Recent advances in the management of pulmonary embolism

Kodati Rakesh
SR Pulmonary medicine

- Clinical decision rules & D dimer
- Outpatient anticoagulation
- Thrombolysis
- Anticoagulation
- Catheter directed therapies
- IVC filter
- Subsegmental PE

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Clinical decision rules

- Dyspnoea at rest or on exertion, pleuritic chest pain, haemoptysis and syncope
- None are specific for the presence of PE
- Clinical decision rules (CDRs)
  - standardize the diagnostic approach
  - identify patients in whom a less or more extensive diagnostic work-up is required
  - have been validated and introduced in clinical practice

Clinical decision rules

Original and simplified Wells clinical decision rule

Items	Score	Simplified score
Previous history of PE or DVT	1.5	1
Heart rate > 100 beats/min	1.5	1
Recent surgery or immobilization	1.5	1
Hemoptysis	1	1
Active malignancy	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Dichotomized clinical probability:		
PE unlikely	≤4	≤1
PE likely	>4	>1

PE, pulmonary embolism; DVT, deep venous thrombosis.

Clinical decision rules

Revised and simplified revised Geneva score

Items	Score	Simplified score
Age > 65 years	1	1
Previous history of PE or DVT	3	1
Heart rate 75-94 beats/min	3	1
Heart rate ≥ 95 beats/min	5	2
Surgery or fracture within 1 month	2	1
Hemoptysis	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep vein palpation and unilateral edema	4	1
Dichotomized clinical probability:		
PE unlikely	≤ 5	≤ 2
PE likely	> 5	> 2

PE, pulmonary embolism; DVT, deep venous thrombosis.

Clinical decision rules

Table 3. **Patients With Unlikely or Likely Clinical Probability of PE on the Basis of 4 CDRs and a CDR Plus D-Dimer Test ($n = 807$)**

Variable	Original Wells Rule	Simplified Wells Rule	Original Revised Geneva Score	Simplified Revised Geneva Score
CDR unlikely				
Number	584	499	553	576
Percentage (95% CI)	72 (69–76)	62 (59–65)	69 (65–72)	71 (68–75)
Prevalence of PE in CDR-unlikely patients				
Number/number	90/584	65/499	88/553	95/576
Percentage (95% CI)	15 (13–18)	13 (10–16)	16 (13–19)	17 (14–20)
CDR likely				
Number	223	308	254	231
Percentage (95% CI)	28 (25–31)	38 (35–41)	32 (28–35)	29 (26–32)
Prevalence of PE in CDR-likely patients				
Number/number	95/223	120/308	97/254	90/231
Percentage (95% CI)	43 (36–49)	39 (34–44)	38 (32–44)	39 (32–45)
CDR unlikely and normal D-dimer result				
Number	184	178	185	190
Percentage (95% CI)	23 (20–26)	22 (19–25)	23 (20–26)	24 (21–27)
Incidence of venous thromboembolism in CDR-unlikely patients with a normal D-dimer result				
Number/number	1/184	1/178	1/185	1/190
Percentage (95% CI)	0.5 (0.0–3.0)	0.6 (0.0–3.1)	0.5 (0.0–3.0)	0.5 (0.0–2.9)

13 – 17 %

< 1 %

Prometheus Study Group, Douma RA et al, Ann Intern Med. 2011

Comparison of the Wells score with the revised Geneva score for assessing suspected pulmonary embolism: a systematic review and meta-analysis

- 11 studies were included

	Sensitivity	Specificity
Wells score	63.8 to 79.3 %	48.8 to 90 %
Revised Geneva score	55.3 to 73.6 %	51.2 to 89 %

Wells score was more effective than the revised Geneva score in discriminate PE in suspected patients

Jun-Hua Shen et al, J Thromb Thrombolysis 2016

D- dimer testing

- Highly sensitive D dimer assays (ELISA, ELFA or latex quantitative assay)
  - Sensitivity is over 95 %
  - Specificity is 35 – 40 %
- Normal D-dimer level excludes acute PE with either a low or a moderate pre-test probability (rule out)
- Not useful for confirmation of PE

D- dimer testing

- Conventional cut-off of 500 μg/L combined with a “unlikely” clinical probability can safely rule out the diagnosis in upto 1/3rd of patients with suspected PE
- Specificity decreased markedly with age, from 67% in those ≤ 40 years old to 10% in those ≥80 years old

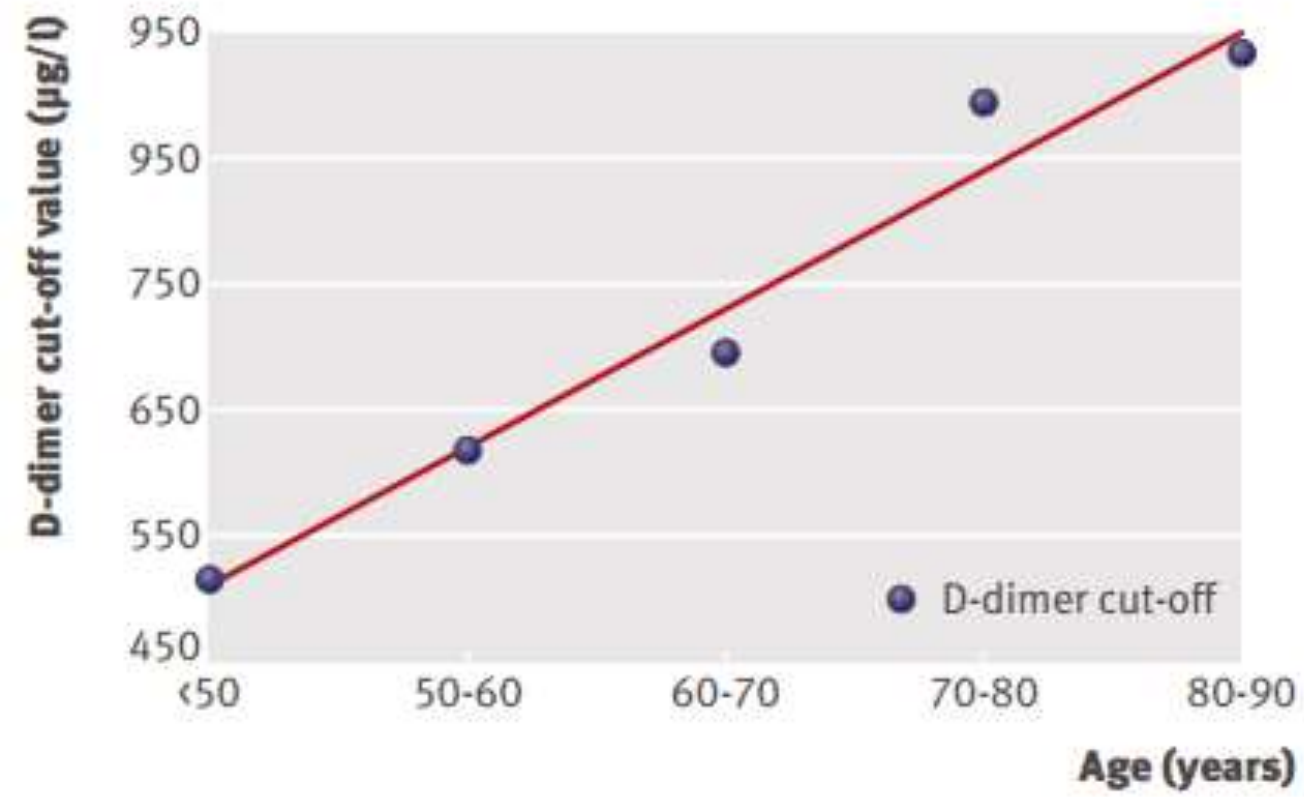
Douma RA et al; BMJ 2010

Doubling of D dimer

Prospective non interventional study in 4 centres of US Of 678 patients enrolled, 126 (19%) were PE+ and 93 (14%) had pneumonia		
	(n = 678) Exclusion rate	PE +
RGS ≤ 6 and threshold < 500 ng /ml	110 (16%)	4/110 (3.8%)
RGS ≤ 6 and a threshold < 1000 ng / mL	208 (31%)	11/208 (5.3%) (10 of these 11 had isolated, subsegmental filling defects)
Increase in specificity from 19.2 % to 35.7 %		
Doubling the threshold for a positive D-dimer with a PE unlikely probability could reduce CTPA scanning with a slightly increased risk of missed isolated subsegmental PE		

Kline JA et al; J Thromb Haemost 2012

Age adjusted D dimer



Douma RA et al; BMJ 2010

Age adjusted D dimer

- New age dependent D-dimer cut-off point in patients aged > 50 years in a derivation set based on ROC curves
- (Patient's age×10) μg/l in patients aged >50 years

Douma RA et al; BMJ 2010

Age adjusted D dimer

	All patients	51-60	61-70	71-80	>80
No (%) of patients	1331	189 (14)	211 (16)	265 (20)	198 (15)
No. below conventional cut-off value	477 (36 %)	97 (51)	63 (30)	40 (15)	11 (6)
No. below age adjusted cut-off value	560 (42%)`	102 (54)	76(36)	75 (28)	41 (21)
Absolute increase in %	6.3	2.6	6.2	13	15
Relative increase in %	17	5.2	21	67	273

Douma RA et al; BMJ 2010

Age adjusted D dimer

Multicenter, prospective management outcome study in 19 centres of Europe	
Objective	To prospectively validate whether an age-adjusted D-dimer cutoff, is associated with an increased diagnostic yield of D-dimer in elderly patients with suspected PE
Interventions	Sequential diagnostic strategy Clinical probability (simplified Geneva score / 2-level Wells score) Highly sensitive D-dimer measurement & CTPA
Follow up	D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff did not undergo CTPA and were left untreated and formally followed-up for a 3-month period
Outcome	Failure rates of this diagnostic strategy Thromboembolic risk in the subgroup between conventional and age related cut off

Marc Righini et al, The ADJUST-PE Study; JAMA 2014

Age adjusted D dimer

Multicenter, prospective management outcome study in 19 centres of Europe (n = 3324)	
D-Dimer Level Lower Than 500 µg/L (n =810)	2 deaths and 8 suspected VTE during follow-up 1 adjudicated VTE (0.1 %)
D-Dimer Level Between 500 µg/L and the Age-Adjusted Cutoff (n =331)	7 deaths and 7 suspected VTE during follow-up 1 adjudicated VTE (0.3%)
Age > 75 years and PE unlikely (n =673)	43 conventional (6.4%) 200 age adjusted cut off (29.7 %) No confirmed VTE

Marc Righini et al, The ADJUST-PE Study; JAMA 2014

Age adjusted D dimer

- Age-adjusted cutoff increased 5-fold the proportion of patients in whom PE could be ruled out without further imaging in patients 75 years or older
- Improvement of cost-effectiveness or quality of care remains yet to be demonstrated

Marc Righini et al, The ADJUST-PE Study; JAMA 2014

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Outpatient anticoagulation

- Introduction of LMWHs and DOACs has enabled early discharge or even complete out of hospital treatment for VTE
- Lead to patient satisfaction
- Reduced health care costs
- Less iatrogenic complications in hospital

Outpatient anticoagulation

- Various parameters were used in selecting home treatment
  - Hestia criteria
  - NT proBNP level
  - PESI

- Preferable method for low risk patient selection is unclear

Outpatient anticoagulation

Hestia rule

Variable
Hemodynamically instable?*
Thrombolysis or embolectomy necessary?
High risk for bleeding?**
Oxygen supply to maintain oxygen saturation >90% >24 h.?
Pulmonary embolism diagnosed during anticoagulant treatment?
Intravenous pain medication >24 h.?
Medical or social reason for treatment in the hospital >24 h.?
Creatinine clearance of less than 30 ml/min?***
Severe liver impairment****
Pregnant?
Documented history of heparin induced thrombocytopenia?
If at least one of the above questions is answered with YES, the patient cannot be treated at home

* Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100 mmHg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit

** Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 x 10^9/L), uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg)

*** Calculated creatinine clearance according to the Cockroft-Gault formula

**** Left to the discretion of the physician

Pulmonary Embolism Severity Index

Predictors	Points
Age	+1 per year
Male sex	+10
Heart failure	+10
Chronic lung disease	+10
Arterial oxygen saturation <90%	+20
Pulse ≥110 beats per minute	+20
Respiratory rate ≥30 breaths per minute	+20
Temperature <36°C	+20
Cancer	+30
Systolic blood pressure <100 mm Hg	+30
Altered mental status	+60

Pulmonary Embolism Severity Score (Sum of the Points)	Risk Class	30-day Mortality Rate
≤65	I	0–1.6%
66–85	II	1.7%–3.5%
86–105	III	3.2%–7.1%
106–125	IV	4.0%–11.4%
>125	V	10.0%–24.5%

Outpatient anticoagulation

- Meta analysis (Wendy Zondag et al, ERJ 2013)
- 13 studies (1657 patients)
- No statistical significance in outpatient vs inpatient

  Rate of recurrent VTE (1.7 vs 1.2 %)

  mortality (1.9 vs 0.74 %)

  major bleeding events (0.97 vs 1 %)

- Home treatment or early discharge of selected low-risk patients with PE is as safe as inpatient treatment

Outpatient anticoagulation

To compare the safety of the Hestia criteria alone with the Hestia criteria combined with NT-proBNP testing			
den Exter PL et al; AJRCCM 2016	Randomized non-inferiority trial 17 Dutch hospitals	550 patients NT pro BNP group 34/275 elevated levels Direct discharge 275 subjects	Primary endpoint (30 days) 0% 1.1 %

Assessment of outpatient eligibility could be based on a clinical decision rule alone, irrespective of NT-proBNP levels
proportion of patients with elevated NT-proBNP levels was considerably lower

Outpatient anticoagulation

	Study design	Primary outcome
PM Roy et al, J Thromb Haemost 2017	Retrospective cohort study 1087 576 inpatients vs 505 outpatients*	<u>14 day rate of adverse events</u> 13.0 % vs 3.3 % OR 5.07 <u>3 month rate of adverse events</u> 21.7 % vs 6.9 % OR 4.9 <u>High risk (PESI III/IV)</u> 16.5 % vs 4.5 % OR 4.16

* patients discharged directly from the emergency room and patients discharged within 48 hours of admission.

Outpatient anticoagulation

- Hospitalized normotensive patients have a higher risk of recurrent VTE, major bleedings or deaths than patients managed as outpatient
  - Immobilisation in hospital
  - Couldn't analyse the comorbidites in in-patient

**Opinion of the physician in charge, underlying medical and social conditions and how outpatient care provided are more important than severity criteria, to define out patient Rx*

PM Roy et al, J Thromb Haemost 2017

Outpatient anticoagulation

- In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (Grade 2B)

**Grade 2B recommendation, CHEST 2016*

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Thrombolysis in PTE

- Systemic thrombolytic therapy accelerates resolution of PE as evidenced by
  - more rapid lowering of pulmonary artery pressure
  - increases in arterial oxygenation
  - resolution of perfusion defects

Thrombolysis in PTE

- Net mortality benefit has been uncertain
- Depends on an individual patient's baseline risk of dying from acute PE and risk of bleeding
- Young patients are less likely to suffer major bleeding, but might also be more able than the elderly to overcome the right ventricle strain and vice versa

Thrombolysis in PTE

- 4 meta-analyses in 2014
- Efficacy and safety of thrombolysis
- Slightly different conclusions among them
- *Cao et al and Nakamura et al*
  Stable PE
  Thrombolysis failed to improve overall mortality or recurrent PE with similar risk of major bleeding
- *Marti et al and Chatterjee et al*
  All PE studies combined
  Significant reduction in overall mortality with thrombolysis

Thrombolysis in PTE

- Large clinical trial of 1005 subjects in 2014
- Double blind placebo controlled trial
- Objectively confirmed normotensive acute PE with an onset below 15 days
- RV dysfunction on ECHO/CT scan (RV/LV diameter >0.9, RV free wall HK, tricuspid systolic velocity >2.6m/s, RV EDd > 30 mm))
- Myocardial injury by positive Troponin T/I

Guy Meyer et al; PEITHO trial, NEJM 2014

Thrombolysis in PTE

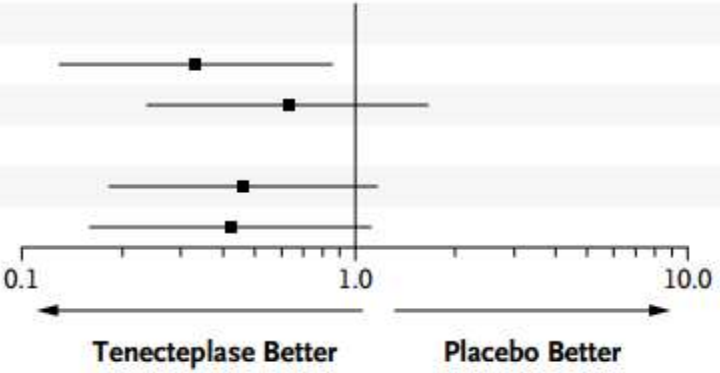
Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		

Thrombolysis in PTE

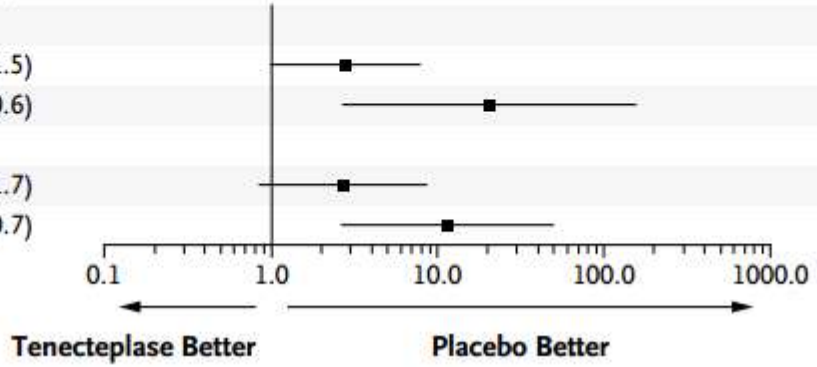
A **Death or Hemodynamic Decompensation**

Subgroup	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.36
≤75 yr	6/344 (1.7)	17/335 (5.1)	0.33 (0.13–0.85)	
>75 yr	7/162 (4.3)	11/164 (6.7)	0.63 (0.24–1.66)	
Sex				0.90
Male	7/242 (2.9)	14/231 (6.1)	0.46 (0.18–1.16)	
Female	6/264 (2.3)	14/268 (5.2)	0.42 (0.16–1.12)	



B **Major Extracranial Bleeding**

Subgroup	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.09
≤75 yr	14/344 (4.1)	5/335 (1.5)	2.80 (1.00–7.86)	
>75 yr	18/162 (11.1)	1/164 (0.6)	20.38 (2.69–154.53)	
Sex				0.13
Male	11/242 (4.5)	4/231 (1.7)	2.70 (0.85–8.61)	
Female	21/264 (8.0)	2/268 (0.7)	11.49 (2.67–49.53)	



Thrombolysis in PTE

- In intermediate-risk pulmonary embolism, fibrinolytic therapy prevented hemodynamic decompensation but increased the risk of major hemorrhage and stroke
- Great caution is warranted when considering fibrinolytic therapy for hemodynamically stable patients with pulmonary embolism (> 75 years and female gender)

Guy Meyer et al; PEITHO trial, NEJM 2014

Safe dose thrombolysis

- Randomized, single- centre open study that enrolled 121 adult patients
- Symptomatic “moderate” PE
- CT scan > 70 % involvement of thrombus in 2 lobar or left or right MPA [or]
- High probability V/Q scan showing mismatch in ≥ 2 lobes
- RV enlargement or hypokinesia and elevation of biomarkers of RV injury although measured, were not a requirement for enrollment

Mohsen sharifi et al, MOPETT trial, Am J Cardiol 2013

Safe dose thrombolysis

- Dose of tPA was $\leq$ 50% of the standard dose (100 mg)
- $\geq$ 50 kg, the total dose was 50 mg
- < 50 kg, the total dose was calculated as 0.5 mg/kg
- 10 mg was given as bolus f/b remainder within 2 hrs

Mohsen sharifi et al, MOPETT trial, Am J Cardiol 2013

Safe dose thrombolysis

Secondary end points

Variable	TG (n = 61; 100%)	CG (n = 60; 100%)	p Value
Recurrent pulmonary embolism	0	3 (5%)	0.08
Total mortality	1 (1.6%)	3 (5%)	0.30
Total mortality plus recurrent pulmonary embolism	1 (1.6%)	6 (10%)	0.049
Hospital stay (days)	2.2 ± 0.5	4.9 ± 0.8	<0.001
Bleeding	0	0	—

Data are presented as mean ± SD or n (%).

Mohsen sharifi et al, MOPETT trial, Am J Cardiol 2013

Safe dose thrombolysis

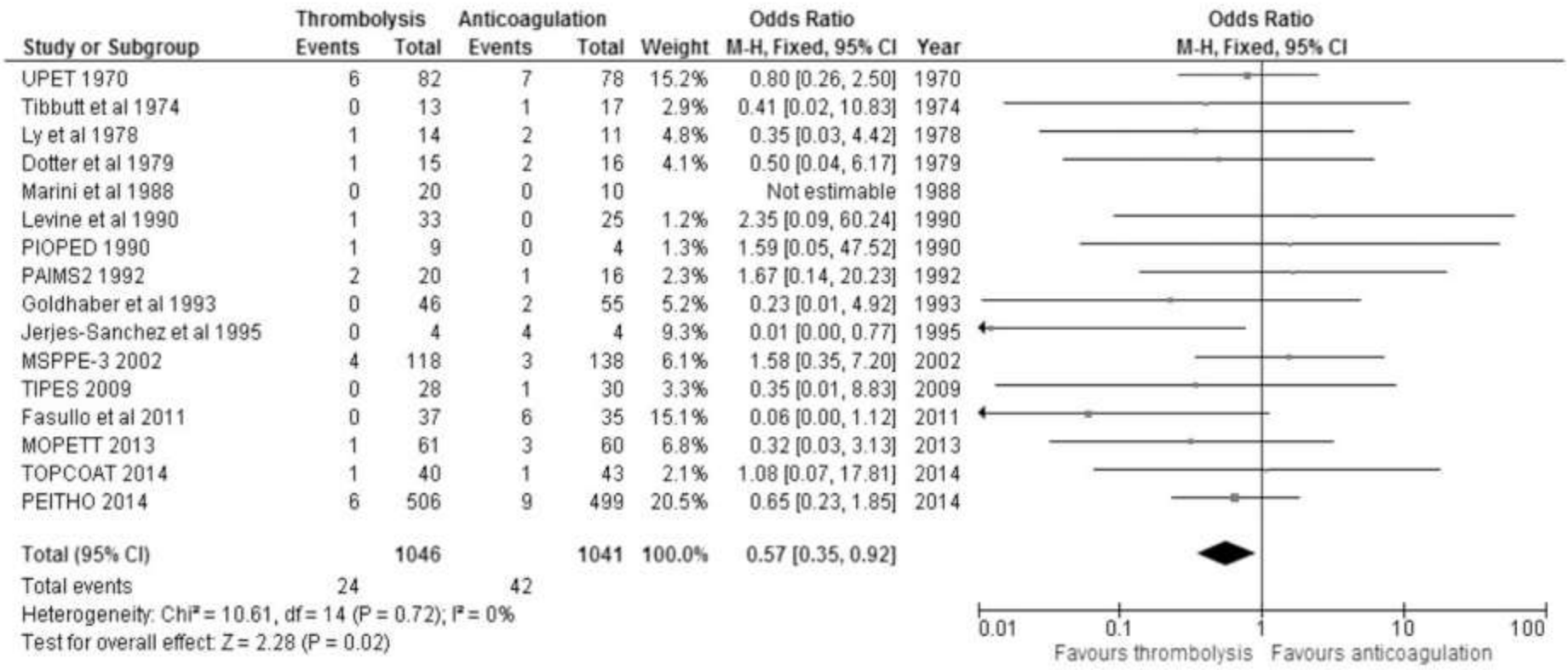
Differences in pulmonary artery systolic pressure between the 2 groups

Timing	Pulmonary Artery Systolic Pressure (mm Hg)		p Value
	TG	CG	
On admission	50 ± 6	51 ± 7	0.4
Within 48 h	34 ± 7	41 ± 4	<0.001
6 mo	31 ± 6	49 ± 8	<0.001
28 ± 5 mo	28 ± 7	43 ± 6	<0.001

Data are presented as mean ± SD.

Mohsen sharifi et al, MOPETT trial, Am J Cardiol 2013

Thrombolysis in PTE



Study or Subgroup	Thrombolysis Events	Thrombolysis Total	Anticoagulation Events	Anticoagulation Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
UPET 1970	6	82	7	78	15.2%	0.80 [0.26, 2.50]	1970
Tibbutt et al 1974	0	13	1	17	2.9%	0.41 [0.02, 10.83]	1974
Ly et al 1978	1	14	2	11	4.8%	0.35 [0.03, 4.42]	1978
Dotter et al 1979	1	15	2	16	4.1%	0.50 [0.04, 6.17]	1979
Marini et al 1988	0	20	0	10		Not estimable	1988
Levine et al 1990	1	33	0	25	1.2%	2.35 [0.09, 60.24]	1990
PIOPED 1990	1	9	0	4	1.3%	1.59 [0.05, 47.52]	1990
PAIMS2 1992	2	20	1	16	2.3%	1.67 [0.14, 20.23]	1992
Goldhaber et al 1993	0	46	2	55	5.2%	0.23 [0.01, 4.92]	1993
Jerjes-Sanchez et al 1995	0	4	4	4	9.3%	0.01 [0.00, 0.77]	1995
MSPPE-3 2002	4	118	3	138	6.1%	1.58 [0.35, 7.20]	2002
TIPES 2009	0	28	1	30	3.3%	0.35 [0.01, 8.83]	2009
Fasullo et al 2011	0	37	6	35	15.1%	0.06 [0.00, 1.12]	2011
MOPETT 2013	1	61	3	60	6.8%	0.32 [0.03, 3.13]	2013
TOPCOAT 2014	1	40	1	43	2.1%	1.08 [0.07, 17.81]	2014
PEITHO 2014	6	506	9	499	20.5%	0.65 [0.23, 1.85]	2014
Total (95% CI)		**1046**		**1041**	**100.0%**	**0.57 [0.35, 0.92]**	
Total events	24		42				

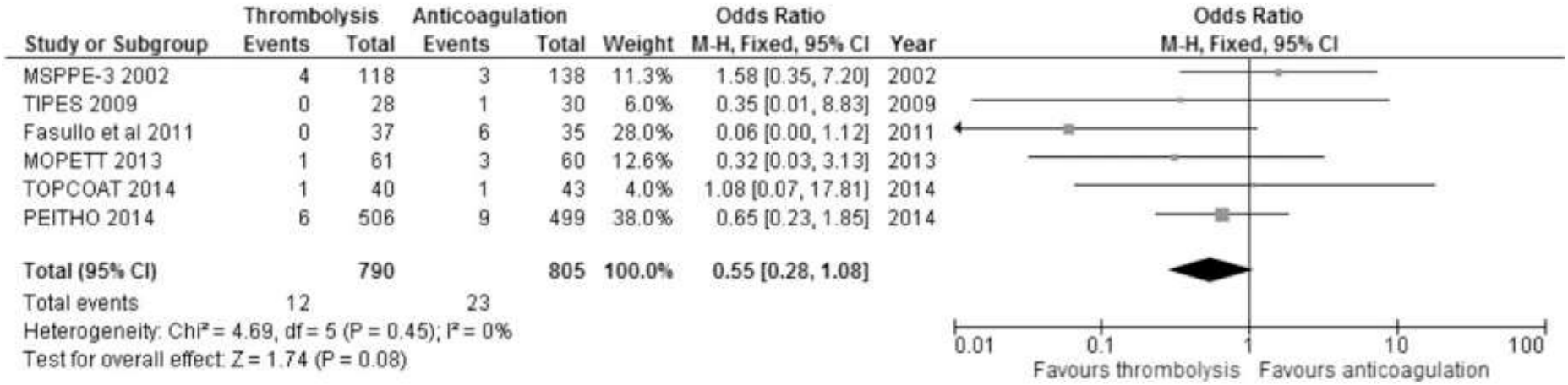
Heterogeneity: $Chi^2 = 10.61$, $df = 14$ ($P = 0.72$); $I^2 = 0\%$

Test for overall effect: $Z = 2.28$ ($P = 0.02$)

Figure 1. OR of overall mortality comparing thrombolysis to anticoagulation.

Wang TF et al; Blood 2015

Thrombolysis in PTE



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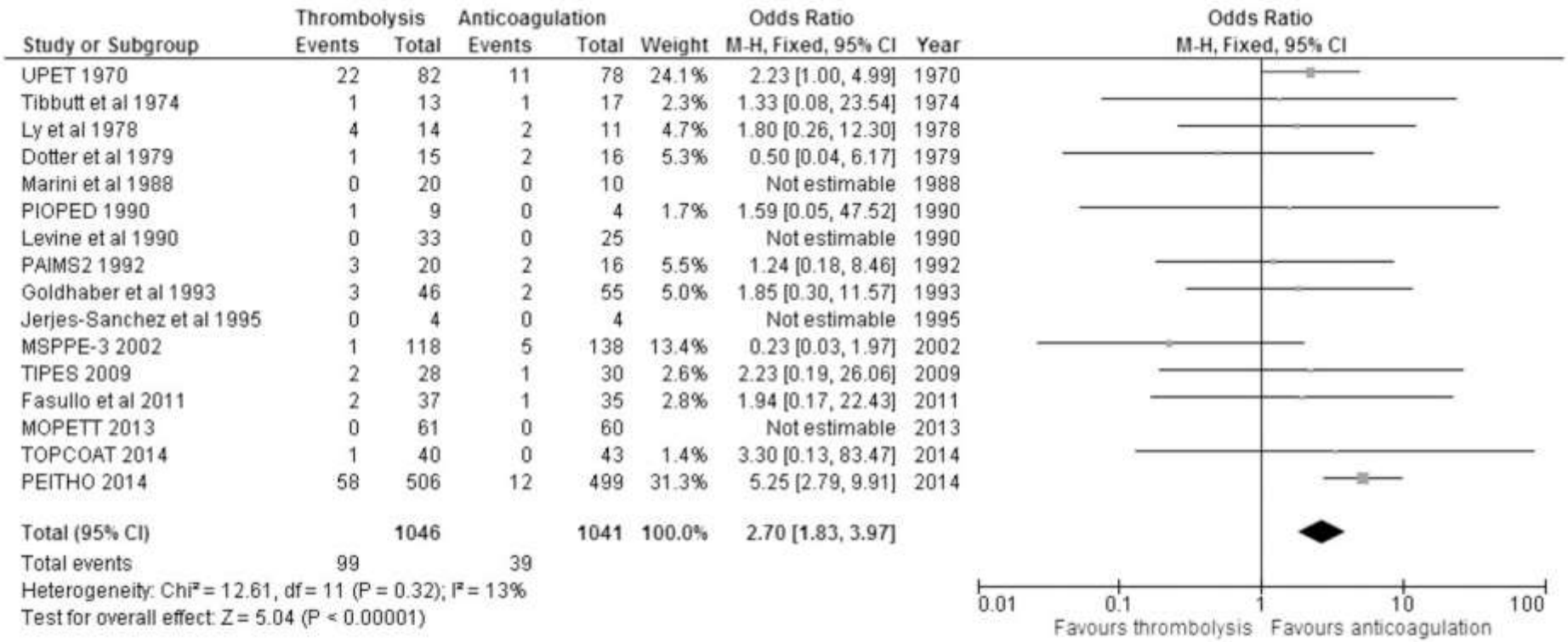
Fasullo et al 2011	0	37	6	35	28.0%	0.06 [0.00, 1.12]	2011
MOPETT 2013	1	61	3	60	12.6%	0.32 [0.03, 3.13]	2013
TOPCOAT 2014	1	40	1	43	4.0%	1.08 [0.07, 17.81]	2014
PEITHO 2014	6	506	9	499	38.0%	0.65 [0.23, 1.85]	2014
Total (95% CI)		**790**		**805**	**100.0%**	**0.55 [0.28, 1.08]**	
Total events	12		23				

Heterogeneity: Chi² = 4.69, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)

Figure 2. OR of overall mortality comparing thrombolysis to anticoagulation in stable PE with clearly defined RVD.

Wang TF et al; Blood 2015

Thrombolysis in PTE



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Ly et al 1978	4	14	2	11	4.7%	1.80 [0.26, 12.30]	1978
Dotter et al 1979	1	15	2	16	5.3%	0.50 [0.04, 6.17]	1979
Marini et al 1988	0	20	0	10		Not estimable	1988
PIOPED 1990	1	9	0	4	1.7%	1.59 [0.05, 47.52]	1990
Levine et al 1990	0	33	0	25		Not estimable	1990
PAIMS2 1992	3	20	2	16	5.5%	1.24 [0.18, 8.46]	1992
Goldhaber et al 1993	3	46	2	55	5.0%	1.85 [0.30, 11.57]	1993
Jerjes-Sanchez et al 1995	0	4	0	4		Not estimable	1995
MSPPE-3 2002	1	118	5	138	13.4%	0.23 [0.03, 1.97]	2002
TIPES 2009	2	28	1	30	2.6%	2.23 [0.19, 26.06]	2009
Fasullo et al 2011	2	37	1	35	2.8%	1.94 [0.17, 22.43]	2011
MOPETT 2013	0	61	0	60		Not estimable	2013
TOPCOAT 2014	1	40	0	43	1.4%	3.30 [0.13, 83.47]	2014
PEITHO 2014	58	506	12	499	31.3%	5.25 [2.79, 9.91]	2014
Total (95% CI)		**1046**		**1041**	**100.0%**	**2.70 [1.83, 3.97]**	
Total events	99		39				

Heterogeneity: $Chi^2 = 12.61$, $df = 11$ ($P = 0.32$); $I^2 = 13\%$

Test for overall effect: $Z = 5.04$ ($P < 0.00001$)

Figure 3. OR of major bleeding events comparing thrombolysis to anticoagulation.

Wang TF et al; Blood 2015

Thrombolysis in PTE

- Thrombolysis reduced overall mortality in all PE but not in stable PE with clearly defined RVD*
- Systemic thrombolytic therapy is associated with a significant reduction of overall mortality in patients with PE, but this reduction is not statistically significant after exclusion of studies including high-risk PE
- Consistently increased major bleeding and intracranial bleeding events

**Wang TF et al; Blood 2015*
Christophe Marti et al; Eur Heart J 2015

Thrombolysis in PTE

- In patients with acute PE associated with hypotension (SBP <90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2B)
- In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B)

Antithrombotic Therapy for VTE Disease, CHEST 2016; 149(2)

- Clinical decision rules & D dimer
- Outpatient anticoagulation
- Thrombolysis
- Anticoagulation
- Catheter directed therapies
- IVC filter
- Subsegmental PE

Choice of anticoagulation

- Direct oral anticoagulants are now the preferred agents for long-term anticoagulation in patients
  - who are not pregnant
  - do not have active cancer
  - severe renal insufficiency

**Grade 2B recommendation, CHEST 2016*

NOACs

- Direct thrombin inhibitors
  - Dabigatran
- Oral Xa inhibitors
  - Rivaroxaban
  - Apaxiban
  - Edoxaban

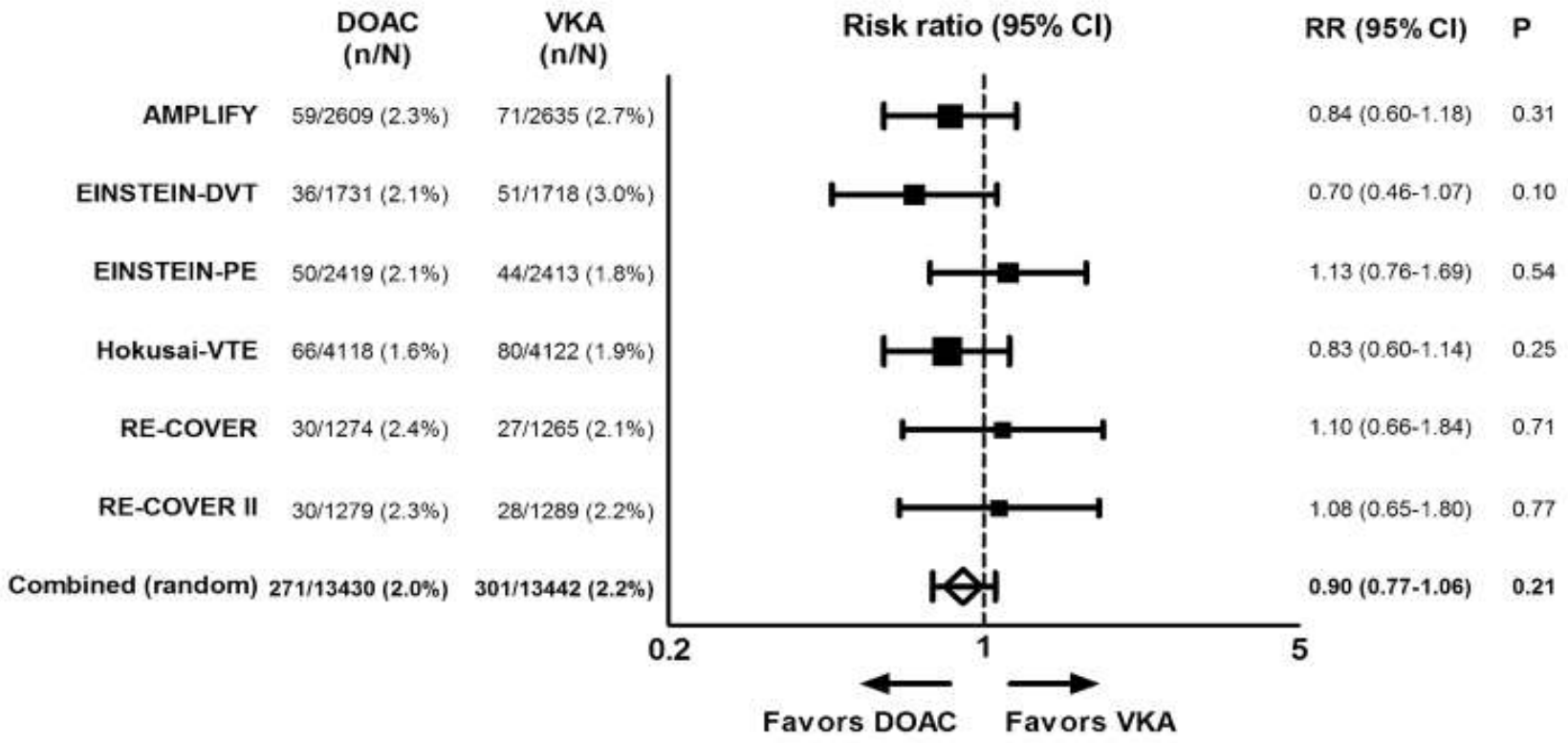
NOACs

- Large phase III clinical trials comparing VKAs with NOACs for VTE
- Non inferiority trials
- Similar efficacy
- Lower risk of bleeding

	Study Design	Intervention	Primary outcome	Safety outcome
RE –COVER 1 NEJM 2009	Acute VTE 2564 Randomized Double blind Double dummy Non-inferiority trial	UFH or LMWH for 8 to 11 days f/b Dabigatran 150mg BD 0r warfarin (INR 2-3)	2.4% In dabigatran group 2.1% in warfarin group HR 1.10 (0.65–1.84)	Major bleed 1.6% vs. 1.9% HR 0.82 (0.45–1.48) Any bleed 16.1% vs. 21.9%
RE-COVER 2 (Circulation Dec 2014)	Acute VTE 2589 patients (20% Asians) Randomized Double blind Double dummy Non-inferiority trial	UFH or LMWH for 5 to 11 days f/b Dabigatran 150mg BD 0r warfarin (INR 2-3)	2.3% In dabigatran group 2.2% in warfarin group HR 1.08 (0.64–1.80)	Any bleed 15.6% vs. 22.1% Major bleed 1.2% vs. 1.7% HR 0.73 (0.48–1.11)

	Study Design	Intervention	Primary outcome	Safety outcome
EINSTEIN PE N Engl J Med 366;14 April 5, 2012	4832 patients Randomized Open label Non-inferiority trial	Rivaroxaban 15 mg BD 3 weeks f/b 20 mg OD Enoxaparin sc f/b warfarin/acenocoumarol	2.1% vs. 1.8% HR 1.12 (0.75–1.68)	Any bleed 10.3% vs. 11.4% Major bleed 1.1% vs. 2.2% HR 0.49 (0.31–0.79)
AMPLIFY N Engl J Med. Aug 2013; 369(9)	Acute VTE 5395 patients Randomized Double blind Non-inferiority trial	Apixaban 10 mg BD 7 days f/b 5 mg BD for 6 months Vs. Enoxaparin sc for 7 days f/b warfarin (INR 2-3)	2.3% vs. 2.7%	Any bleed 4.3% vs. 9.7% (Significant reduction)
Hokusai VTE study J Thromb Hemost 2o13 online ; 1 (17)	4921 DVT patients 3319 PTE patients Randomized Double blind	Initial LMWH f/b Edoxaban 60 mg OD (30 mg-CrCl < 30-50 mL/m) Vs.	3.2% vs. 3.5% (symptomatic recurrent VTE)	Clinically relevant bleed 8.5% vs. 10.3%

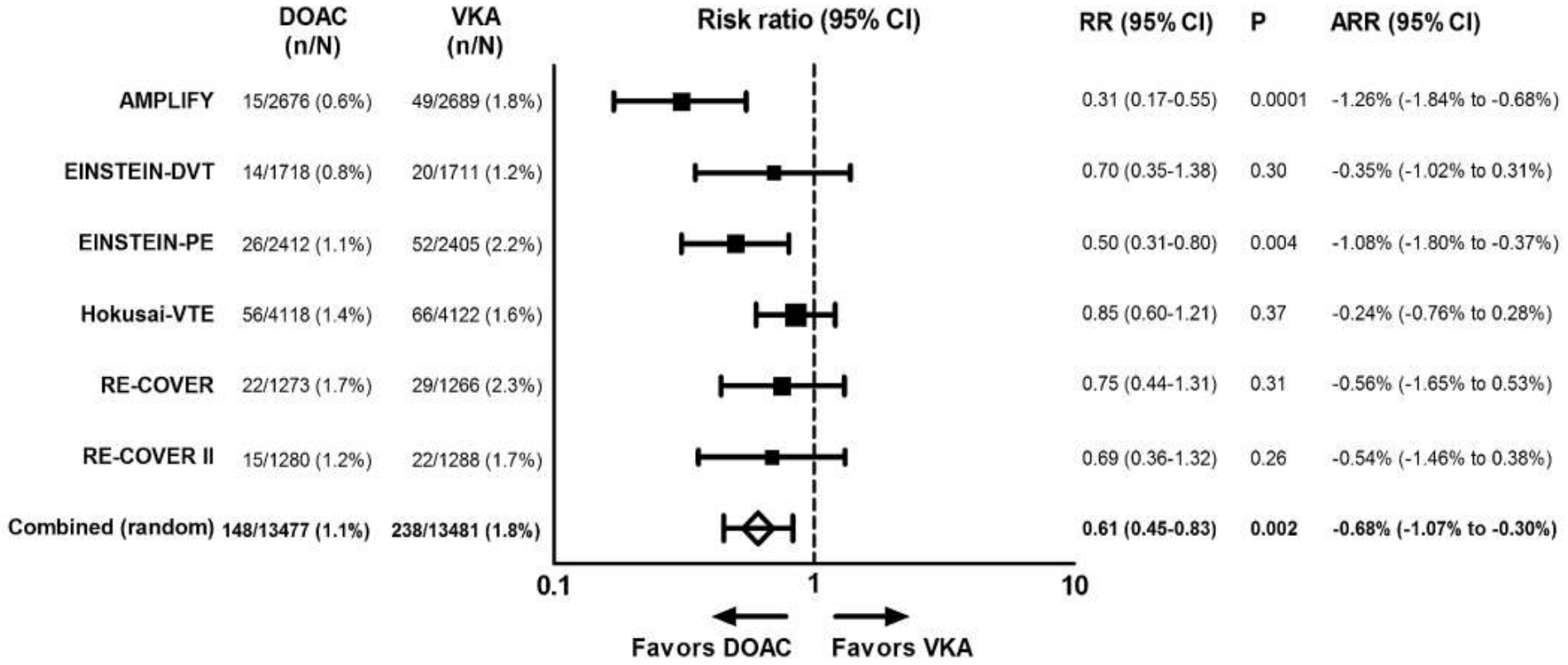
NOACs



First recurrent VTE or VTE related death, Heterogeneity: $I^2 = 0\%$; P = .53

Nick van Es et al, Blood, 2014

NOACs



Bleeding, Heterogeneity: $I^2 = 51\ \%$; $P = .07$

Nick van Es et al, Blood, 2014

NOACs avoided in..

- Severe renal failure
- Mechanical heart valves
- Concomitant and indispensable use of drugs that are strong inhibitors or inducers of P-glycoprotein and/or CYP 3A4
- Caution in patients with extreme body weights

Choice of anticoagulation

- LMWH was suggested over VKA therapy or DOACs in patients with DVT of the leg or PE and cancer (“cancer-associated thrombosis”)

**Grade 2C recommendation, CHEST 2016*

Choice of anticoagulation in cancer

- LMWH was more effective than VKA in patients with cancer
- Substantial rate of recurrent VTE in patients cancer who are on VKA
- Difficulty of keeping VKA in therapeutic range
- Difficulty with oral therapy (eg, vomiting)
- Easier to withhold or adjust for invasive interventions or thrombocytopenia develops

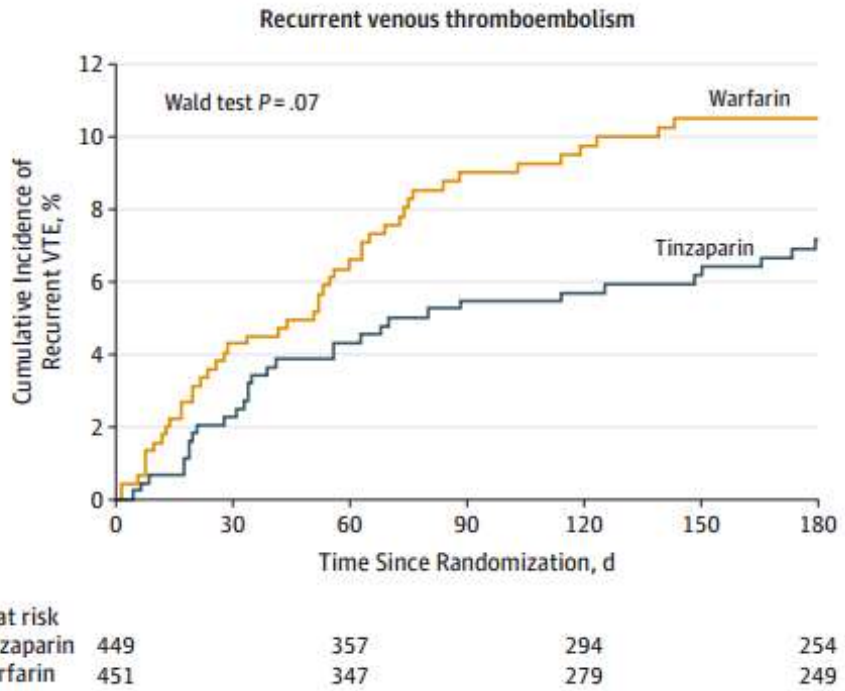
Choice of anticoagulation in cancer

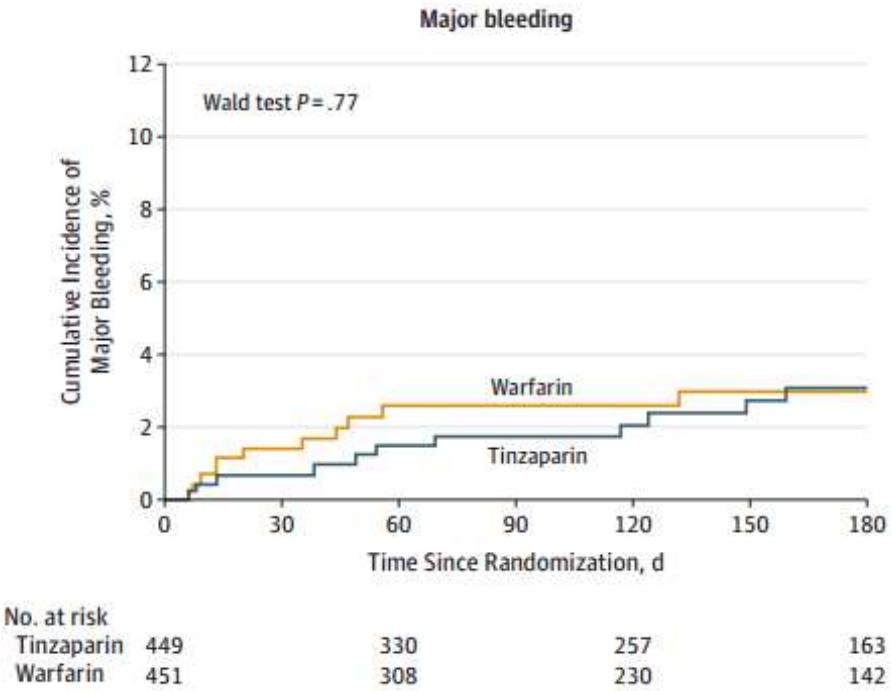
- CLOT trial 2003
- Dalteparin Vs Warfarin in DVT, PE in cancer
- 672 subjects
- 27 of 336 vs 53 of 336 (P=0.002)
- No difference in bleeding
- In patients with cancer and acute VTE, dalteparin was more effective than an coumarin in reducing the risk of recurrent VTE without increasing the risk of bleeding

Agnes YY Lee et al; N Engl J Med 2003;349

	Study Design	Intervention	Primary outcome	Safety outcome
CATCH trial JAMA 2015;314(7)	Randomized Open label trial 900 patients with active cancer & documented proximal DVT or PE, with a life expectancy > 6 months	Tinzaparin 175 IU/kg OD for 6 months vs Tinzaparin for 5 to 10 days f/b warfarin at a INR (2.0-3.0) for 6 m	Recurrent VTE 31/449 vs 45/451 6.9 % vs 10 % (p = 0.07) HR - 0.65 [95% CI, 0.41-1.03]	Major bleed 2.7 % vs 2.4 % Non major bleed 10.9 % vs 15.3 % (P = 0.004)

Choice of anticoagulation in cancer





Agnes YY Lee et al; JAMA 2015;314(7)

Choice of anticoagulation in cancer

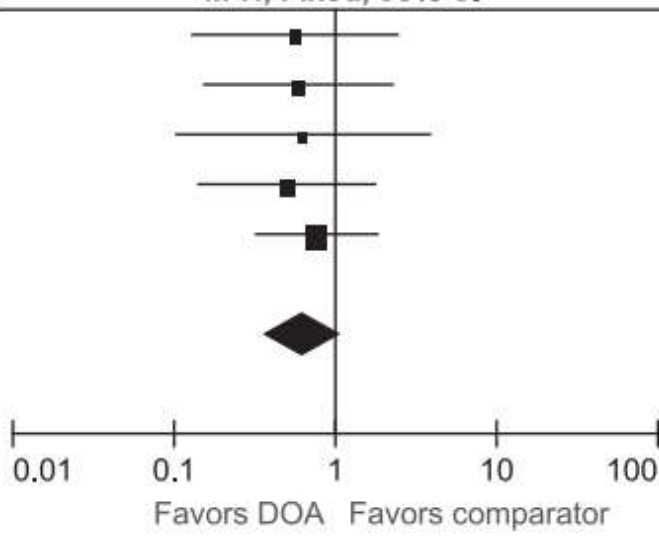
- Role of NOACs in cancer related VTE
- Clinically attractive drugs for the treatment in v/o their fixed-dose regimens and oral administration
- Systematic review and meta analysis 2015
- Subgroup analyses of RCTs which included very few and highly selected patients with cancer

Choice of anticoagulation in cancer

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
Total (95% CI)		**595**		**537**	**100.0%**	**0.63 [0.37, 1.10]**
Total events	23		32			

Heterogeneity: Chi² = 0.36, df = 4 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.62 (P = 0.10)



VTE Recurrence in cancer

Maria Cristina Vedovati et al, CHEST 2015; 147(2):475-483

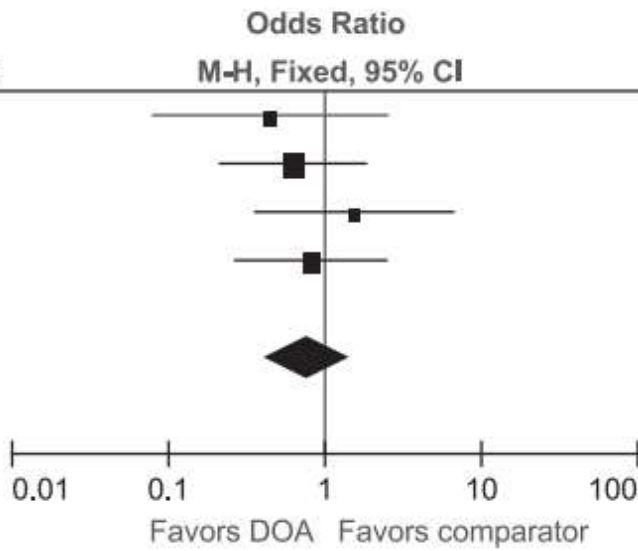
Choice of anticoagulation in cancer

A

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	2	87	4	80	18.2%	0.45 [0.08, 2.51]
EINSTEIN DVT & PE 2013	6	232	8	196	37.7%	0.62 [0.21, 1.83]
HOKUSAI 2013	5	109	3	99	13.4%	1.54 [0.36, 6.61]
RECOVER I & II 2013	6	159	7	152	30.7%	0.81 [0.27, 2.47]
Total (95% CI)		**587**		**527**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	19		22			

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.70); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)



Major bleeding with NOACs

Maria Cristina Vedovati et al, CHEST 2015; 147(2):475-483

Choice of anticoagulation in cancer

- Analysis is not powered to show differences among individual agents
- No studies specific to the cancer population have been conducted so far
- No trials of NOACs comparing with LMWH available, which is the standard of care

Maria Cristina Vedovati et al, CHEST 2015; 147(2):475-483

Duration of anticoagulation

- PE provoked by surgery or non surgical transient risk factors – recommended for 3 months
- First unprovoked PE –

  Low or moderate bleeding risk – suggested extended therapy

  High bleeding risk – 3 months recommended

Antithrombotic Therapy for VTE Disease, CHEST 2016; 149(2)

Duration of anticoagulation

- Second unprovoked PE
  - Low risk – recommend extended
  - Moderate risk – suggest extended
  - High risk – suggest 3 months

- In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals

Antithrombotic Therapy for VTE Disease, CHEST 2016; 149(2)

	Study Design	Intervention	Primary outcome	Secondary outcome
PADIS - PE trial JAMA 2015;314(1)	Randomized Double blind trial 371 adults with first unprovoked symptomatic PE Randomization after 6 months of VKA	VKA for 18 months (n= 184) vs Placebo for 18 months (n= 187)	**Recurrent VTE or major bleed** 6/184 vs 25/187 3.3 % vs 13.5 % (p = 0.001) HR - 0.22 **VTE** 1.7 % vs 13.5 % (p < 0.001) HR – 0.15 **Major bleed** 2.2 % vs 0.5 % P = 0.22	41-m follow up composite outcome 33 (20.8 %) vs 42 (24.0 %) P = 0.22

Duration of anticoagulation

- High rate of recurrent VTE was noted in placebo group than warfarin with HR 0.15 (CI 0.05-0.43)
- Additional extended therapy reduced the composite outcome of recurrent venous thrombosis and major bleeding compared with placebo
- However, benefit was not maintained after discontinuation of anticoagulation therapy

Francis Couturaud et al; JAMA 2015;314(1)

- Clinical decision rules & D dimer
- Outpatient anticoagulation
- Thrombolysis
- Anticoagulation
- Catheter directed therapies
- IVC filter
- Subsegmental PE

Catheter directed therapies

TABLE 1 Catheter-Based Therapies

Device	Size	Mechanism of Action
Pigtail catheter	6- to 8-F	Fragmentation
Peripheral balloon	5 to 10 mm	Fragmentation
Catheter-directed fibrinolysis	4- to 6-F	Direct infusion of fibrinolytic agent
Ultrasound-accelerated thrombolysis	6-F	Direct infusion of fibrinolytic agent plus ultrasound for clot separation. Currently the only catheter-based therapy FDA-approved for PE treatment.
Guide catheter	6- to 10-F	Manual aspiration
Pronto Xl catheter	6- to 14-F	Manual aspiration
Penumbra Indigo system	6- to 8-F	Suction pump aspiration
Inari FlowTriever	22-F sheath	Disruption, retraction, and aspiration of clot
AngioVac	26-F sheath and 18-F cannula	Large-volume aspiration with return of filtered blood utilizing a centrifugal pump

Fragmentation, aspiration and fibrinolysis

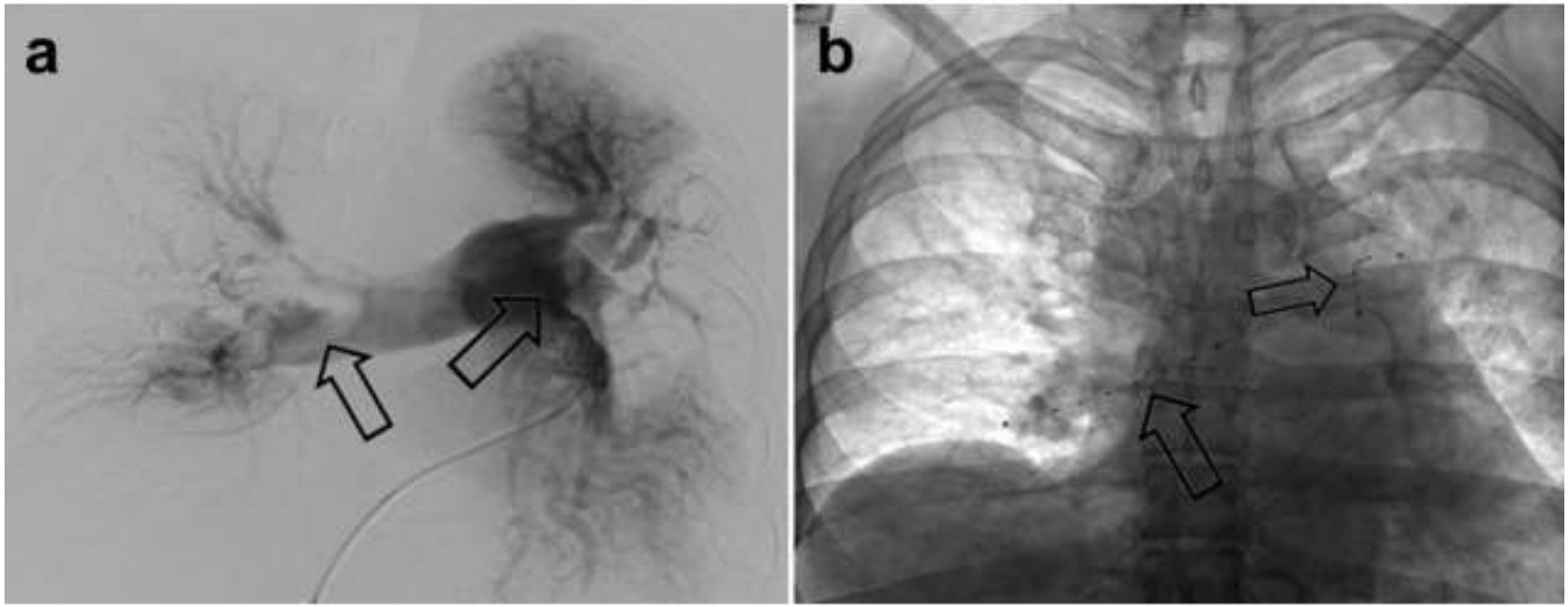
Wissam A. Jaber et al; JACC 2016

Catheter directed therapies

- Pulmonary arterial injury
- Pericardial tamponade
- Major bleeding
- Hemodynamic deterioration
- Distal embolization
- Access site bleeding

Wissam A. Jaber et al; JACC 2016

Catheter directed thrombolysis



Catheter directed thrombolysis

- In emergent situations, systemic thrombolytic therapy can be given while CDT is being arranged, and active thrombus fragmentation and aspiration can be combined with CDT

Antithrombotic Therapy for VTE Disease, CHEST 2016; 149(2)

Catheter directed thrombolysis

Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial	
Participants	59 subjects with intermediate risk PE (Confirmed by CT) RV/LV chamber ratio >1 in apical 4 chamber view
Intervention	USAT regimen of 10 mg rtPA over 15 hours per treated lung via the EkoSonic Endovascular System (n=30) Or UFH alone (n=29)
Results (mean RV/LV ratio at 24 hrs)	USAT group (1.28 ± 0.19 to 0.99 ± 0.17)($P < 0.001$) Heparin group, (1.20 ± 0.14 and 1.17 ± 0.20)($P = 0.31$) The mean decrease in RV/LV ratio from baseline to 24 hours was 0.30 ± 0.20 vs 0.03 ± 0.16 ($P < 0.001$) No major bleeding or recurrent VTE in either group at 90 d f/u
Conclusion	Standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours

Nil Kucher et al; Circulation 2014

Catheter directed thrombolysis

The SEATTLE II Study, prospective, single-arm, multicenter trial to evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis	
Participants	150 patients with acute massive (n =31) or sub massive (n = 119) PE and CT RV/LV ≥ 0.9
Intervention	24 mg of t PA administered as 1 mg/h for 24 h with a U/L catheter or 1 mg/h/catheter for 12 h with B/L catheters
Results	Reduction of RV/LV diameter (1.55 to 1.13) (p <0.001) PA systolic pressure (51.4 to 36.9 measured at 48 hrs (p <0.001) 17 major bleeding events
Conclusion	CDT improved RV function, thrombus burden and minimized intracranial hemorrhage

Gregory Piazza et al; JACC 2015

Catheter directed thrombolysis

- Improved short term, surrogate outcomes
- Effect on clinical and long term outcomes not known
- No randomized trials comparing with systemic thrombolytic therapy are available
- FDA approved

Catheter directed therapies

- 594 patients in 35 studies
- Clinical success rate from CDT was 86.5% which increased to 91.2 % with co administered thrombolysis
- Minor procedural complications - 7.9%
- Major procedural complications - 2.4%

WT kuo et al; J Vasc Interv Radiol 2009

Systemic vs Catheter directed thrombolysis

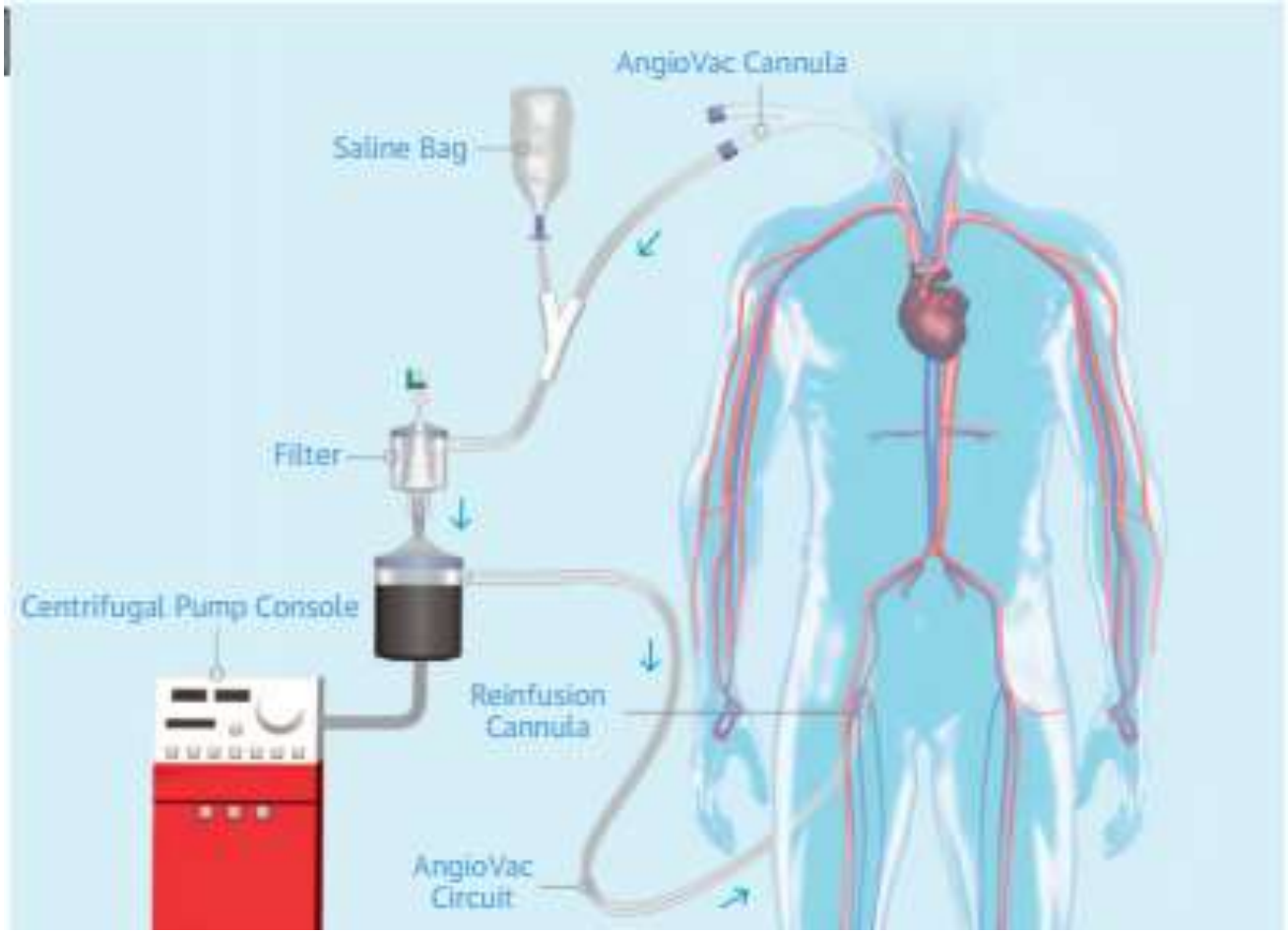
	Systemic lysis (n= 1169)	CDT (n= 352)	Odds ratio	P value
In hospital mortality	21.81 %	13.36 %	0.55 (0.36–0.85)	0.007
In hospital mortality + ICH	22.89 %	13.36 %	0.52 (0.34–0.80)	0.003
Hemorrhage requiring transfusion	4.61	3.23	0.69 (0.30–1.59)	0.38
LOS	7 (5–10)	7 (5–10)	0.82 (0.11 - 1.74)	0.09
Costs	17,713	24,714	-	<0.0001

Nish Patel et al; Catheterization and Cardiovascular Interventions 2015

Catheter based thrombus removal

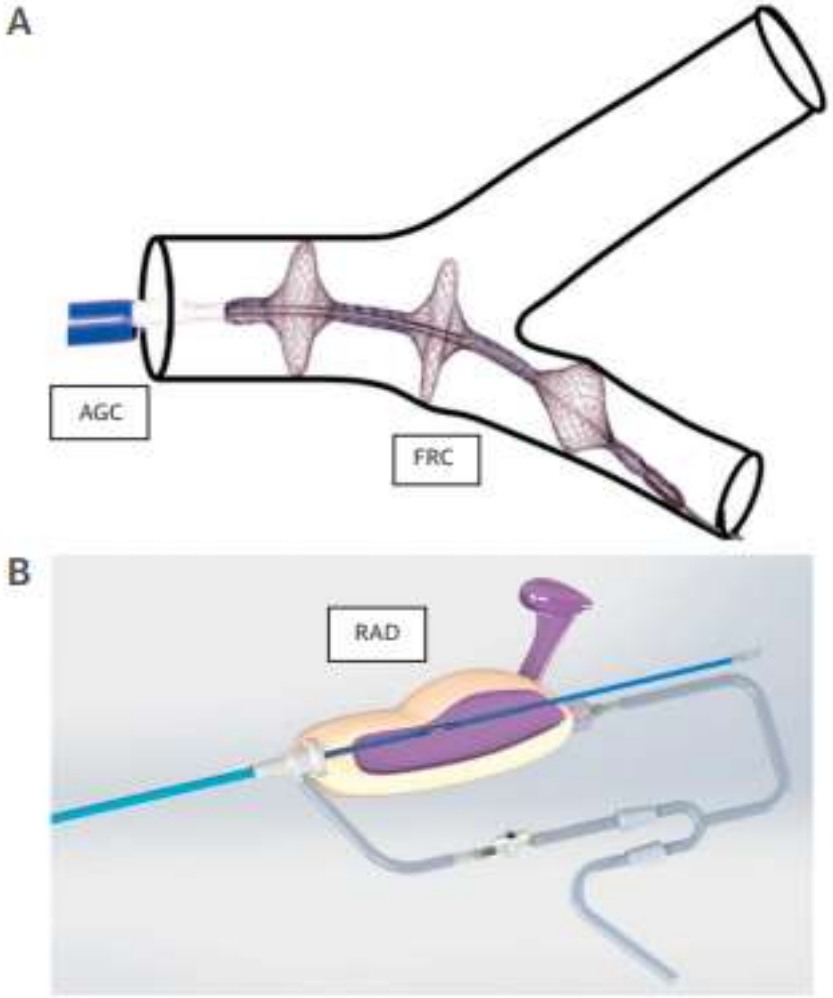
- Aspiration thrombectomy
- Thrombus fragmentation
- Rotational embolectomy
- Rheolytic thrombectomy

Angiovac device



Removal of large proximal pulmonary emboli, intracardiac masses and caval thrombus

Flowtriever device



Catheter directed therapies

- Catheter-directed therapies may be considered for patients with
  - persistent hemodynamic instability despite systemic thrombolysis
  - those at risk of death before systemic thrombolysis can manifest effectiveness
  - those at high risk of bleeding

Antithrombotic Therapy for VTE Disease, CHEST 2016; 149(2)

Catheter directed therapies

- Decrease major bleeding including ICH
- Higher risk of
  - vascular access-related complications
  - contrast induced nephropathy
  - costs
- Never be performed faster than systemic lysis
- Reserved for use in centers with appropriate expertise

- Clinical decision rules & D dimer
- Outpatient anticoagulation
- Thrombolysis
- Anticoagulation
- Catheter directed therapies
- IVC filter
- Subsegmental PE

IVC filter

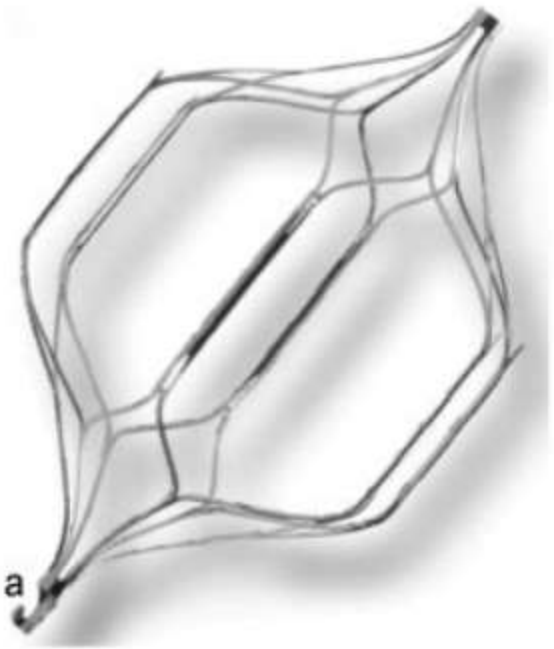
	ACCP	AHA	ACR	SIR
Acute VTE and inability to anticoagulate	✓	✓	✓	✓
Anticoagulation failure		✓	✓	✓
Hemodynamically unstable patients, as an adjunct to anticoagulation	✓	✓	✓	✓
Massive PE treated with thrombolysis	✓	×	✓	✓
Mobile thrombus			✓	✓
Iliocaval DVT			✓	✓
Prophylaxis in high risk (polytrauma & bariatric sx)	×		✓	✓

IVC filter

- Permanent IVC filter initially reduced the occurrence of symptomatic or asymptomatic PE who are having proximal DVT
- It was offset by a significant increase in recurrent DVTs, which could be related to thrombosis at the filter site
- No effect was observed on either immediate or long-term mortality

PREPIC study N Engl J Med 1998;338:409-15

IVC filter



Retrieval IVC filter

- Optional filters (rIVCF) are designed to be retrieved or left in place after the temporary risk of PE or contraindication to anticoagulation has resolved
- Provide benefit without long term risks
- Lack of trials to support indications for the selective use of temporary filters

Retrieval IVC filter

- No RCTs have been performed comparing the performance of rIVCF and pIVCF
- rIVCFs have higher complication rates than pIVCF
- Adverse events increase proportionally with prolonged filter dwell time
- Filter migration, filter fracture, and perforation of the caval wall or adjacent structures by filter components

Retrieval IVC filter

Table 2. Complications Reported with Permanent and Potentially Retrievable Devices

	Total	pIVCFs (% Total)	rIVCFs (% Total)	*P* Value
All complications	1,606	212 (13.2%)	1,394 (86.8%)	< .0001
Fracture	350	16 (4.6%)	334 (95.4%)	< .0001
Migration	215	46 (21.4%)	169 (78.6%)	< .0001
Limb embolization	154	4 (2.6%)	150 (97.4%)	< .0001
Tilt	197	3 (1.5%)	194 (98.5%)	< .0001
IVC penetration	228	14 (6.1%)	214 (93.9%)	< .0001
VTE/PE	30	8 (26.7%)	22 (73.3%)	< .007
IVC thrombus	41	8 (19.5%)	33 (80.5%)	< .001
Placement issue	318	99 (31.1%)	219 (68.9%)	< .0001
Other	73	14 (19.2%)	59 (80.8%)	< .0001

Jessica M. Andreoli et al; J Vasc Interv Radiol 2014

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IVC Filter Lawsuit Information Center

- Have you or a loved one suffered dangerous complications following the catastrophic failure of an IVC filter?
- Since 2010, the FDA has issued two warnings regarding the risks potentially associated with retrievable IVC filters,
such as the Bard Rec
- Attorneys On Call 24

Get the help y

Call anytim

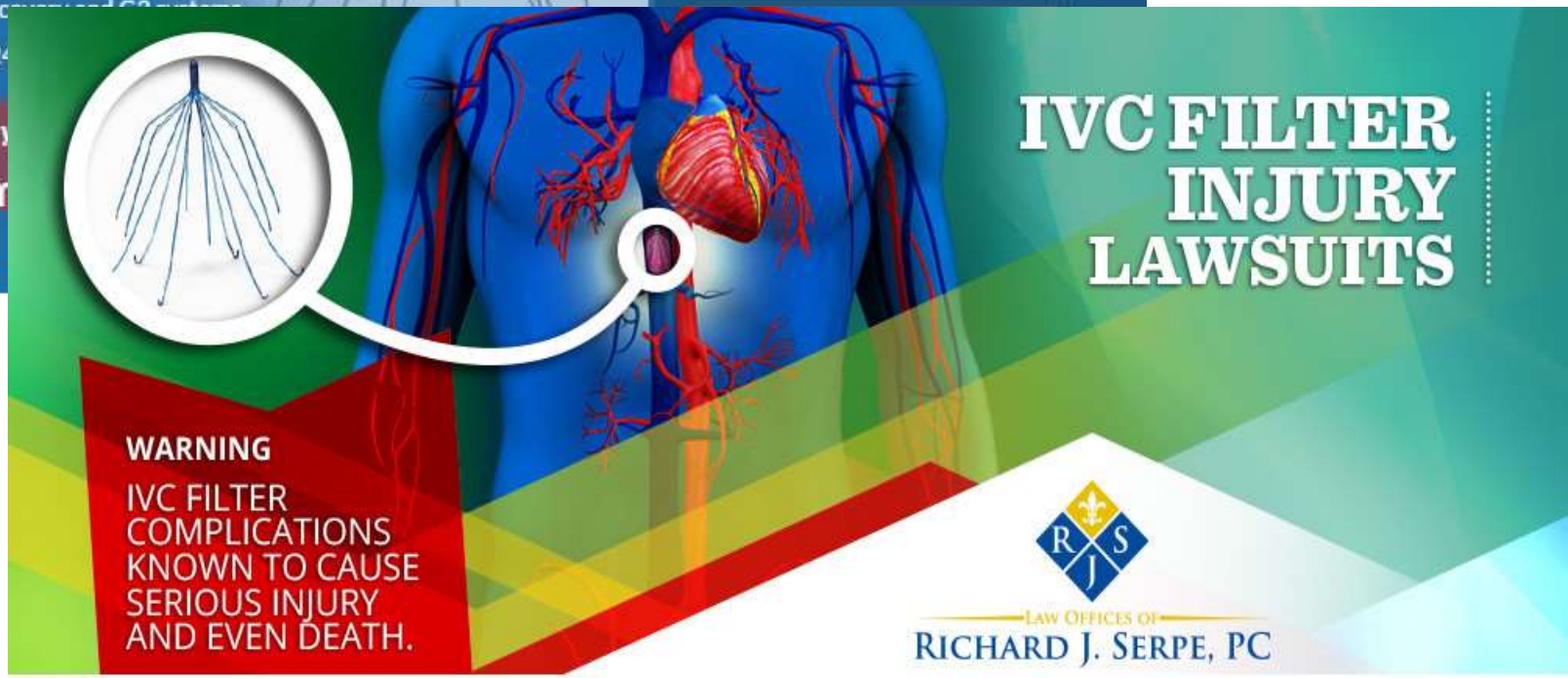
Free Case Evalution

Have your or a loved one suffered serious complications following the failure of a IVC Filter?

Full Name

Email

Telephone



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	Study Design	Intervention	Outcomes
Patrick Mismett et al; PREPIC 2 TRIAL JAMA 2015;313(6)	Randomized Open labelled trial 400 patients of acute PE with acute lower limb DVT or superficial VT <u>1 severity criteria</u> > 75 years cancer, chronic cardiorespiratory insufficiency, stroke in last 6 m, large DVT	Full-dose anticoagulation for at least 6 months Filter group (n= 200) vs Control group (n= 199) 6 months follow up	Recurrent PE at 3 m 3 % vs 1.5 % (p = 0.50) Recurrent PE at 6 m 3.5 % vs 2.0% (p = 0.54) Mortality at 6 m 10.6 % vs 7.5 % (p = 0.29)

IVC filter

- Decision which IVC filters to use, when to use them, and for how long they should remain in place remains a highly complex process with many variables to consider
- Mechanical prophylaxis not entirely benign
- Morbidity risks increase over time
- Should be removed when risk for PE has resolved
- Post placement clinical follow-up is critical to optimizing retrieval rates

- Clinical decision rules & D dimer
- Outpatient anticoagulation
- Thrombolysis
- Anticoagulation
- Catheter directed therapies
- IVC filter
- Subsegmental PE

Subsegmental PE

- Fourth order arteries with diameter of 3mm
- Advent of multi-detector CTPA has allowed better assessment of PE regarding visualisation of the peripheral pulmonary arteries, increasing its rate of diagnosis
- Incidence of isolated SSPE
  - 4.7% of patients with PE by single-detector CT
  - 9.4% of patients with PE by multi-detector CT

Subsegmental PE

- Clinical impact of a SSPE diagnosis is unknown
- Could be imaging artifacts
- Low inter-observer variability between radiologists
- 60 patients with SSPE diagnosed by CTPA & no DVT who did not receive anticoagulation Rx have been reported in the literature
- None of these patients suffered recurrent symptomatic VTE (PE or DVT) during the 3-month follow-up period

Carrier M et al, J Thromb Haemost 2012

Subsegmental PE

	SSPE (n = 116)	Proximal PE* (n = 632)	PE ruled out (n = 2980)	*P* value SSPE vs proximal PE	*P* value SSPE vs PE ruled out
Age, mean ± SD	56 ± 17	57 ± 18	52 ± 18	.46	.02
Age >60, n (%)	50 (43.1)	301 (47.6)	1004 (33.7)	.37	.04
Male sex, n (%)	64 (55.2)	309 (48.9)	1212 (40.7)	.23	.002
Outpatients, n (%)	87 (75)	496 (78.5)	2431 (81.6)	.41	.07
VTE risk factors					
Immobilization, n (%)	20 (17.2)	108 (17.1)	273 (9.2)	.97	.004
Paralysis, pareses, or recent leg plaster, n (%)	5 (4.3%)	37 (5.9%)	63 (2.1)	.51	.11
Previous VTE, n (%)	17 (14.7)	128 (20.3)	395 (13.3)	.16	.66
Recent surgery, n (%)	15 (12.9)	72 (11.4)	155 (5.2)	.64	<.001
Active malignancy, n (%)	21 (18.1)	113 (17.9)	347 (11.6)	.95	.04
Estrogen use, women, n (%)	15 (30.0)	93 (29.2)	360 (20.7)	.91	<.001

SSPE and more proximal PE.
3-month risk of recurrent VTE (3.6% vs 2.5%; P = 0 .42)
Mortality (10.7% vs 6.5%; P =0.17)

Patients with symptomatic SSPE appear to mimic those with segmental or more proximal PE as regards their risk profile and short-term clinical course

Risk profile and clinical outcome of symptomatic subsegmental acute PE, Blood 2013

Subsegmental PE

Ongoing cohort study

A Study to Evaluate the Safety of Withholding Anticoagulation in Patients with subsegmental PE Who Have a Negative Serial Bilateral Lower Extremity Ultrasound (SSPE)

NCT 01455818

Subsegmental PE

- To perform a CTPA only when necessary, i.e. in patients with a high clinical probability or a positive D-dimer
- Review of SSPE expert thoracic radiologist
- DVT scan should be done in all
- If DVT is detected, patients require anticoagulation
- If DVT is not detected, there is uncertainty whether patients should be anticoagulated

Antithrombotic Therapy for VTE Disease, CHEST 2016; 149(2)

Subsegmental PE

- It should be individualized, taking into account the bleeding risk and risk of recurrent VTE
- If a decision is made not to anticoagulate, there is the option of doing one or more follow-up US examinations of the legs to detect (and then treat) evolving proximal DVT

Antithrombotic Therapy for VTE Disease, CHEST 2016; 149(2)

Take home message

- Age adjusted D dimer and CDRs excludes PE in low clinical probability
- Thrombolysis in intermediate PE can be done with caution in selected subjects
- NOACs are recommended for anticoagulation unless contraindicated
- Duration and indication of IVCF usage is unclear