

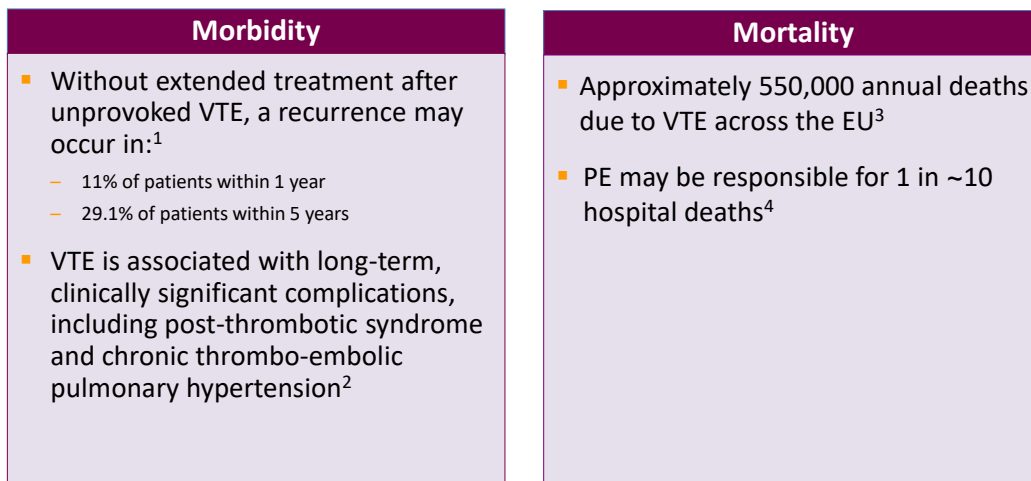
Acute and extended treatment of venous thromboembolism – the role of the NOACs

Menno Huisman
Department of Thrombosis and Hemostasis
Leiden University Medical Center
Leiden the Netherlands – m.v.huisman@lumc.nl

Disclosures Menno Huisman

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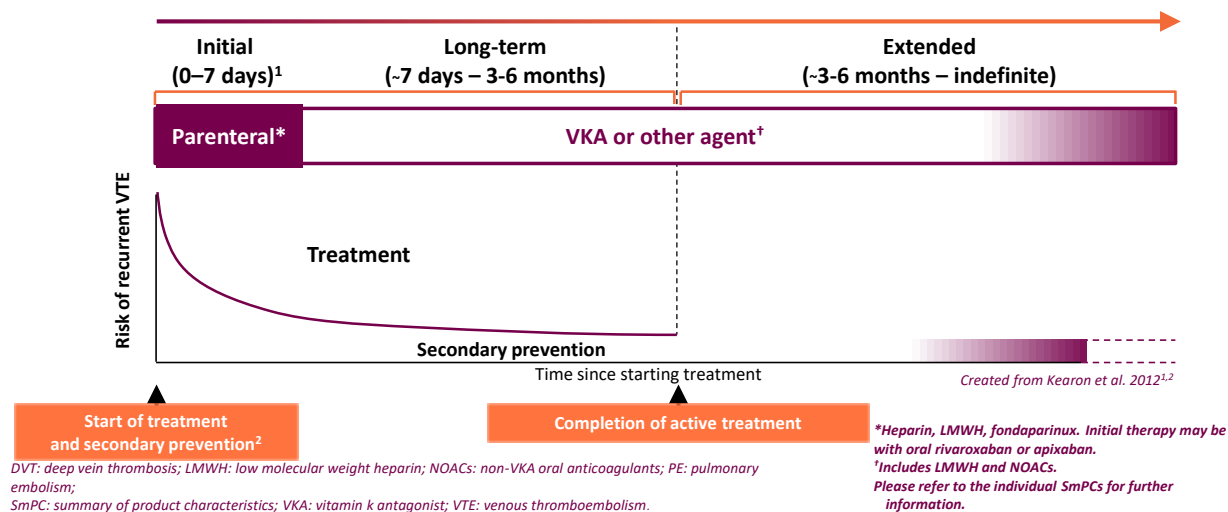
Significant morbidity and mortality of VTE¹⁻⁴



EU: European Union; PE: pulmonary embolism; VTE: venous thromboembolism.

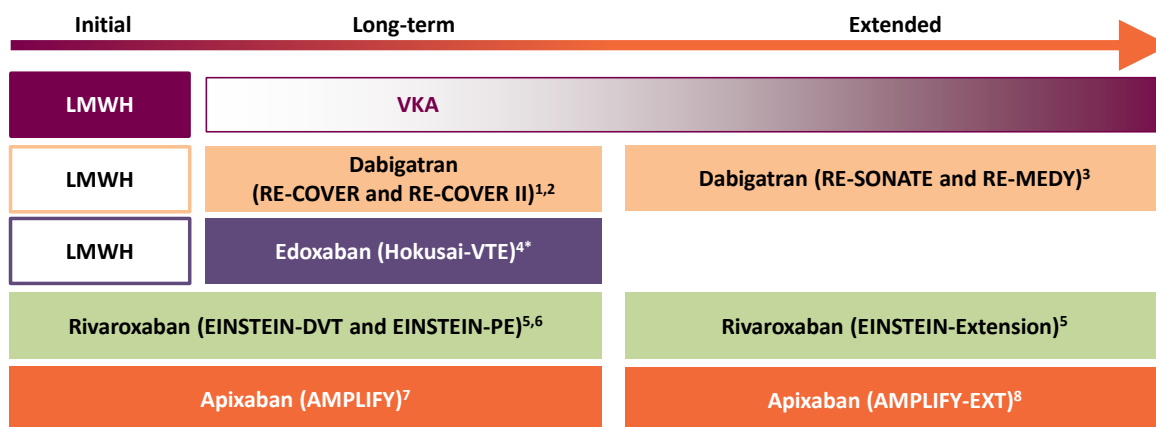
1. Prandoni et al. *Haematologica*. 2007;92:199–205; 2. Palareti. *Scientifica*. 2012;2012:1–17; 3. Cohen et al. *Thromb Haemost*. 2007;98:756–764; 4. Geerts et al. *Chest*. 2004;126(3 suppl):3385–4005.

Phases of anticoagulation treatment for DVT and PE^{1,2}



1. Kearon et al. *Chest*. 2012;141(2 suppl):e419s–e494s;
 2. Kearon. *J Thromb Haemost*. 2012;10:507–511.

Overview of NOAC trials in VTE¹⁻⁸



All four NOACs are licensed for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. Please refer to individual SmPCs for further information.

DVT: deep vein thrombosis; NOAC(s): non-VKA oral anticoagulant(s); PE: pulmonary embolism; SmPCs: Summary of Product Characteristics; VTE: venous thromboembolism; VKA: vitamin K antagonist.

- Schulman et al. *N Engl J Med.* 2009;361:2342–2352; 2. Schulman et al. *Circulation.* 2014;129:764–772; 3. Schulman et al. *N Engl J Med.* 2013;368:709–718; 4. The Hokusai-VTE Investigators. *N Engl J Med.* 2013;369:1406–1415; 5. The EINSTEIN Investigators. *N Engl J Med.* 2010;363:2499–2510; 6. The EINSTEIN-PE Investigators. *N Engl J Med.* 2012;366:1287–1297; 7. Agnelli et al. *N Engl J Med.* 2013;369:799–808; 8. Agnelli et al. *N Engl J Med.* 2013;368:699–708.

Acute DVT and PE treatment: NOAC trial designs

Head-to-head studies do not exist, therefore comparisons between agents cannot be made

NOAC	Trial	Number of patients	Design	Parenteral required before NOAC?	NOAC dosing	Treatment length (months)
Apixaban	AMPLIFY ¹	5,395 DVT: 3,532 PE: 1,836*	Double-blind	No	Apixaban 10 mg BID for 7 days, then 5 mg BID	6
Rivaroxaban	EINSTEIN-DVT ²	DVT: 3,449	Open-label	No	Rivaroxaban 15 mg BID for 21 days, then 20 mg once daily	3, 6 or 12 [†]
	EINSTEIN-PE ³	PE: 4,832				
Dabigatran	RE-COVER ⁴	2,539	Double-blind	LMWH, UFH, or fondaparinux ≥5 days	Dabigatran 150 mg BID	6
	RE-COVER II ⁵	2,568				
Edoxaban	Hokusai-VTE ⁶	8,240 DVT: 4,921 PE: 3,319*	Double-blind	Enoxaparin or UFH ≥5 days	Edoxaban 60 mg OD [‡]	3–12 [§]

*Patients presenting with PE may also present with concomitant DVT.

[†]Duration of treatment was determined by the treating physician before randomisation. Most patients received 6 or 12 months of therapy.

[‡]Patients with a body weight ≤60 kg or CrCl 30–50 mL/min, or patients receiving concomitant potent P-gp inhibitors received edoxaban 30 mg OD.

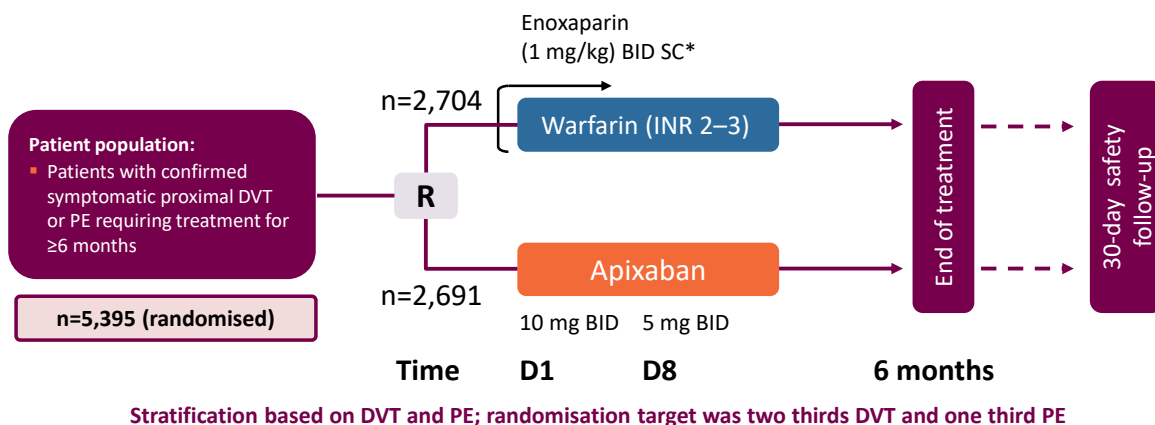
[§]Duration of treatment was determined by the treating physician based on the patient's clinical features and patient preference.

BID: twice daily; CrCl: creatinine clearance; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NOAC: non-VKA oral anticoagulant; OD: once daily; P-gp: P-glycoprotein; PE: pulmonary embolism;

UFH: unfractionated heparin; VTE: venous thromboembolism.

- Agnelli et al. *N Engl J Med.* 2013;369:799–808; 2. Bauersachs et al. *N Engl J Med.* 2010;363:2499–2510; 3. Büller et al. *N Engl J Med.* 2012;366:1287–1297; 4. Schulman et al. *N Engl J Med.* 2009;361:2342–2352; 5. Schulman et al. *Circulation.* 2014;129:764–772; 6. The Hokusai-VTE Investigators. *N Engl J Med.* 2013;369:1406–1415.

AMPLIFY: 6-month double-blind active-controlled non-inferiority treatment study¹



*For at least 5 days and then discontinued if blinded INR was 2.0 or higher.

BID: twice daily; D: day; DVT: deep vein thrombosis; INR: international normalised ratio; R: randomisation; PE: pulmonary embolism SC: subcutaneous.

Created from Agnelli et al. 2013¹

1. Agnelli et al. *N Engl J Med.* 2013;369:799–808.

AMPLIFY: Baseline patient characteristics*

	Apixaban (n=2691)	Conventional therapy (n=2704)
Age, years (±SD)	57.2±16.0	56.7±16.0
Male, no. (%)	1569 (58.3)	1598 (59.1)
Weight, kg (mean)	84.6±19.8	84.6±19.8
Creatinine clearance, no. (%)		
≤30 mL/min	14 (0.5)	15 (0.6)
>30 – ≤50 mL/min	161 (6.0)	148 (5.5)
>50 – ≤80 mL/min	549 (20.4)	544 (20.1)
>80 mL/min	1721 (64.0)	1757 (65.0)
Data missing	246 (9.1)	240 (8.9)
Qualifying diagnosis, no. (%)		
DVT	1749 (65.0)	1783 (65.9)
PE	678 (25.2)	681 (25.2)
PE with DVT	252 (9.4)	225 (8.3)
Risk factors for recurrent VTE, no. (%)[†]		
Previous VTE	463 (17.2)	409 (15.1)
Known thrombophilia	74 (2.8)	59 (2.2)
Active cancer	66 (2.5)	77 (2.8)

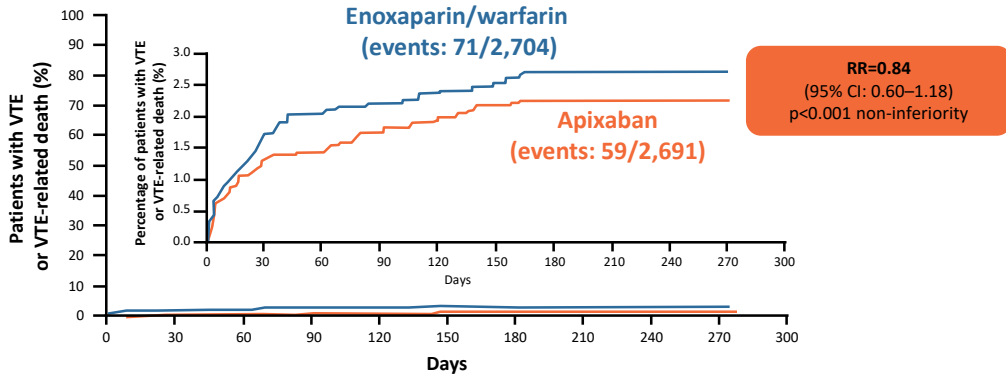
*Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. VTE denotes venous thromboembolism. There were no significant differences between the study groups in the baseline characteristics listed here. [†]Patients may have undergone more than one imaging test.

Created from Agnelli et al. 2013¹

DVT: deep vein thrombosis; PE: pulmonary embolism; SD: standard deviation; VTE: venous thromboembolism.

1. Agnelli et al. *N Engl J Med.* 2013;368:699–708.

First recurrent VTE/VTE-related death: apixaban non-inferior to enoxaparin/warfarin¹



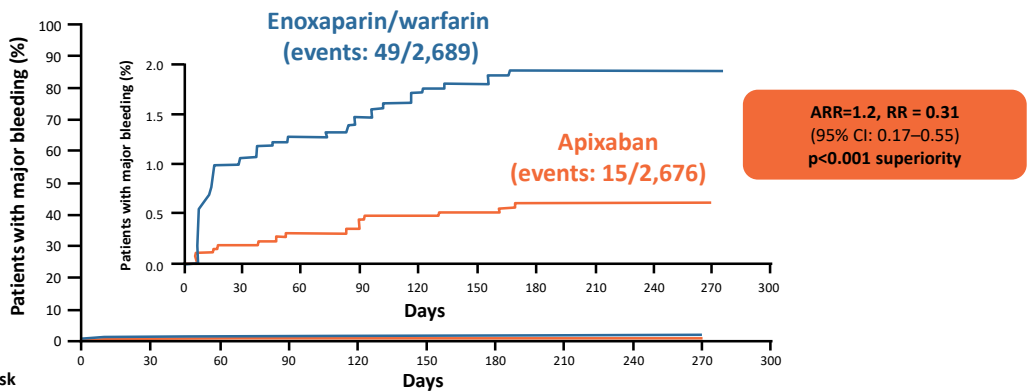
No. at risk	Days										
	0	30	60	90	120	150	180	210	240	270	300
Apixaban	2,691	2,606	2,586	2,563	2,541	2,523	62	4	1	0	0
Enoxaparin/warfarin	2,704	2,609	2,585	2,555	2,543	2,533	43	3	1	1	0

Adapted from Agnelli et al. 2013¹

CI: confidence interval; RR: relative risk; VTE: venous thromboembolism.

1. Agnelli et al. *N Engl J Med.* 2013;369:799-808.

Apixaban significantly reduced major bleeding by 69% vs enoxaparin/warfarin¹



Number at risk	Days										
	0	30	60	90	120	150	180	210	240	270	300
Apixaban	2,676	2,519	2,460	2,409	2,373	2,339	61	4	1	0	0
Enoxaparin/warfarin	2,689	2,488	2,426	2,383	2,339	2,310	43	3	1	1	0

Adapted from Agnelli et al. 2013¹

ARR: absolute risk ratio; CI: confidence interval; RR: relative risk.

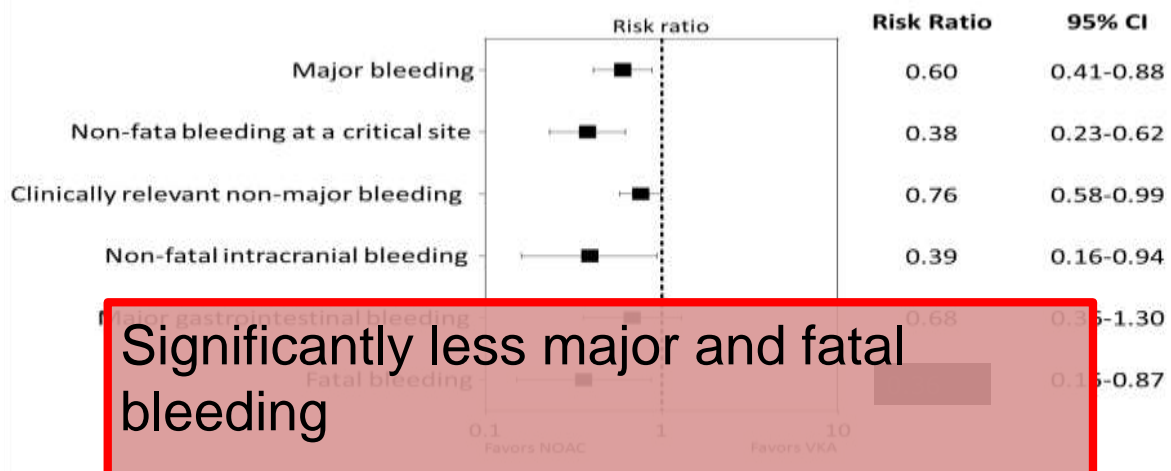
1. Agnelli et al. *N Engl J Med.* 2013;369:799-808.

Meta-analysis DOAC efficacy in VTE



van der Hulle *et al*, J Thromb Haemost 2014;12:320-8

Meta-analysis of NOAC safety in VTE



van der Hulle *et al*, J Thromb Haemost 2014;12:320-8

Prevention of recurrent DVT and PE: NOAC trial designs

Head-to-head studies do not exist, therefore comparisons between agents cannot be made

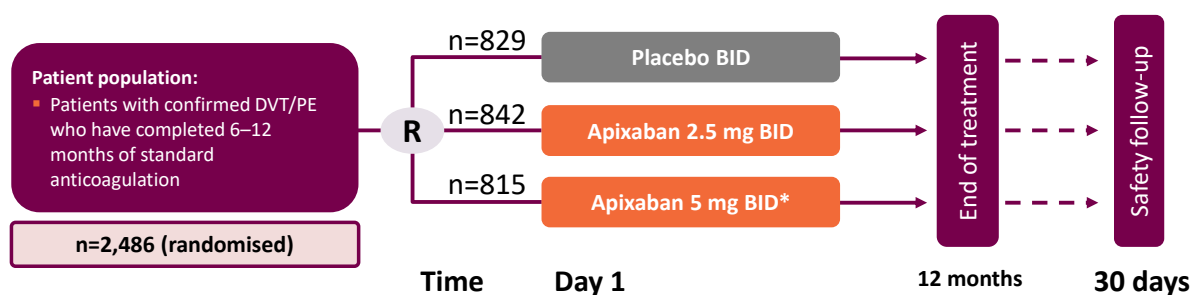
Study drug	Trial	Number of patients	Treatment before randomisation	Study drug dosing	Comparator	Treatment length (months)
Dabigatran	RE-SONATE ¹	1,343	6–18 months of VKA or dabigatran	Dabigatran 150 mg BID	Placebo	6
Rivaroxaban	EINSTEIN-EXT ²	1,196	6 or 12 months of VKA or rivaroxaban	Rivaroxaban 20 mg OD	Placebo	6 or 12
Apixaban	AMPLIFY-EXT ³	2,482	6–12 months of standard therapy or apixaban	Apixaban 2.5 mg or 5 mg BID*	Placebo	12
Dabigatran	RE-MEDY ¹	2,856	3–12 months of VKA or dabigatran	Dabigatran 150 mg BID	Warfarin INR 2.0–3.0	6–36

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE⁴

BID: twice daily; DVT: deep vein thrombosis; INR: international normalized ratio; NOAC: non-VKA oral anticoagulant; OD: once daily; PE: pulmonary embolism; VKA: vitamin K antagonist.

1. Schulman et al. *N Engl J Med.* 2013;368:709–718; 2. Bauersachs et al. *N Engl J Med.* 2010;363:2499–2510; 3. Agnelli et al. *N Engl J Med.* 2013;368:699–708; 4. Apixaban SmPC. Available at <http://www.ema.europa.eu>.

AMPLIFY-EXT: 12-month double-blind placebo-controlled extended treatment study¹



Created from Agnelli et al. 2013¹

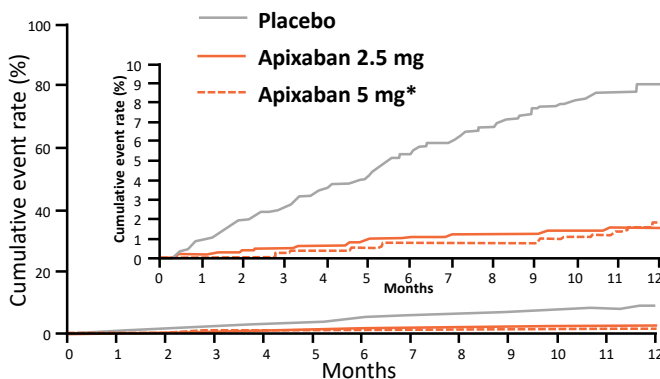
The n value for each study arm was based on the calculation that 810 patients were required in each group for the study to have 90% power to show the superiority of apixaban over placebo (~60% RRR), at a two-sided alpha level of 0.05

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE in those who have been treated for 6 months.²

BID: twice daily; DVT: deep vein thrombosis; RRR: relative risk reduction PE: pulmonary embolism.

1. Agnelli et al. *N Engl J Med.* 2013;368:699–708, 2. Apixaban SmPC. Available at <http://www.ema.europa.eu>.

VTE/VTE-related death: apixaban demonstrated superior efficacy to placebo¹



Apixaban 2.5 mg:
ARR=7.1%, RR=0.19
(0.11–0.33)

Apixaban 5 mg*:
ARR=7.1%, RR=0.20
(0.11–0.34)

No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Apixaban 2.5 mg	840		836		825		818		818		818		533
Apixaban 5 mg	813		807		799		791		791		791		513
Placebo	826		796		768		743		743		743		471

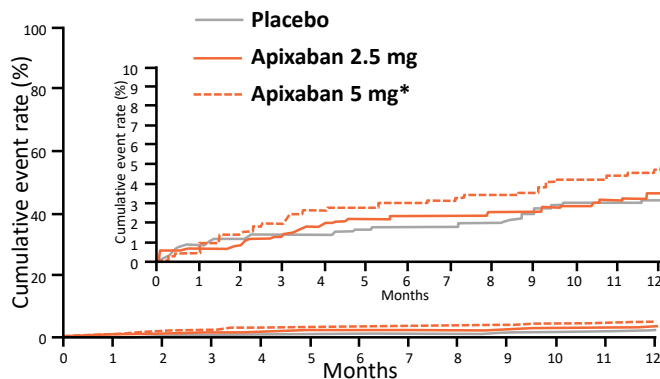
ARR: absolute risk reduction; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.

Created from Agnelli et al. 2013¹

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE in patients who have been treated for 6 months².

1. Agnelli et al. *N Engl J Med* 2013;368:699–708;
2. Apixaban SmPC. Available at <http://www.ema.europa.eu>.

Apixaban demonstrated a similar incidence of major/CRNM bleeding as placebo¹



Apixaban 5 mg*:
ARI=1.6%, RR = 1.62
(0.96–2.73)

Apixaban 2.5 mg:
ARI=0.5%, RR=1.20
(0.69–2.10)

No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Apixaban 2.5 mg	840		786		759		737		737		737		354
Apixaban 5 mg	811		751		716		689		689		689		331
Placebo	823		749		687		651		651		651		298

Created from Agnelli et al. 2013¹

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE in patients who have been treated for 6 months².

ARI: absolute risk increase; CRNM: clinically relevant non-major; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.

1. Agnelli et al. *N Engl J Med*. 2013;368:699–708;
2. Apixaban SmPC. Available at <http://www.ema.europa.eu>.

Study Limitations:

- Only 15% of the patients in this study were >75 yr
- Few had a body weight <60kg or moderate/severe renal impairment

AMPLIFY-EXT: clinical interpretation¹

	Apixaban 2.5 mg	Apixaban 5 mg*
NNT to prevent one recurrent VTE (fatal or non-fatal) during 1 year vs placebo	14	14
NNH – one major or clinically relevant non-major bleed vs placebo	200 [†]	63

*Only apixaban 2.5 mg BID is licensed for prevention of recurrent DVT/PE in patients who have been treated for 6 months² cited from Agnelli et al. 2013¹

[†]Only 15% of patients were ≥75 years of age and few had a body weight ≤60 kg or moderate or severe renal impairment.

DVT: deep vein thrombosis; NNH: number needed to harm; NNT: number needed to treat; PE: pulmonary embolism; VTE: venous thromboembolism.

1. Agnelli et al. *N Engl J Med.* 2013;368:699–708;
2. Apixaban 5mgPC. Available at <http://www.ema.europa.eu>.

A potential strategy for the long-term treatment of VTE: a dichotomised approach¹

- In patients with proximal DVT/PE: 3 months anticoagulant therapy recommended vs no therapy (Grade 1B)
- In patients with DVT of the leg and PE, and no cancer*: NOAC recommended vs VKA for long-term anticoagulant therapy (first 3 months)(Grade 2B)
 - If not NOAC: VKA therapy suggested over LMWH (Grade 2C)
- Not necessary to change OAC choice after 3 months in patients with DVT/PE who receive extended therapy (Grade 2C)

*There is no data to support the use of NOACs for treatment of VTE in patients with active cancer.

[†]Licensed NOACs for the treatment of VTE include apixaban, rivaroxaban, dabigatran or edoxaban

DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NOACs: non-VKA oral anticoagulants;

PE: pulmonary embolism; VKA: vitamin k antagonist; VTE: venous thromboembolism.

1. Kearon et al. *Chest.* 2016;149:315–352

Conclusions (1)

- NOAC trials in acute treatment of DVT and PE:
 - Differences exist in the design of the trials, mainly with respect to initial parenteral anticoagulation, and duration and dosing frequency for all-oral treatments¹
 - All NOACs were non-inferior to the standard of care for reducing the risk of recurrent VTE and related death, but they have varied bleeding profiles¹
- NOAC trials vs placebo in prevention of recurrent DVT and PE:
 - All NOACs studied in this setting were superior to placebo for reducing the risk of their primary efficacy endpoints; safety outcomes suggest varied bleeding profiles²⁻⁴

DVT: deep vein thrombosis; NOAC(s): non-VKA oral anticoagulant(s); PE: pulmonary embolism; VTE: venous thromboembolism.

1. Cohen et al. *Adv Ther.* 2014;31:473–493; 2. Agnelli et al. *N Engl J Med.* 2013;368:699–708; 3. Schulman et al. *N Engl J Med.* 2013;368:709–718; 4. Bauersachs et al. *N Engl J Med.* 2010;363:2499–2510.

Conclusions (2)

- In the AMPLIFY trial, apixaban showed comparable efficacy and significantly lower major bleeding (69% RRR, 1.2% ARR) vs LMWH/warfarin¹
- In the AMPLIFY-EXT trial, apixaban 2.5 mg BID demonstrated superior efficacy with a similar incidence of major and major and clinically relevant bleeding vs placebo²

BID: twice daily; ARR: absolute risk ratio; BID: twice daily; LMWH: low molecular weight heparin; RRR: relative risk reduction.

1. Agnelli et al. *N Engl J Med.* 2013;369:799–808; 2. Agnelli et al. *N Engl J Med.* 2013;368:699–708.