NOACs in Pulmonary Embolism

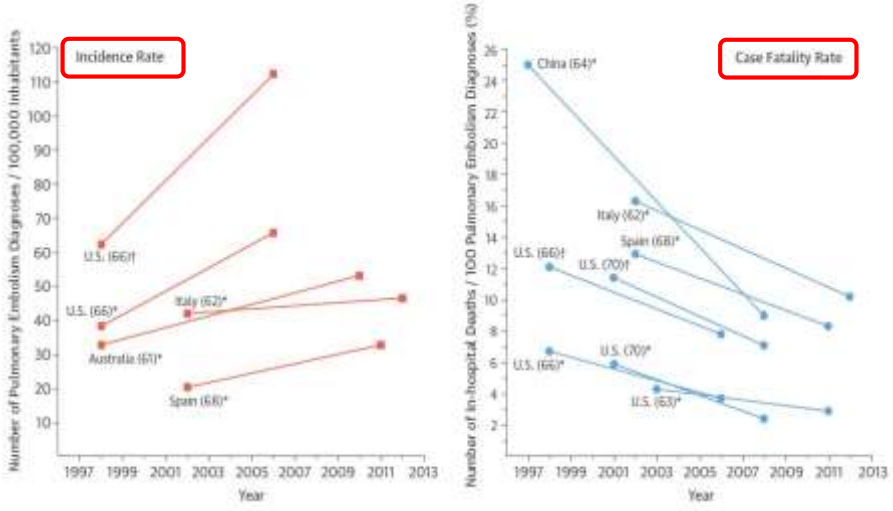
Sameh Emil , M.D ,FSCAI
Prof of Cardiology MMA

Introduction

- Venous thromboembolism (VTE) is the third most common cardiovascular disease after MI and stroke
- Current standard of treatment : heparin/vitamin K antagonist (VKA)
- New oral anticoagulants with and without heparin are effective and safe in the treatment of VTE

Pulmonary Embolism

Global Trends

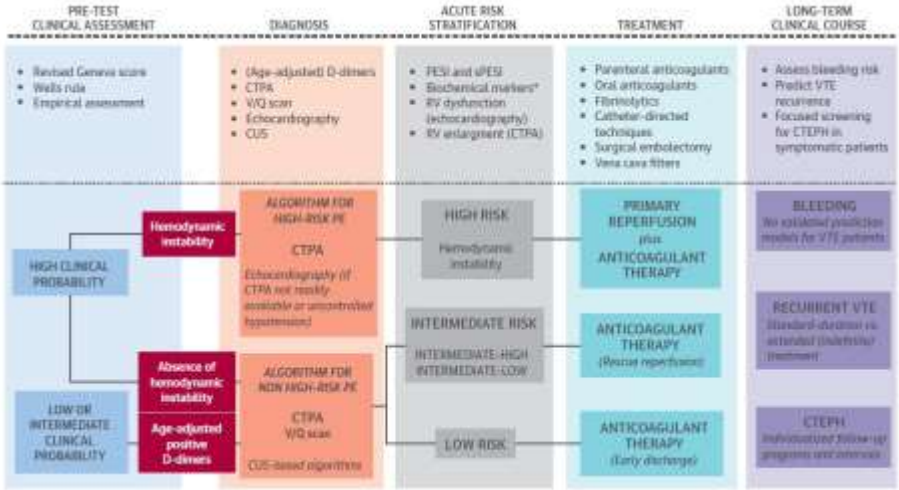


STATE-OF-THE-ART REVIEW

Management of Pulmonary Embolism

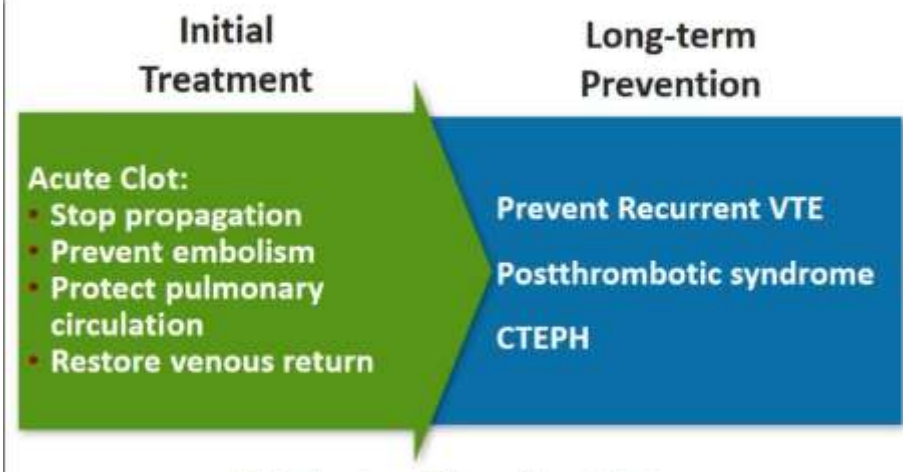
An Update

Stavros V. Konstantinides, MD, PhD,[a,b] Stefano Barco, MD,[a] Mareike Lankeit, MD,[a] Guy Meyer, MD[c]



(J Am Coll Cardiol 2016;67:976-90)

Goals of VTE treatment



Minimize Bleeding Risk

CTEPH = chronic thromboembolic pulmonary hypertension

New concepts in anticoagulation therapy

Conventional therapy

- Heparin plus VKA

New therapy

- Single drug approach
- Higher initial dose

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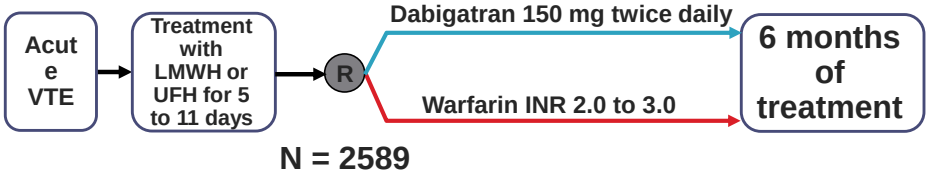
Acute VTE Treatment Trials

	RE-COVER	EINSTEIN[b,c]	AMPLIFY[d]	Hokusai[e]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
N	2589	8281	5395	8240
Design	2 x blind	PROBE	2 x blind	2 x blind
Indication	VTE	DVT or PE	VTE	VTE
Heparin bridge	Yes	No	No	Yes
Duration, mo	6	3, 6, 12	6	3-12

a. Schulman S, et al. *Circulation.* 2014;129:764-772; b. Bauersachs R, et al. *N Engl J Med.* 2010;363:2499-2510 ; c. Büller HR, et al. *N Engl J Med.* 2012;366:1287-1297; d. Agnelli G, et al. *N Engl J Med.* 2013;369:799-808; e. Büller HR, et al. *N Engl J Med.* 2013;369:1406-1415.

RE-COVER II
Study Design

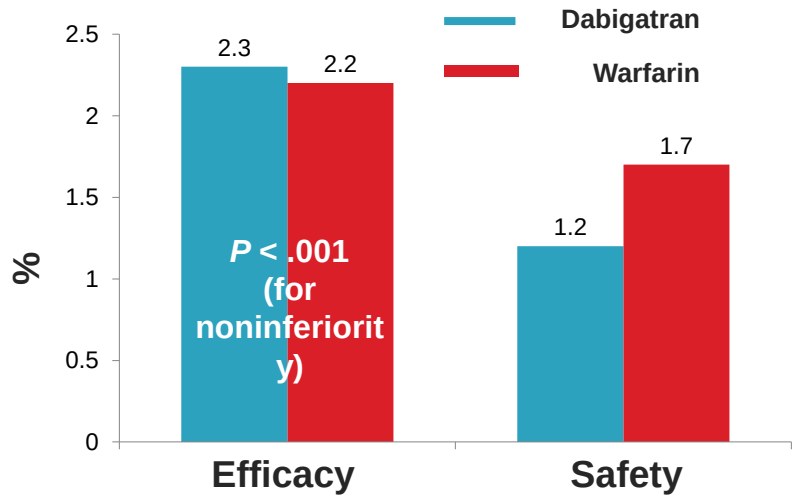


N = 2589

- Primary efficacy outcomes: Symptomatic recurrent VTE and related death
- Principal safety outcome: Major bleeding

Schulman S, et al. *Circulation.* 2014;129:764-772.

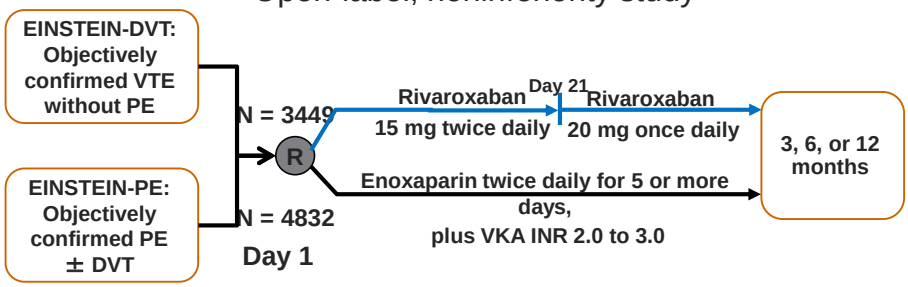
RE-COVER II
Results



.Schulman S, et al. *Circulation.* 2014;129:764-772

EINSTEIN DVT/PE
Study Designs

- Open-label, noninferiority study

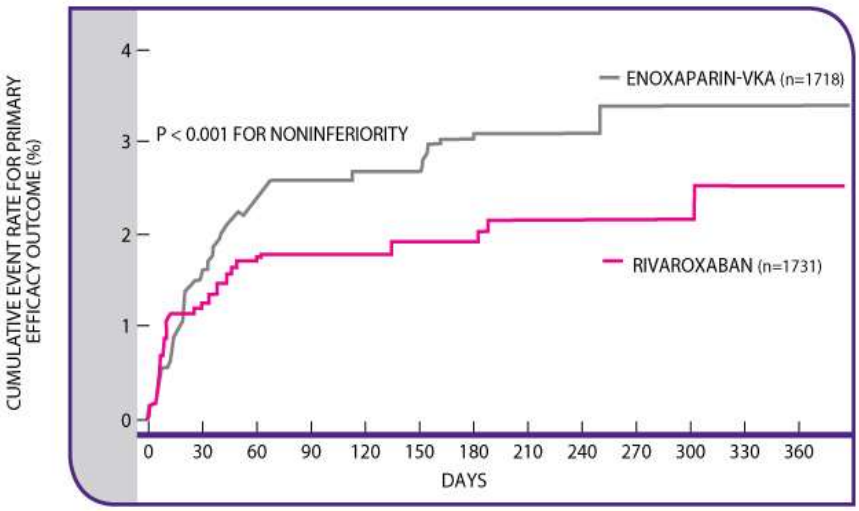


- Primary efficacy outcome: Symptomatic recurrent VTE
- Principal safety outcome: Major or nonmajor clinically relevant bleeding

Bauersachs R, et al. *N Engl J Med*. 2010;363:2499-2510.
Büller HR, et al. *N Engl J Med*. 2012;366:1287-1297.

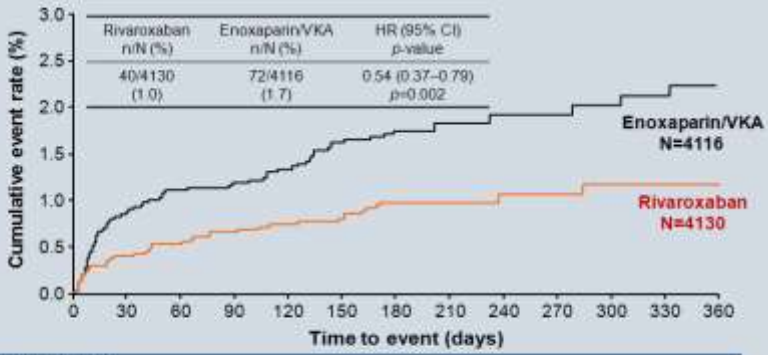
EINSTEIN DVT/PE

Result - Efficacy



EINSTEIN-DVT and EINSTEIN-PE
Pooled analysis: Major bleeding

First major bleeding



Number of patients at risk													
Rivaroxaban	4130	3921	3862	3611	3479	3433	2074	1135	1095	1025	969	947	499
Enoxaparin/VKA	4116	3868	3784	3525	3394	3348	1835	1109	1065	990	950	916	409

Safety population

Prins MH, et al. *Thromb J.* 2013;11:21.[30]

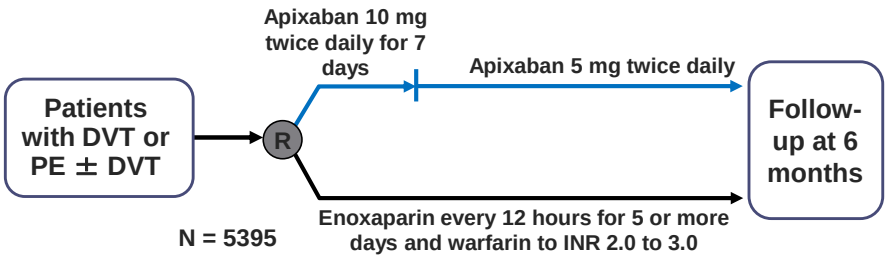
EINSTEIN Pooled Data
Fragile Patients

- Elderly (>75 years)
- Body weight ≤ 50 kg
- Renal failure (Cr Cl < 50 mL/min)

Outcome	Rivaroxaban, % (n = 791)	Enoxaparin/VKA, % (n = 782)	HR (95% CI)	*P* Value
Recurrence of thromboembolism	2.7	3.8	0.68 (0.39-1.18)	--
Overall	2.1	2.3	0.89 (0.66-1.19)	< .001
Major bleeding	1.3	4.5	0.27 (0.13-0.54)	--
Overall	1.0	1.7	0.54 (0.37-0.79)	.002

Büller HR, et al. ASH 2012. Abstract 20.

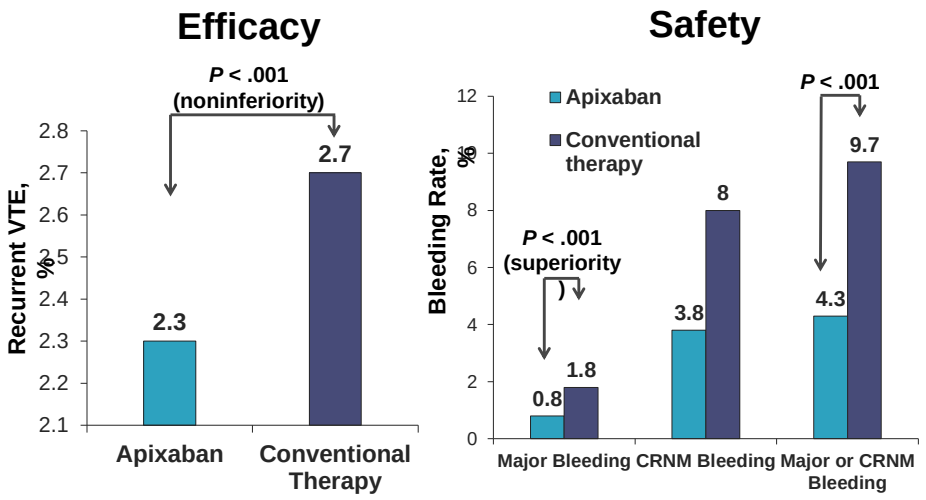
AMPLIFY
Study Design



- Primary efficacy outcome: Symptomatic recurrent VTE or VTE-related death
- Principal safety outcome: Major bleeding

gnelli G, et al. *N Engl J Med.* 2013;369:799-808.

AMPLIFY
Results

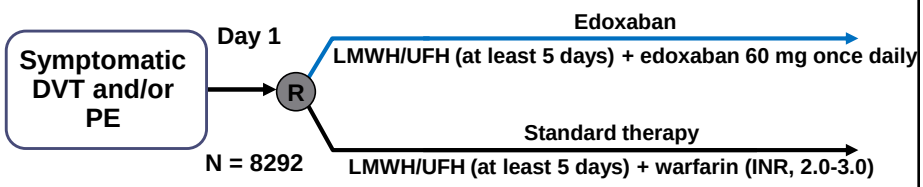


CRNM= Clinically Relevant Non Major

gnelli G, et al. *N Engl J Med.* 2013;369:799-808.

Hokusai-VTE
Study Design

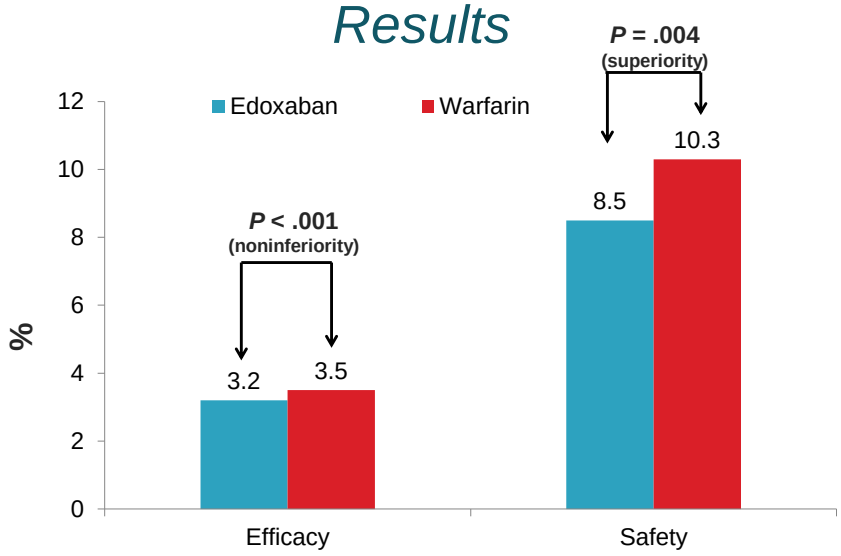
Maximum treatment period of 12 months



- Primary efficacy outcome:
  - Symptomatic recurrent VTE or VTE-related death
- Principal safety outcome:
  - Major or CRNM bleeding during treatment

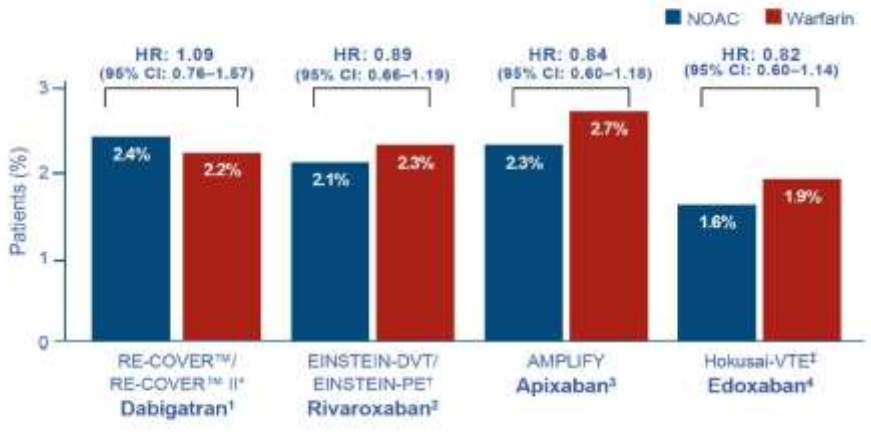
Raskob, G et al. *J Thromb Haemost.* 2013;11:1287-1294.

Hokusai-VTE
Results



Büller HR, et al. *N Engl J Med.* 2013;369:1406-1415.

Treatment of acute DVT/PE: NOACs non-inferior to warfarin for prevention of recurrent DVT/PE in Phase III trials

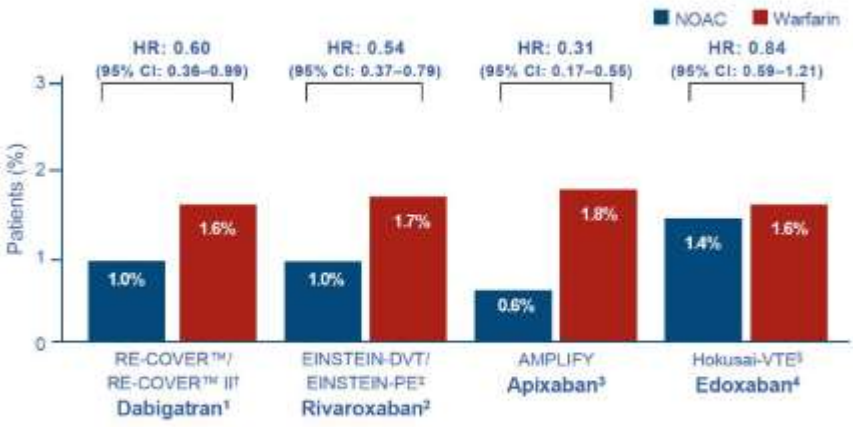


Direct comparisons cannot be made as no head-to-head data are available

*Pooled data from RE-COVER™ and RE-COVER™ II; †Pooled analysis; ‡On treatment

1. Schulman S et al. Circulation 2014;129:764–72; 2. Prins MH et al. Thromb J 2013;11:21; 3. Agnelli G et al. N Engl J Med 2013;369:799–808; 4. The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–15

Treatment of acute DVT/PE: NOACs associated with less major bleeding than warfarin in Phase III trials*



Direct comparisons cannot be made as no head-to-head data are available

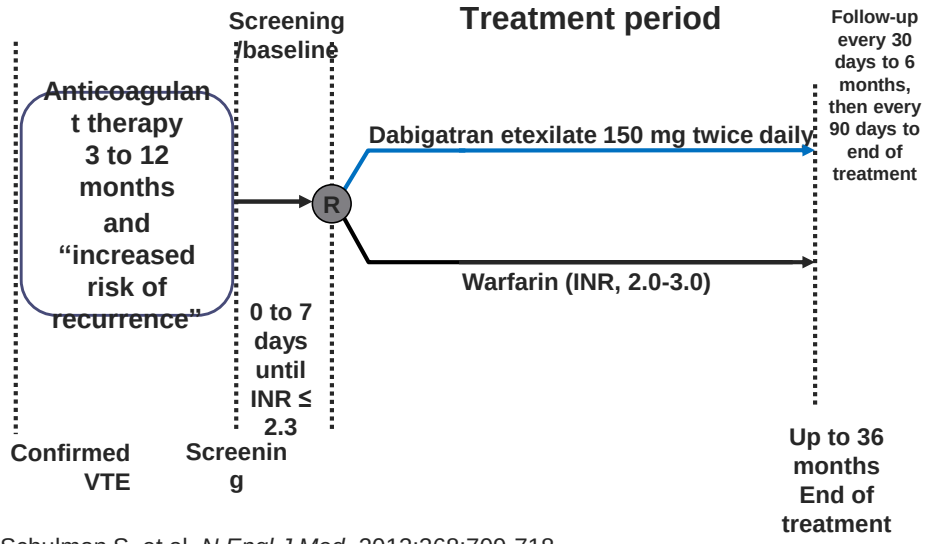
*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin; numerical reduction for edoxaban vs warfarin; †Pooled data from RE-COVER™ and RE-COVER™ II; oral drug treatment period only; ‡Pooled analysis; §On treatment

1. Schulman S et al. Circulation 2014;129:764–72; 2. Prins MH et al. Thromb J 2013;11:21; 3. Agnelli G et al. N Engl J Med 2013;369:799–808; 4. The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–15

Phase 3 Secondary Prevention (Extension) Trials

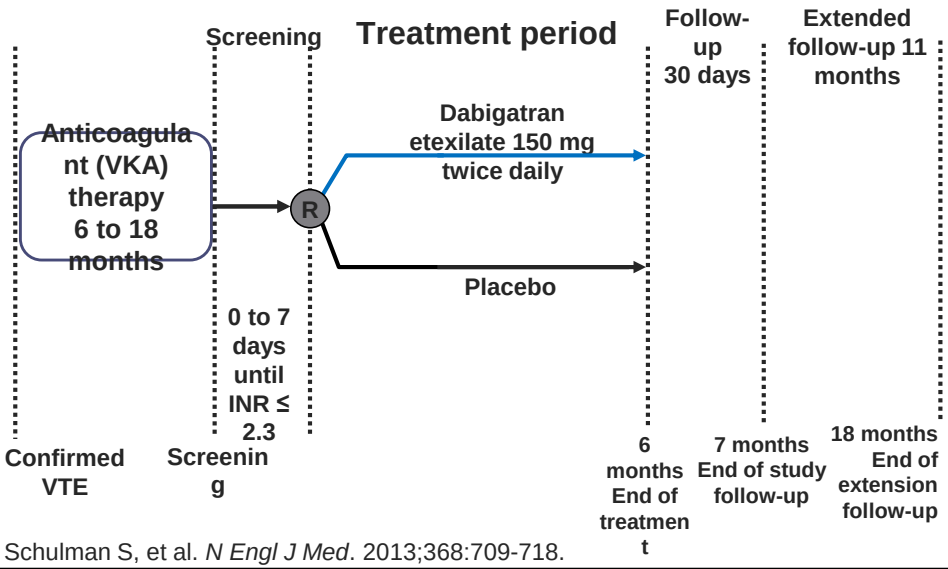
Study	Oral Agent Tested	Comparator	N*	Treatment Duration
RE-MEDY	Dabigatran etexilate 150 mg BID	Warfarin PRN (INR 2.0-3.0) (All patients received 3-6 months of anticoagulation for symptomatic acute VTE before randomization)	2700	18 months
RE-SONATE	Dabigatran etexilate 150 mg BID	Placebo (All patients received 6-18 months of VKA for symptomatic acute VTE before randomization)	1462	6 months
AMPLIFY-EXT	Apixaban 2.5 mg BID 5.0 mg BID	Placebo (All patients completed intended treatment for DVT or PE before randomization)	2430	12 months
EINSTEIN-EXT	Rivaroxaban 20 mg QD	Placebo (All patients received 6-12 months of anticoagulant treatment for symptomatic acute VTE before randomization)	1197	6-12 months

RE-MEDY Study Design



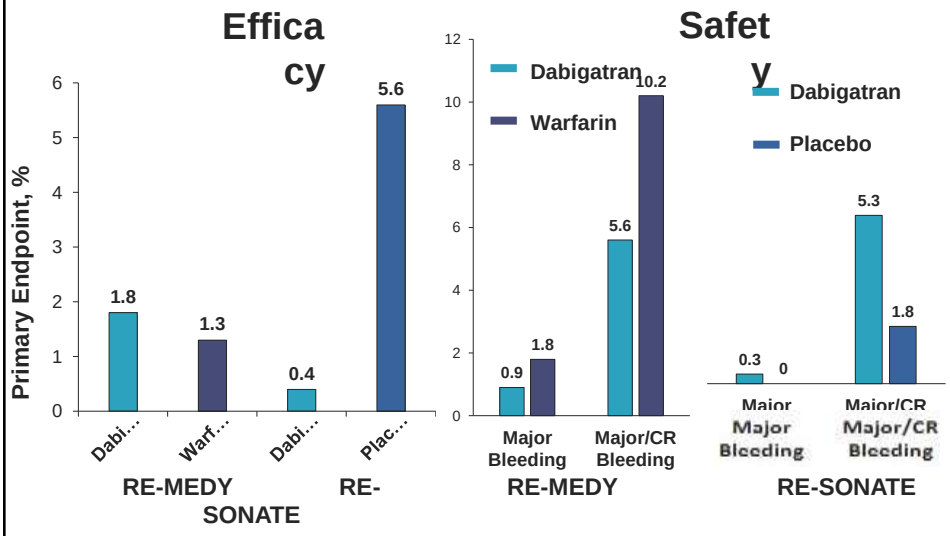
Schulman S, et al. *N Engl J Med*. 2013;368:709-718.

RE-SONATE Study Design



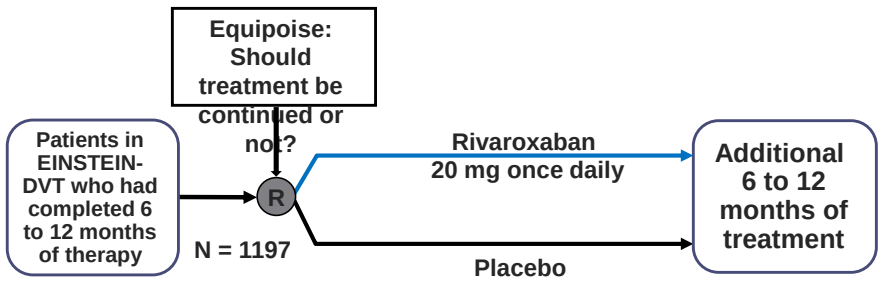
Schulman S, et al. *N Engl J Med*. 2013;368:709-718.

RE-MEDY, RE-SONATE
Results



Schulman S, et al. *N Engl J Med*. 2013;368:709-718.

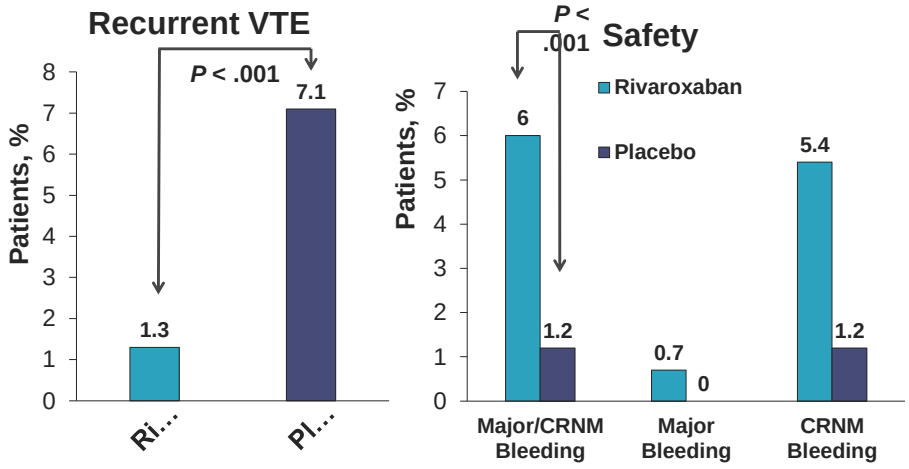
EINSTEIN-Extension
Study Design



- Primary efficacy outcome: Symptomatic recurrent VTE
- Principal safety outcome: Major bleeding

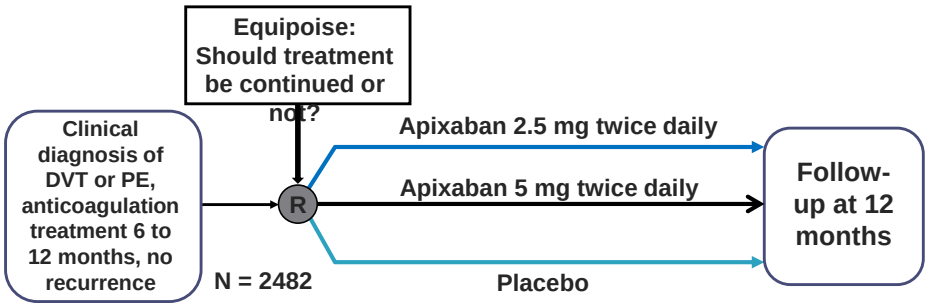
Bauersachs R, et al. *N Engl J Med*. 2010;363:2499-2510.

EINSTEIN-Extension
Results



Bauersachs R, et al. *N Engl J Med*. 2010;363:2499-2510.[5]

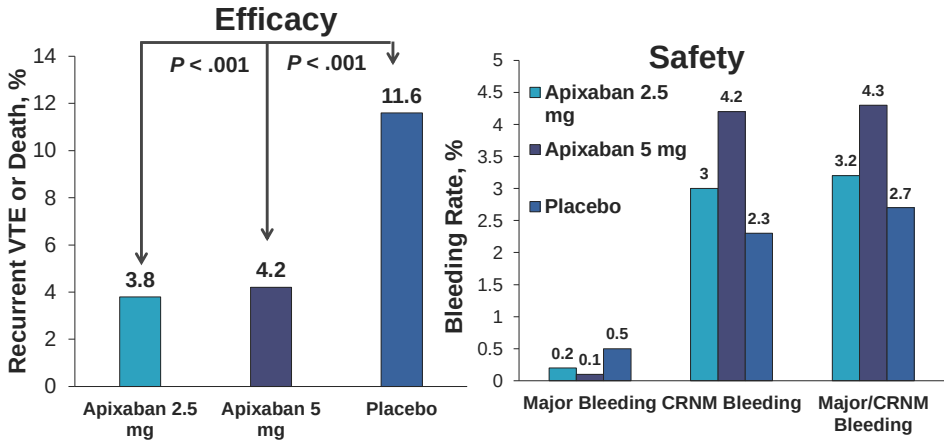
AMPLIFY-EXT
Study Design



- Primary endpoint: VTE recurrence or death
- Secondary outcome measures: Major bleeding

Agnelli G, et al. *N Engl J Med*. 2013;368:699-708.

AMPLIFY-EXT
Results



Agnelli G, et al. *N Engl J Med*. 2013;368:699-708.[13]

Recurrent VTE in Extension VTE Trials

Incidence of Recurrent VTE

Trial	Agent	NOAC, %	Warfarin, %	HR (95% CI)
RE-MEDY[a]	Dabigatran	1.8	1.3	1.44 (0.78-2.64)
		NOAC, %	**Placebo, %**	**HR (95% CI)**
RE-SONATE[a]	Dabigatran	0.4	5.6	0.08 (0.02-0.25)
EINSTEIN-EXT[b]	Rivaroxaban	1.3	7.1	0.18 (0.09-0.39)
AMPLIFY-EXT[c]	Apixaban 2.5 mg	1.7	8.8	0.19 (0.11-0.33)
	Apixaban 5 mg	1.7	8.8	0.20 (0.11-0.34)

a. Schulman S, et al. *N Engl J Med*. 2013;368:709-718; b. Bauersachs R, et al. *N Engl J Med*. 2010;363:2499-2510; c. Agnelli G, et al. *N Engl J Med.* 2013;368:699-708.

Major Bleeding in Extension VTE Trials

Incidence of Major Bleeding

Trial	Agent	NOAC, %	Warfarin, %	HR (95% CI)
RE-MEDY[a]	Dabigatran	0.9	1.8	0.52 (0.27-1.02)
		NOAC, %	**Placebo, %**	**HR (95% CI)**
RE-SONATE[a]	Dabigatran	0.3	0	Not estimable
EINSTEIN-EXT[b]	Rivaroxaban	0.7	0	Not estimable
AMPLIFY-EXT[c]	Apixaban 2.5 mg	0.2	0.5	0.49 (0.09-2.64)
	Apixaban 5 mg	0.1	0.5	0.25 (0.03-2.24)

a. Schulman S, et al. *N Engl J Med*. 2013;368:709-718; b. EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499-2510; c. Agnelli G, et al. *N Engl J Med*. 2013;368:699-708.

Acute phase treatment

Recommendations	Class	Level
PE without shock or hypotension (intermediate or low risk)		
Anticoagulation - new oral anticoagulants		
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B
As an alternative to VKA treatment, administration of edoxaban is recommended following acute-phase parenteral anticoagulation.	I	B
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.	III	A

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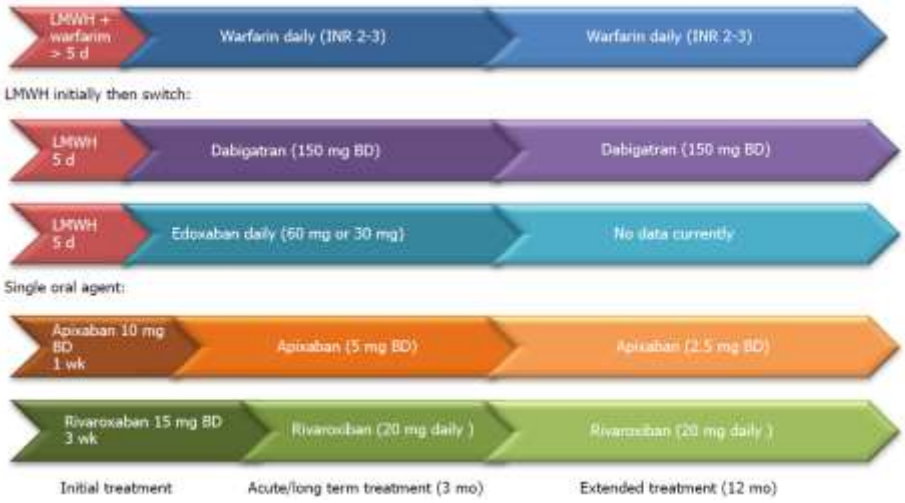
Current standard of care



World J Hematol 2015 February 6; 4(1): 1-9

Assessment of pre-test probability

Clinical prediction rules for pulmonary embolism		
	Clinical decision rule points	
Wells rule	**Original version**	**Simplified version**
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0-1	N/A
Intermediate	2-6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0-4	0-1
PE likely	≥5	≥2

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European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Assessment of pre-test probability (cont'd)

Clinical prediction rules for pulmonary embolism (cont.)		
	Clinical decision rule points	
Revised Geneva score	**Original version**	**Simplified version**
Previous DVT or PE	3	1
Heart rate 75-94 b.p.m. ≥95 b.p.m.	3 5	1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	≥11	≥5
Two-level score		
PE unlikely	0-5	0-2
PE likely	≥6	≥3

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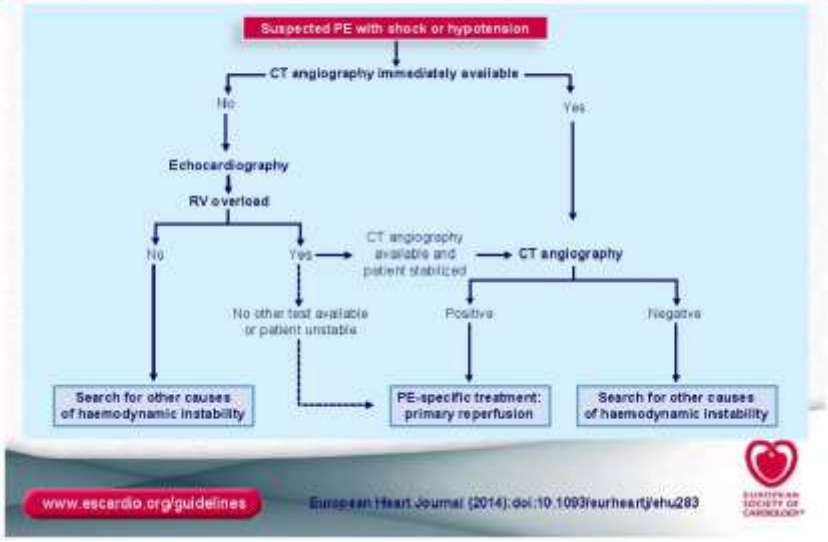
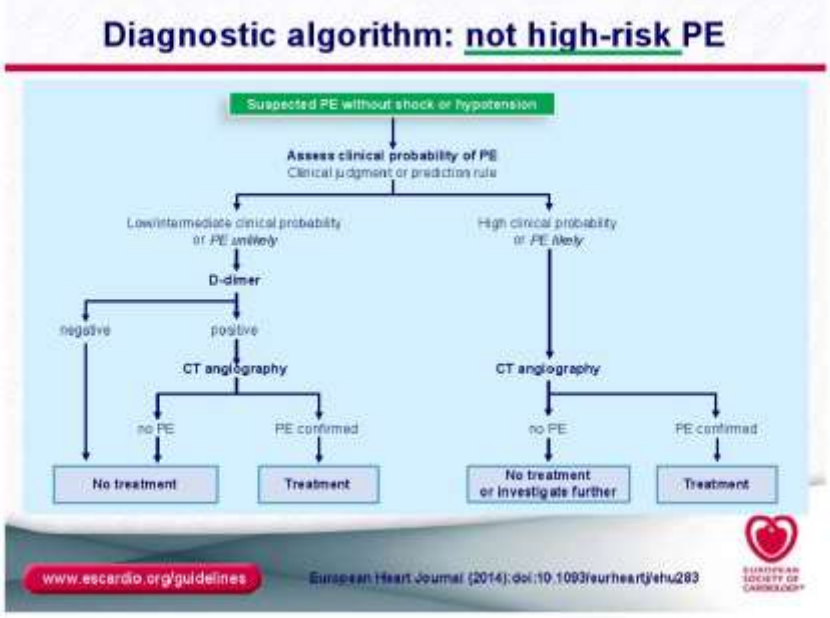
European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Diagnostic algorithm: high-risk PE



Diagnostic algorithm: not high-risk PE



Classification of early mortality risk

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI Class III-V or sPESI ≥1	Signs of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High		+	(+)	+	(+)
Intermediate	Intermediate-high	–	+	Both positive	
	Intermediate-low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assesed, both negative	

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European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Original and simplified pulmonary embolism severity index (PESI)

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male sex	+10	–
Cancer	+30	1
Chronic heart failure	+10	1
Chronic pulmonary disease	+10	
Pulse rate ≥110 b.p.m.	+20	1
Systolic blood pressure <100 mmHg	+30	1
Respiratory rate >30 breaths per minute	+20	–
Temperature <36°C	+20	–
Altered mental status	+60	–
Arterial oxyhaemoglobin saturation <90%	+20	1

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European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Original and simplified pulmonary embolism severity index (PESI)

Parameter	Original version	Simplified version
	Risk strata	
	Class I: ≤65 points very low 30-day mortality risk (0-1.6%) **Class II: 66-85 points** low mortality risk (1.7-3.5%) **Class III: 86-105 points** moderate mortality risk (3.2-7.1%) **Class IV: 106-125 points** high mortality risk (4.0-11.4%) **Class V: >125 points** very high mortality risk (10.0-24.5%)	**0 points** = 30-day mortality risk 1.0% (95% CI 0.0%-2.1%) **≥1 point(s)** = 30-day mortality risk 10.9% (95% CI 8.5%-13.2%)

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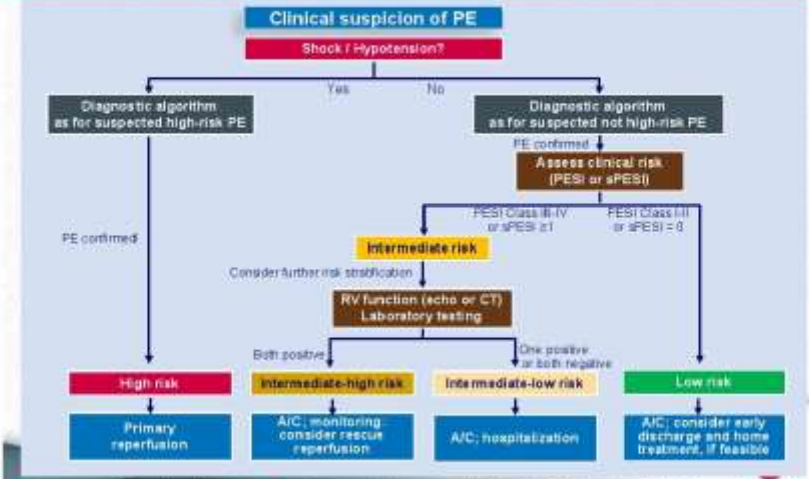
Risk-adjusted management algorithm



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Thrombolytic treatment of PE

Approved thrombolytic regimens for pulmonary embolism	
Streptokinase	250 000 IU as a loading dose over 30 minutes, followed by 100 000 IU/h over 12-24 hours.
	Accelerated regimen: 1.5 million IU over 2 hours.
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg per hour over 12-24 hours.
	Accelerated regimen: 3 million IU over 2 hours.
rtPA	100 mg over 2 hours; or
	0.6 mg/kg over 15 minutes (maximum dose 50 mg).

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European Heart Journal (2014):doi:10.1093/eurheartj/ehu283