohsen Sharifi, MD[1,2]; Curt Bay, PhD[2]; Mahshid Mehdipour[2]; Jalaladdin Sharifi, MD[1]; for the TORPEDO Investigators

[1]Arizona Cardiovascular Consultants, Mesa, Arizona, USA. [2]A.T. Still University, Mesa, Arizona, USA.

Randomisation: Percutaneous endovenous intervention (PEVI) + anticoagulation (N=91) vs anticoagulation only (N=92)

At mean follow-up 30 months:

- Recurrent VTE 4.5% (PEVI) and 16% (control) (P=0.02)
- PTS 6.8% (PEVI) and 29.6% (control) (P<0.001)

CaVenT

Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial

*Ylva Haig, Tone Enden, Ole Grøtta, Nils-Einar Kløw, Carl-Erik Slagsvold, Waleed Ghanima, Leiv Sandvik, Geir Hafsahl, Pål Andre Holme, Lars Olaf Holmen, Anne Mette Njaaastad, Gunnar Sandbæk, Per Morten Sandset, on behalf of the CaVenT Study Group**

209 patients with first time iliofemoral DVT within 21 days from symptom onset – CDT versus no CDT

5-year follow-up

- Data available for 176 patients (84%)
- Absolute reduction of PTS was 28% (95% CI 14-42); NNT 4 (95% CI 2-7)
- No difference in QoL score

Conclusions

Additional CDT resulted in a persistent and increased clinical benefit during follow-up for up to 5 years, supporting the use of additional CDT in patients with extensive proximal DVT

ATTRACT

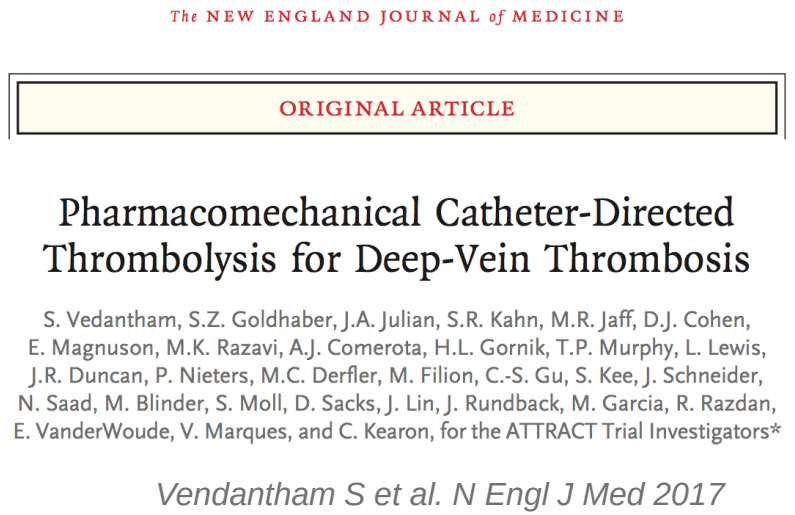
Phase 3, multi-centre, open-label, assessor-blinded RCT

56 centres in the USA (Dec 2009 - Dec 2014)

Patients with symptomatic proximal DVT (femoropopliteal and iliofemoral); 16-75 years old; symptoms not more than 14 days

PMT vs no procedural intervention (control)

692 patients (337 PMT and 355 control group)



Vendantham S et al. N Engl J Med 2017

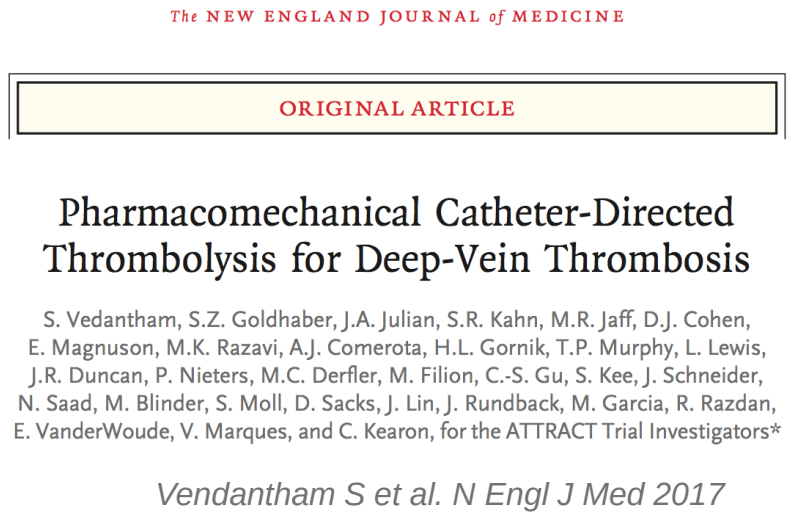
ATTRACT

PTS rate over 24-month was the same both groups;

- 157 of 336 patients (47%) in PMT group
- 171 of 355 patients (48%) in control group
- risk ratio 0.96; 95% CI, 0.82 to 1.11; P=0.56

Major bleeding within 10 days

- 6 patients (1.7%) in PMT
- 1 patient (0.3%) in control group (P=0.049)



Vendantham S et al. N Engl J Med 2017

ATTRACT

Moderate-to-severe PTS (Villalta score 10 or more) were significantly less in the PMT than control group (18% v 24%) (P=0.04)

The severity of the post-thrombotic syndrome (assessed by mean Villalta score and Venous Clinical Severity Score) was significantly lower in the PMT than the control group at all visits between 6 and 24 months

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

S. Vedantham, S.Z. Goldhaber, J.A. Julian, S.R. Kahn, M.R. Jaff, D.J. Cohen, E. Magnuson, M.K. Razavi, A.J. Comerota, H.L. Gornik, T.P. Murphy, L. Lewis, J.R. Duncan, P. Nieters, M.C. Derfler, M. Filion, C.-S. Gu, S. Kee, J. Schneider, N. Saad, M. Blinder, S. Moll, D. Sacks, J. Lin, J. Rundback, M. Garcia, R. Razdan, E. VanderWoude, V. Marques, and C. Kearon, for the ATTRACT Trial Investigators*

Vendantham S et al. N Engl J Med 2017

Limitations of ATTRACT

- Definition of PTS (limitation of Villalta); binary outcome
- Inclusion of femoropopliteal DVT
- Small number of patients treated per centre (12 per centre)
- Low stent rate (about 30%) and stents may not be appropriate for today
- Lack of dedicated imaging pre- and post-op

Cardiovasc Intervent Radiol (2018) 41:1313–1317
https://doi.org/10.1007/s00270-018-2016-y

CIRSE CrossMark

REVIEW

Just How Attractive is the ATTRACT Trial?

Gerard J. O'Sullivan[1] · Rick de Graaf[2] · Steven A. Black[3]

Thrombolysis on outcomes of DVT

Meta-analysis

- 1 Jan 2000 – 10 Dec 2017
- 6 RCTs with 1365 patients with DVT

- Clinical heterogeneity in different times of symptom onset, clinical charateristics of patients, different strategies of thrombolysis , and duration of follow-up

PLOS ONE

RESEARCH ARTICLE

Effects of thrombolysis on outcomes of patients with deep venous thrombosis: An updated meta-analysis

Zhenhua Xing, Liang Tang, Zhaowei Zhu, Xinqun Hu*

Department of Cardiovascular Medicine, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Table 1. Detailed characteristics of included studies.

Study	Study design	Country	Age	Male (%)	Onset of symptoms	Follow-up
Schweizer 2000	Multicenter	Germany	40	43	5.6 d	12 m
Elsharawy 2002	Single-center	Egypt	47	69	4.5 d	6 m
Enden 2009	Multicenter	Norway	52	32	6.4 d	6 m
Enden 2012	Multicenter	Norway	52	37	6.6 d	24 m
Ugurlu 2002	Single-center	Turkey	48	62	5 d	-
Vedantham 2017	Multicenter	America	52.5	61.5	-	24 m

1. Xing Z et al. Plos ONE 2018

Study or Subgroup	thrombolysis Events	Total	anticoagulation only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Schweizer 2000	78	100	46	50	21.9%	0.85 [0.74, 0.97]	2000
Enden2012	37	90	55	99	18.7%	0.74 [0.55, 1.00]	2012
Vedantham 2017	157	336	171	355	59.4%	0.97 [0.83, 1.14]	2017
Total (95% CI)		**526**		**504**	**100.0%**	**0.90 [0.80, 1.01]**	
Total events	272		272				

Heterogeneity: Chi² = 3.26, df = 2 (P = 0.20); I² = 39%

Test for overall effect: Z = 1.82 (P = 0.07)

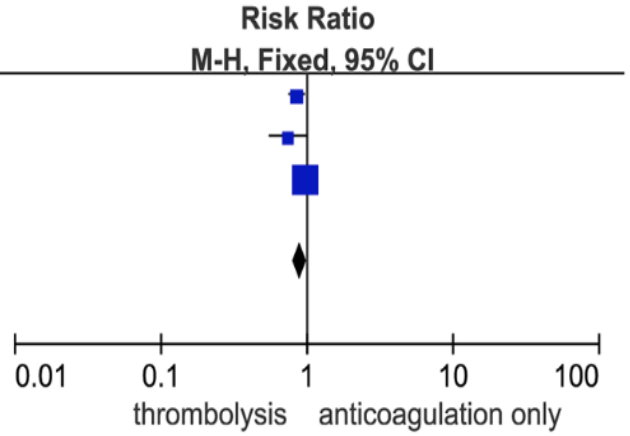


Fig 2. Thrombolysis + anticoagulation group vs. anticoagulation-only group on the outcomes of PTS.

PTS

Thrombolysis + anticoagulation was not associated with significant reduction in PTS when compared to anticoagulation alone (52% versus 54%; RR: 0.90, [0.80–1.01], $P = 0.19$, $I^2 = 39\%$)

Sensitivity analysis showed that one trial (Vedantham 2017) affected the results

1. *Xing Z et al. Plos ONE 2018*

Study or Subgroup	thrombolysis Events	Total	anticoagulation only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Schweizer 2000	3	100	0	50	4.5%	3.53 [0.19, 67.13]	2000
Elsharawy 2002	0	18	0	17		Not estimable	2002
Ugurlu 2002	2	50	0	47	3.5%	4.71 [0.23, 95.53]	2002
Enden 2009	2	50	0	53	3.3%	5.29 [0.26, 107.63]	2009
Enden2012	3	90	0	99	3.2%	7.69 [0.40, 146.90]	2012
Vedantham 2017	19	336	13	355	85.5%	1.54 [0.77, 3.08]	2017
Total (95% CI)		**644**		**621**	**100.0%**	**2.07 [1.12, 3.81]**	
Total events	29		13				

Heterogeneity: Chi² = 2.24, df = 4 (P = 0.69); I² = 0%

Test for overall effect: Z = 2.32 (P = 0.02)

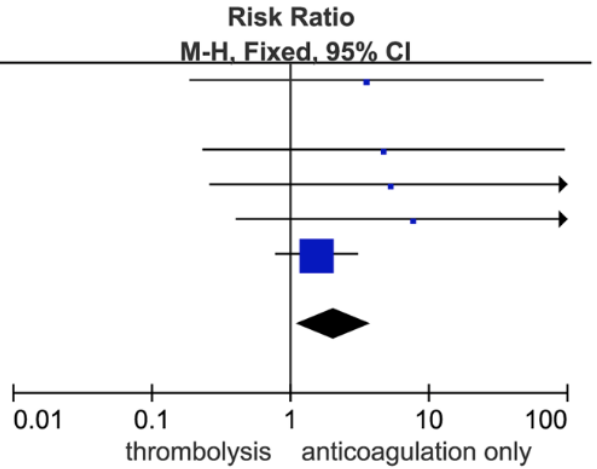


Fig 3. Thrombolysis + anticoagulation group vs. anticoagulation-only group on the outcomes of major bleeding.

Major bleeding

Thrombolysis increased risk of major bleeding

(4.5%) thrombolysis group

(2.1%) anticoagulation only group *P* = 0.02

Trial sequential analysis indicated lack of firm evidence of this due to low incidence of major bleeding, hence more clinical trials are needed to verify results

1. *Xing Z et al. Plos ONE 2018*

Questions needing answers

Examples:

Does thrombolysis reduce PTS in DVT involving iliac vein / IVC?

Does thrombolysis reduce the severity of PTS?

What is the role of stenting in acute iliocaval DVT?

Who should we offer lysis

Select carefully and responsibly:

- DVT involving iliac / IVC
- Significant symptoms
- Very low bleeding risk

Patient needs to be counselled the risks and benefits, including alternative treatment (no intervention) – as well as implication of stenting

MDT discussion

Further studies are needed

Conclusions

Acute DVT is common and is associated with significant morbidity and mortality

The evidence-based care for acute lower limb DVT is changing as the technology of diagnostic and treatment modalities is evolving fast

The treatment aims of acute DVT are no longer just diagnosis and prevention of PE and DVT recurrence with anticoagulation. The choice and duration of anticoagulant, detailed investigation of DVT and recurrence risk, and prevention of PTS are also important to patients

Multidiciplinary team approach and involving the patient in decision making are important

ALL INVITED!!!

Deep Venous Intervention MDT Meeting

(previously Pan-London Venous MDT Meeting)

Date: Wednesday 19 December 2018

Time: 18:00 – 20:30

Venue: Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG

PLEASE EMAIL chunglim@nhs.net if interested (including to be put onto future meeting list if can't make it this time!)

PLEASE IEP IMAGES TO ROYAL FREE PACS IF YOU HAVE CASES TO DISCUSS!!!

Provisional agenda:

1800 – 1900: MDT case discussion

1900 – 1930: Refreshment

1930 – 1955: Discussion on consensus statement

1955 – 2020: Discussion on venous registry