MTEV: Chez quel patient envisager un traitement à long terme

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Prévention secondaire de MTEV au long cours

Risque de récidive?

Quel antithrombotique ?

Quels patients ?

Prévention MTEV au long cours

Risque de récidive?

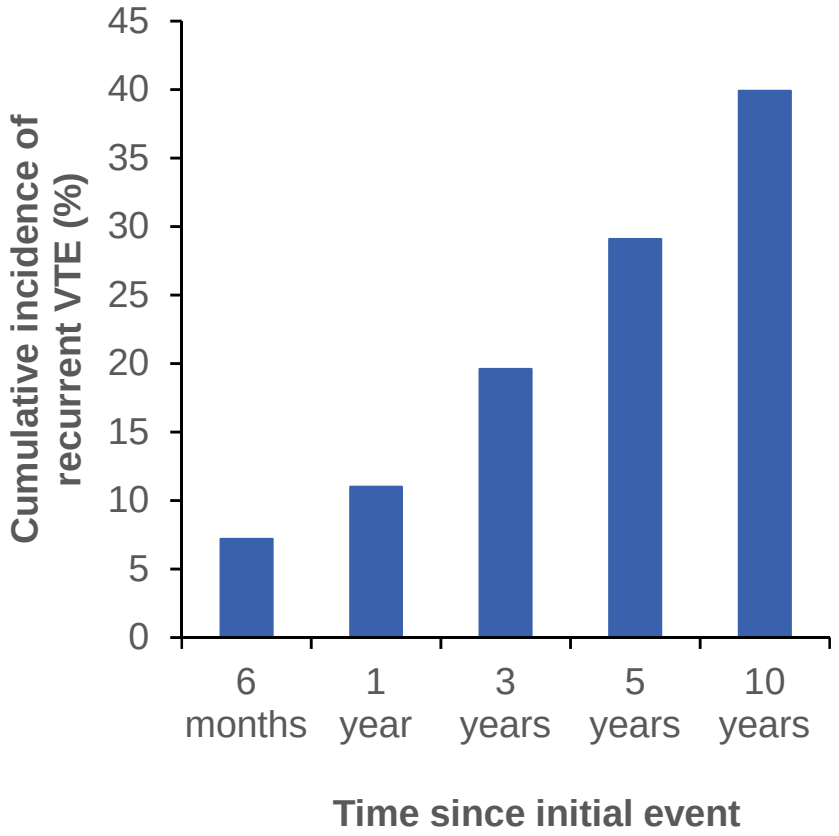
Quel anticoagulant?

Quels patients ?

High Risk of Recurrent VTE After Discontinuing Anticoagulation

- Anticoagulation effectively resolves VTE, but stopping treatment increases the cumulative risk of VTE recurrence[1]
- The cumulative incidence of recurrent VTE is approximately 10% in the first year if anticoagulation is stopped[1]
- NOACs are well suited for extended treatment because:[2]
  - They do not require injections
  - No routine coagulation monitoring is required
  - They have very few known drug–drug and food–drug interactions

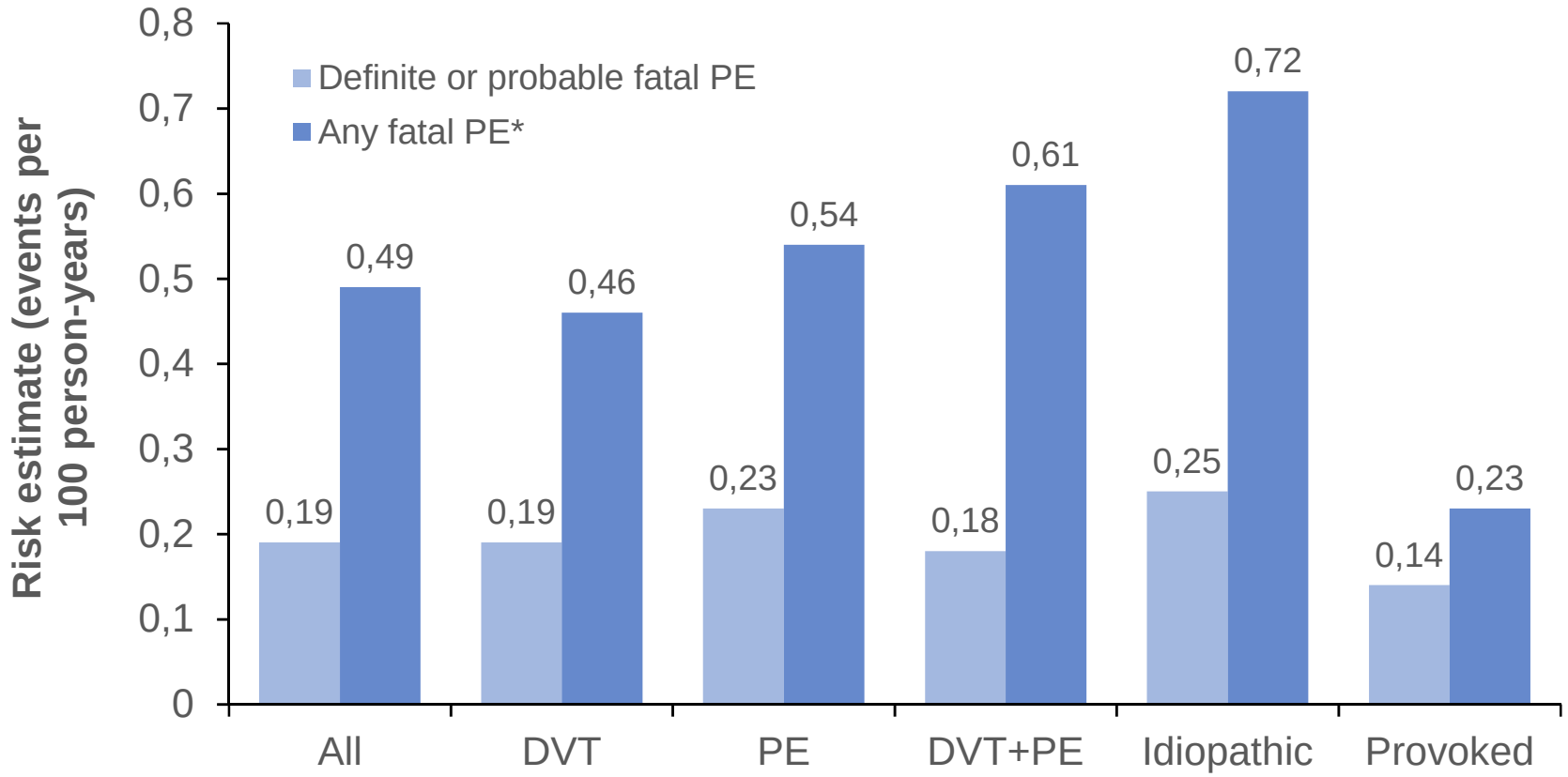
Cumulative incidence of VTE recurrence over time



1. Prandoni P *et al*, *Haematologica* 2007;92:199–205; 2. Schulman S, *J Int Med* 2014;275:1–11

Risk of Fatal PE After Treatment Cessation in Different Patient Groups

Fatal PE events per 100 person-years of follow-up



Mean duration of anticoagulation: 6 months (range, 3–39 months); mean duration of follow-up: 54 months (range, 1–120 months)
*Consists of definite or probable fatal PE plus possible fatal PE (undetermined cause of sudden death)

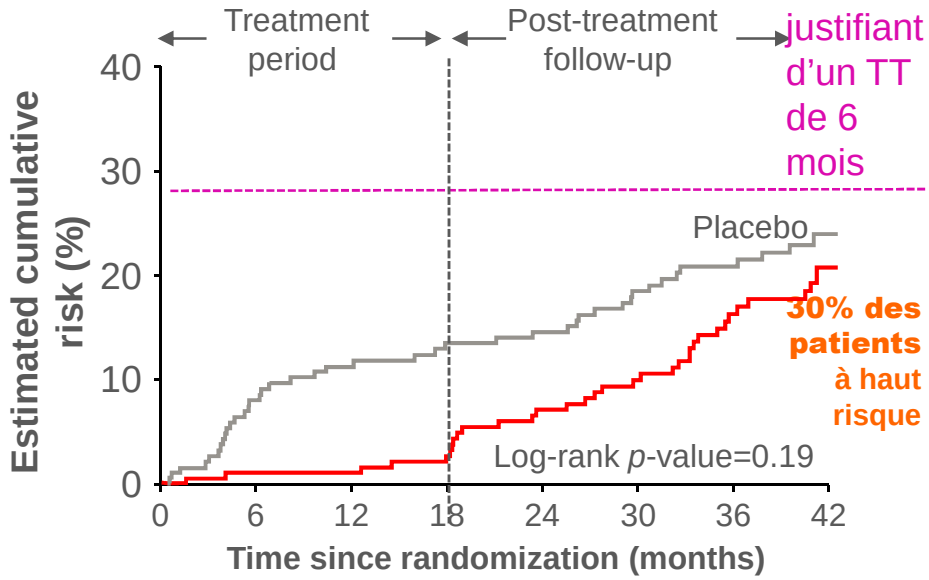
1. Douketis JD *et al, Ann Intern Med* 2007;147:766–774

PADIS EP: VTE recurs even after extended periods of anticoagulation with VKA

- 371 patients with unprovoked PE
- Rx to extended warfarin vs placebo 18 months, follow-up 24 months
- Entire study period: 42 months

- **Composite outcome (recurrent VTE or major bleeding):** unadjusted HR
  - 0.23 (95% CI 0.09–0.55) during treatment period
  - 0.74 (95% CI 0.47–1.17) for entire study period

70% de patients à risque modéré justifiant d'un TT de 6 mois

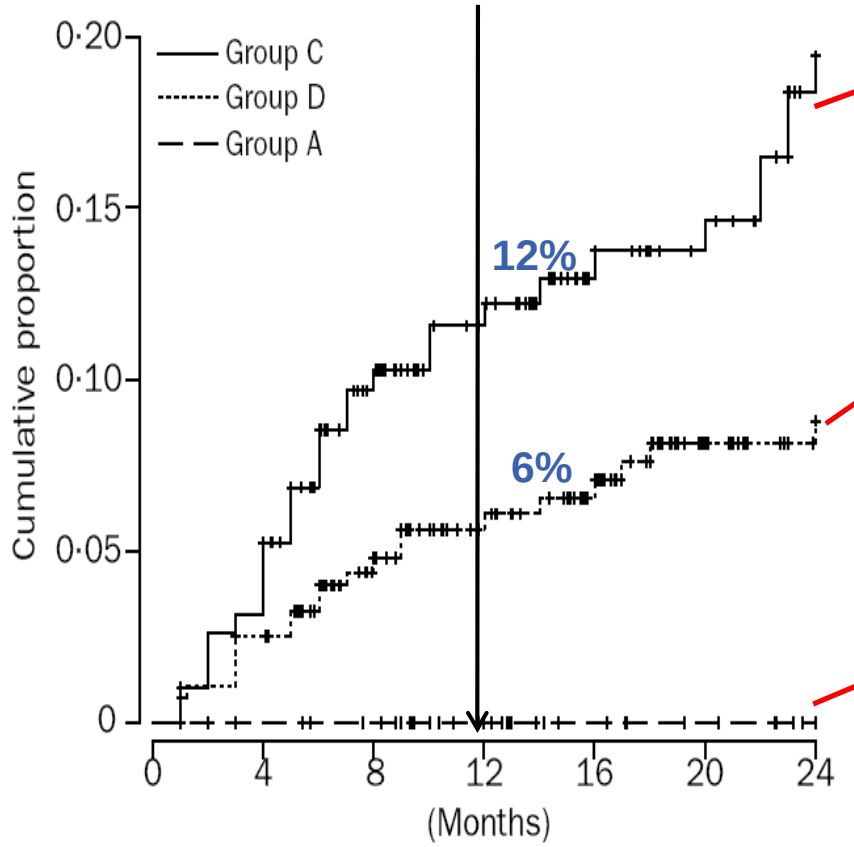


No. at risk								
Placebo	187	170	162	158	155	140	117	104
Warfarin	184	182	180	174	168	150	120	110

Couturaud F *et al, JAMA* 2015;314:31–40

Impact of Clinical Risk Factors in VTE Recurrence

Prospective cohort of non-selected patients who had a first episode of objectively proven VTE. FU in the first 2 years after anticoagulant therapy is stopped.



Number at risk

Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53

Figure 1: **Cumulative proportions of recurrent thrombosis after cessation of anticoagulant therapy**

Data for group B are not included because it was a small group with no recurrences.

Baglin T et al Lancet 2003 362:523-26

C: MTEV idiopathique
Récidive cumulée:19.4%

D: facteur de risque non chir: plâtre, OP, voyage...
Récidive cumulée: 8.8%

A: MTEV + post-opératoire
Récidive cumulée: 0%

- 570 patients
- 1er épisode MVTE
  - EP 29%, TVP 57%
- 4 groupes
- AVK pendant 24 sem
- Suivi 2 ans

Prévention MTEV au long cours

Risque de récidive?

Quel antithrombotique?

Quels patients ?

Prévention MTEV au long cours

Risque de récidive ETEV

Quel antithrombotique?

- -ASA
- -AVK pleine dose, dose réduite
- -AOD pleine dose, mi dose

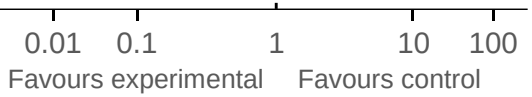
Extended Anticoagulant and ASA Treatment for Secondary Prevention of Thromboembolic Disease: A Systematic Review and Meta-Analysis unprovoked VTE with equipoise patients

Risk of recurrent thromboembolic events

	Experimental		Control		Weight	Odds ratio (95% CI)	Odds ratio (95% CI)
	Events	Total	Events	Total			
VKA	4	263	42	270	19.0%	0.09 (0.03–0.25)	-91% S
NOAC	39	2936	150	2085	45.7%	0.16 (0.11–0.24)	
ASA	65	616	97	608	35.3%	0.62 (0.44–0.87)	-38% S
Total	108	3815	289	2963	100.0%	0.21 (0.11–0.42)	

Risk of major bleeding

	Experimental		Control		Weight	Odds ratio (95% CI)	Odds ratio (95% CI)
	Events	Total	Events	Total			
VKA	7	263	1	270	20.2%	5.13 (0.87–30.15)	+413%NS
NOAC	9	2936	4	2085	37.6%	1.88 (0.19–18.06)	
ASA	9	616	7	608	42.2%	1.28 (0.47–3.48)	+28% NS
Total	25	3815	12	2963	100.0%	1.64 (0.69–3.90)	



Patients treated for at least 3 months with a VKA or a NOAC and then randomized to receive an oral anti-thrombotic agent or placebo for at least 6 additional months.

Marik PE *et al. PLoS ONE* 2015;10:e0143252

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Prévention MTEV au long cours

Risque de récidive ETEV

Quel antithrombotique?

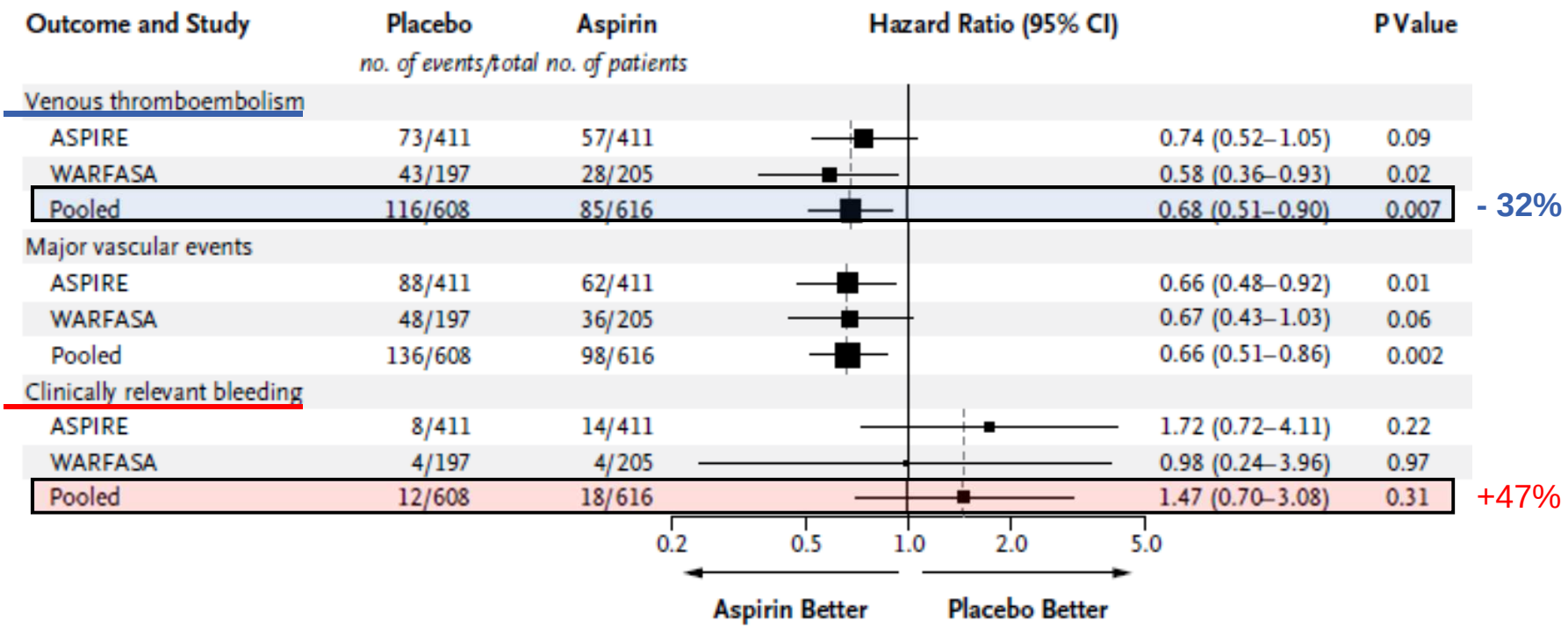
-ASA

pleine dose, dose réduite

-AOD pleine dose, mi dose

Warfasa & Aspire Trials : Aspirin 100mg vs placebo

N= 1224



In conclusion, the findings of the ASPIRE study, especially when considered together with data from the WARFASA study, provide consistent evidence that low-dose aspirin is beneficial in preventing recurrent venous thromboembolism and major vascular events in patients who have had a first episode of unprovoked venous thromboembolism. Thus, aspirin is an attractive option for such patients once they have completed an initial course of anticoagulation therapy.

Venous thromboembolism : 1st recurrence of symptomatic DVTor PE
Major vascular events is a composite of VTE, MI, stroke, or CV death.
Clinically relevant bleeding includes major or clinically relevant non major bleeding.

Warfasa Becattini N Engl J 2012 ; Aspire T.A.Brighton et al, N Engl J Med 2012

Prévention MTEV au long cours

Risque de récidive ETEV

Quel antithrombotique ?

-ASA

-AVK pleine dose, dose réduite

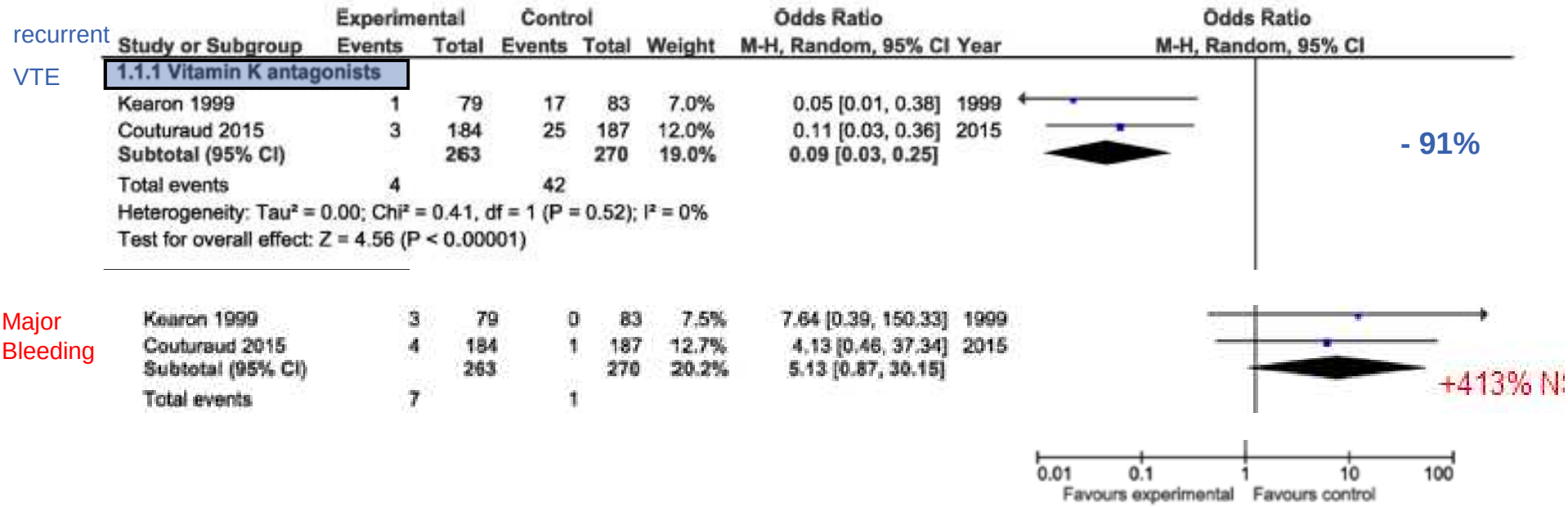
-AOD pleine dose, mi dose

Comparison of the risk for patients receiving VKA INR 2-3 t (versus placebo

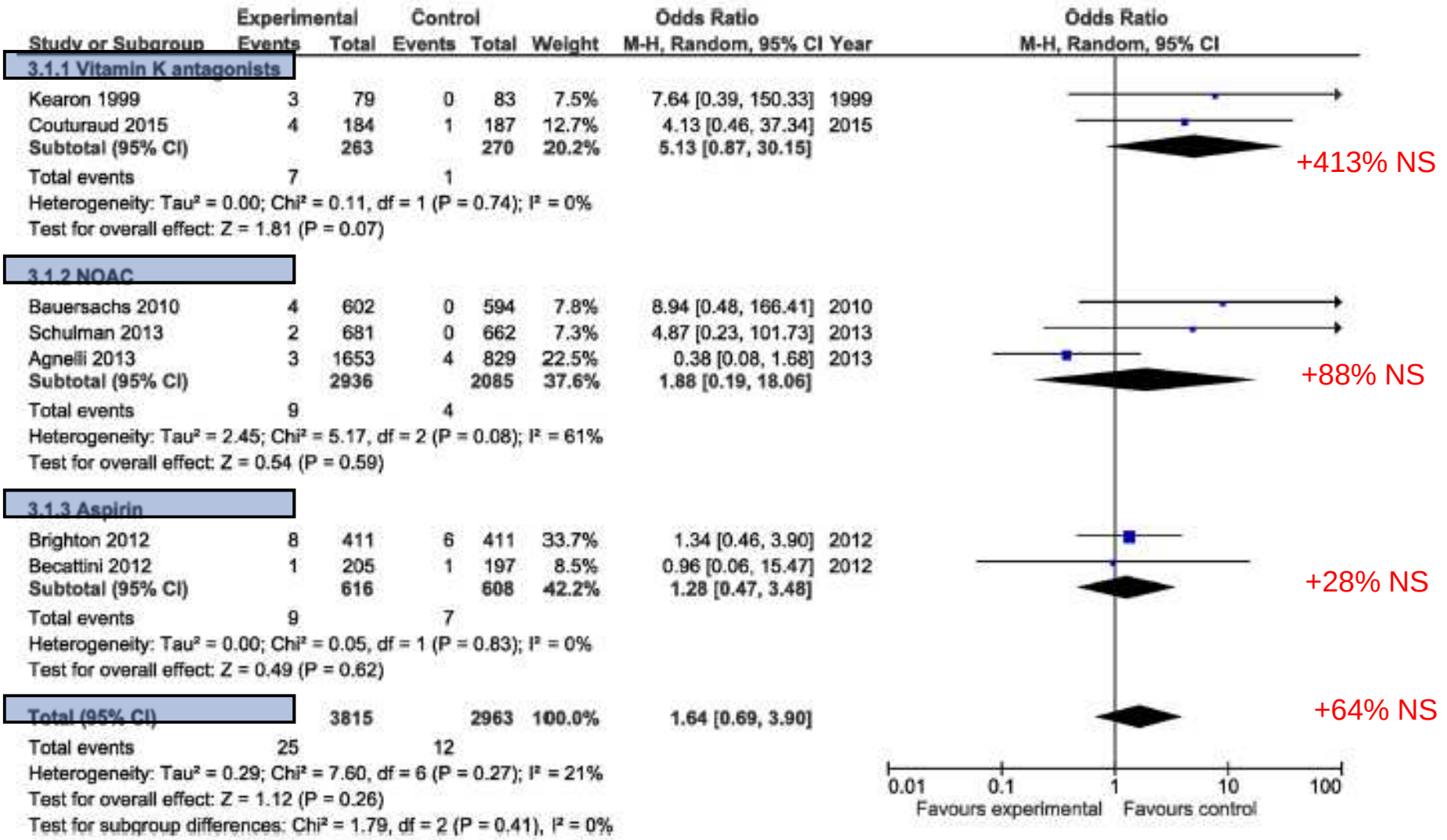
N = 6778 patients unprovoked VTE

recurrent VTE

Major Bleeding



Comparison of the risk of major bleeds during study period for patients receiving anticoagulant (intervention) versus control (placebo). **N = 6778 patients unprovoked VTE**



P.E.Marik et al, Plos One, November 2015

ELATE :Long-term VKA with an INR [1.5-1.9] vs [2-3]

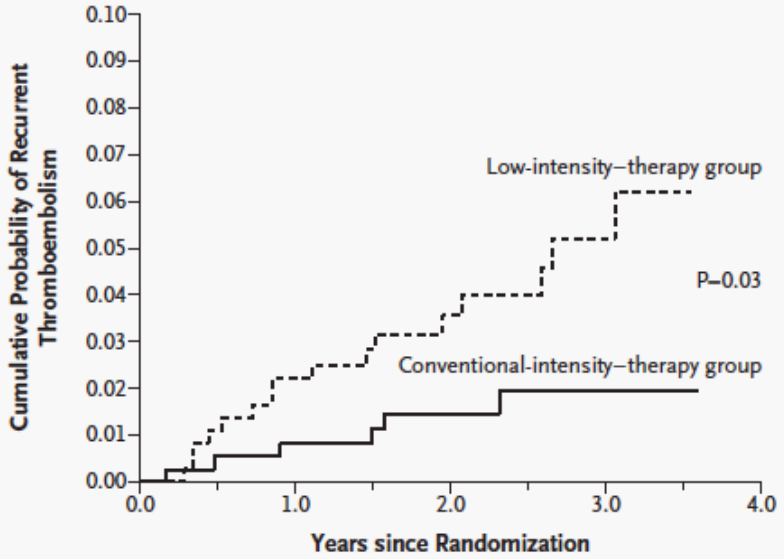


Figure 2. Cumulative Probability of Recurrent Venous Thromboembolism.

738 patients

Double Blind

2/3 recurrent unprovoked VTE

Optimal intensity of anticoagulation if the patient is considered at high risk of recurrent VTE

Table 2. Main Outcomes According to Treatment Group.*

Outcome	Low-Intensity–Therapy Group (N=369)		Conventional-Intensity–Therapy Group (N=369)		Hazard Ratio (95% CI)	Difference between Rates (95% CI)	P Value
	No. of Events	No./100 Person-Yr	No. of Events	No./100 Person-Yr		*no./100 person-yr*	
Major bleeding episode	9	1.1	8	0.9	1.2 (0.4 to 3.0)	0.1 (–0.8 to 1.1)	0.76
Any bleeding episode	39	4.9	31	3.7	1.3 (0.8 to 2.1)	1.2 (–0.8 to 3.2)	0.26
Recurrent venous thromboembolism	16	1.9	6	0.7	2.8 (1.1 to 7.0)	1.2 (0.2 to 2.7)	0.03
Death	16	1.9	8	0.9	2.1 (0.9 to 4.8)	1.0 (–0.2 to 2.1)	0.09

Kearon, NEJM 2003

Prévention MTEV au long cours

Risque de récidive ETEV

Risque de saignements

Guidelines

Quel antithrombotique ?

- ASA
- AVK pleine dose, dose réduite
- AOD pleine dose, mi dose

‘Equipoise’ patients

Einstein Choice / Abstract [3]

CONCLUSIONS

Among patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in bleeding rates. (Funded by Bayer Pharmaceuticals; EINSTEIN CHOICE ClinicalTrials.gov number, NCT02064439.)

Einstein Extension / §Patients [2]

For the Continued Treatment Study, patients were eligible if they had objectively confirmed, symptomatic DVT or pulmonary embolism and had been treated for 6 to 12 months with acenocoumarol or warfarin (in the EINSTEIN studies or from routine care) or rivaroxaban (in the EINSTEIN studies) and if there was equipoise with respect to the need for continued anticoagulation.

Amplify-extension / Abstract[1]

METHODS

In this randomized, double-blind study, we compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy. The study drugs were administered for 12 months.

[1] Agnelli G et al, *N Engl J Med* 2013: DOI: 10.1056/NEJMoa1207541, [2] Bauersachs R et al *N Engl J Med* 2010;363:2499–2510, [3] Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

‘Equipoise’ patients

	AMPLIFY Extension[1]	EINSTEIN Extension[2]	EINSTEIN Choice[3]
Text in publi-cation	Although the inclusion of a placebo group could be criticized, patients who were enrolled in the trial had already received anticoagulation therapy for 6 to 12 months, and the entry criteria mandated clinical equipoise regarding the continuation or cessation of therapy.	For the Continued Treatment Study, patients were eligible if they had objectively confirmed, symptomatic DVT or pulmonary embolism and had been treated for 6 to 12 months with acenocoumarol or warfarin (in the EINSTEIN studies or from routine care) or rivaroxaban (in the EINSTEIN studies) and if there was equipoise with respect to the need for continued anticoagulation	All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation.

[1] Agnelli G et al, *N Engl J Med* 2013: DOI: 10.1056/NEJMoa1207541
[2] Bauersachs R et al *N Engl J Med* 2010;363:2499–2510
[3] Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

‘Equipoise’ patients

	AMPLIFY Extension [1]	EINSTEIN Extension [2]	EINSTEIN Choice [3]
Inclusion criteria	a) Subjects who have: • an unprovoked index event OR a provoked index event with a risk for recurrence as described in the eligibility checklist. • an objectively documented index event of symptomatic proximal DVT or symptomatic PE; b) Subjects should be randomized within approximately 7 days of the last dose of their initial 6-to 12-month treatment.		1. Patients with confirmed symptomatic pulmonary embolism and/or deep vein thrombosis who have been treated with anticoagulant therapy for 6-12 months and did not interrupt anticoagulation for longer than one week. 2. Written informed consent

[1] Agnelli G et al, *N Engl J Med* 2013: DOI: 10.1056/NEJMoa1207541 - PROTOCOL
[2] Bauersachs R et al *N Engl J Med* 2010;363:2499–2510
[3] Weitz JI *et al,* Thromb Haemost 2015, 114 - Rationale & design

Extension studies with NOACs : characteristics

Indication for an extended therapy	Certain	Uncertain	Uncertain	Uncertain
	REMEDY (dabigatran)	AMPLIFY-EXT (apixaban)	EINSTEIN-EXT (rivaroxaban)	EINSTEIN-CHOICE (rivaroxaban)
Males	60%	58%	58%	55%
Age (mean)	55	56	58	58
Weight	Moy. 86 kg	<60 kg 7% ≥60 kg 93%	<50 kg 1% 50-100 kg 82% >100 kg 15%	IMC<30 64,5% IMC≥30 35,5%
DVT	65%	65%	64%	50%
PE	35%	35%	36%	50%
Unprovoked	93,5%	93%	73%	40%
Provoked	6,5%	7%	27%	60%
≥2 MVTE	36%	12%	17%	17%
Thrombophilia	18%	4%	8%	6.5%
Active Cancer	4,2%	1,8%	4,5%	2,5%

Schulman et al. NEJM 2013, Agnelli et al. NEJM 2013, Büller et al. NEJM 2010, Weitz et al NEJM 2017

Extension studies with NOACs : results

	REMEDY dabigatran		AMPLIFY-EXT apixaban			EINSTEIN-EXT rivaroxaban		EINSTEIN-CHOICE rivaroxaban		
Arm	Dab.	War.	A.5	A.2.5	Pl.	R.20	Pl.	R.20	R.10	ASA
VTE recidive	1.8	1.3	1.7	1.7	8.8	1.3	7.1	1.5	1.2	4.4
Major bleeding	0.9	1.8	0.1	0.2	0.5	0.7	0	0.5	0.4	0.3
NMCR bleeding			4.2	3.0	2.3	5.4	1.2	2.7	2.0	1.8
Maj. Bl. + NMCR	5.6	10.2	4.3	3.2	2.7	6.0	1.2	3.3	2.4	2.0
Death	1.2	1.3	0.5	0.8	1.7	0.2	0.3	0.7	0.2	0.6

Schulman et al. NEJM 2013, Agnelli et al. NEJM 2013, Büller et al. NEJM 2010, Weitz et al NEJM 2017

AMPLIFY EXTENSION STUDY

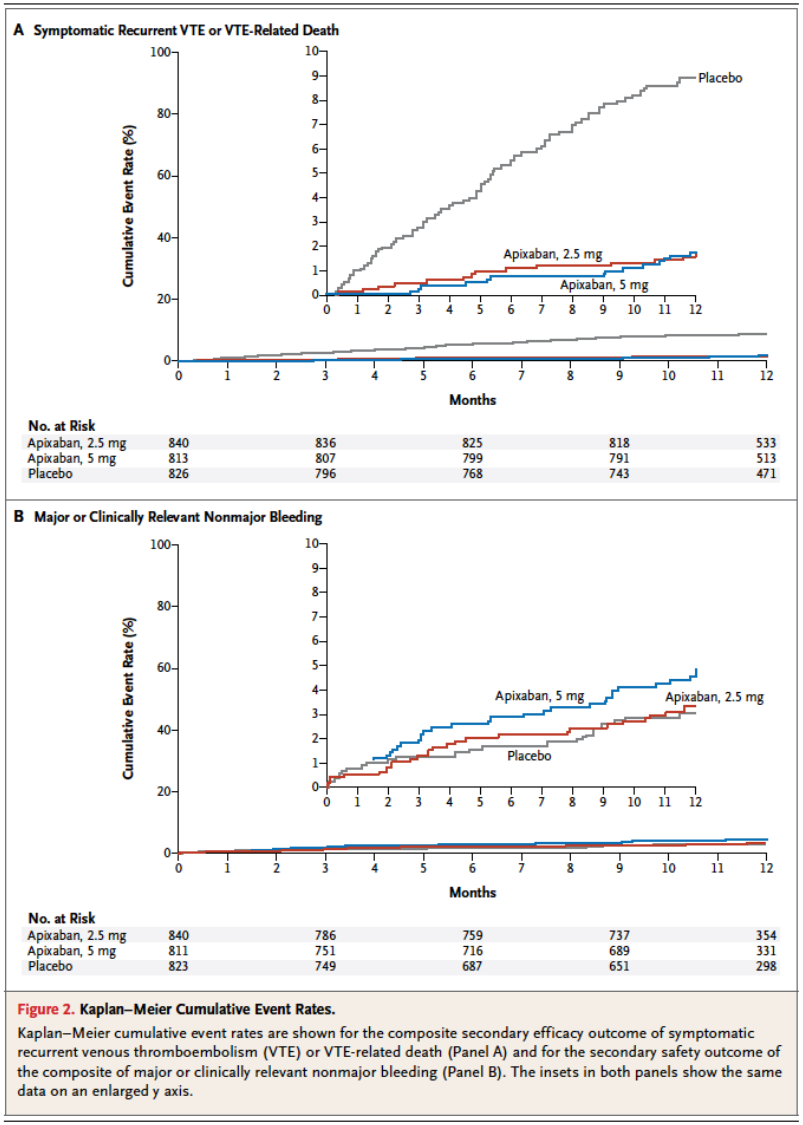


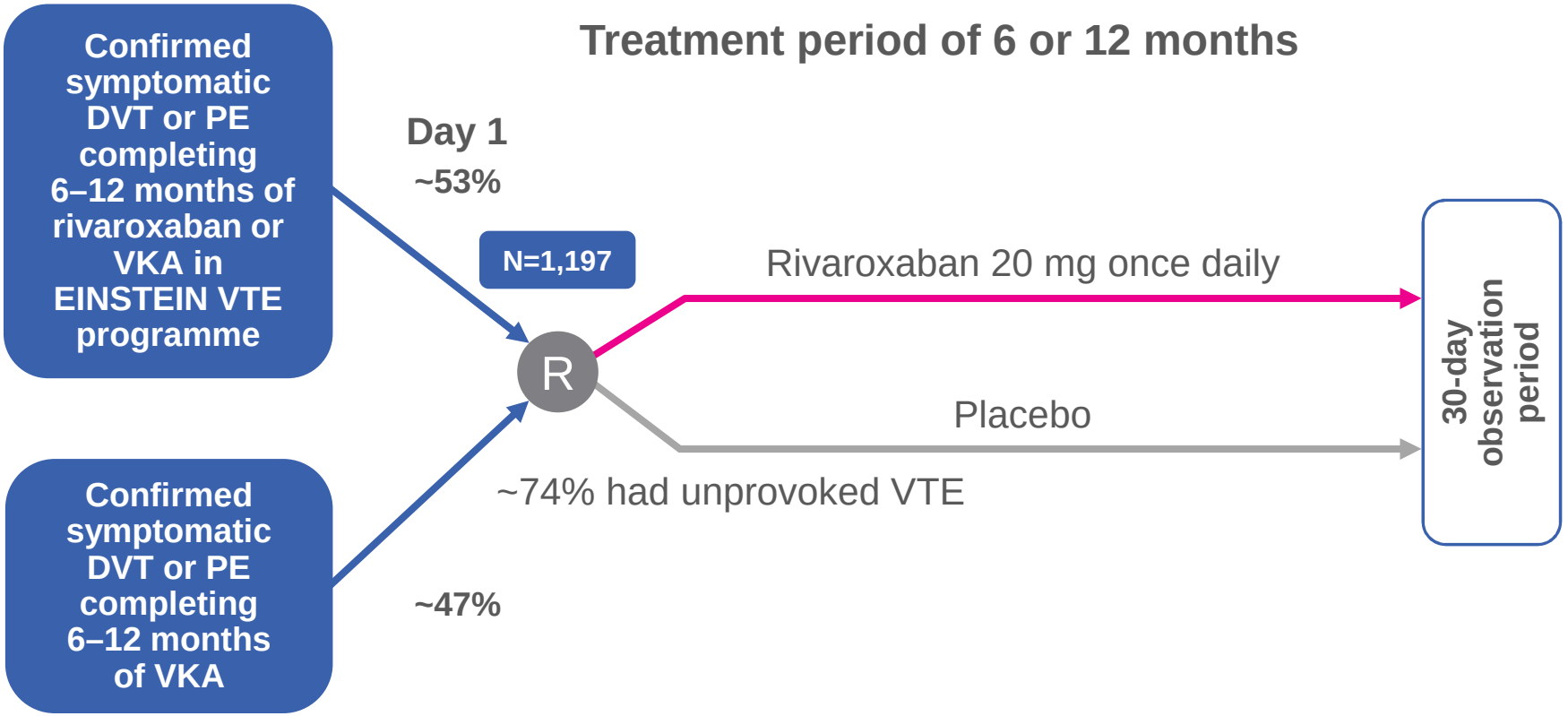
Figure 2. Kaplan–Meier Cumulative Event Rates.

Kaplan–Meier cumulative event rates are shown for the composite secondary efficacy outcome of symptomatic recurrent venous thromboembolism (VTE) or VTE-related death (Panel A) and for the secondary safety outcome of the composite of major or clinically relevant nonmajor bleeding (Panel B). The insets in both panels show the same data on an enlarged y axis.

Agnelli et al NEJM 2012

EINSTEIN EXT: Study Design

Randomized, double-blind, placebo-controlled, event-driven (n=30) superiority study



The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

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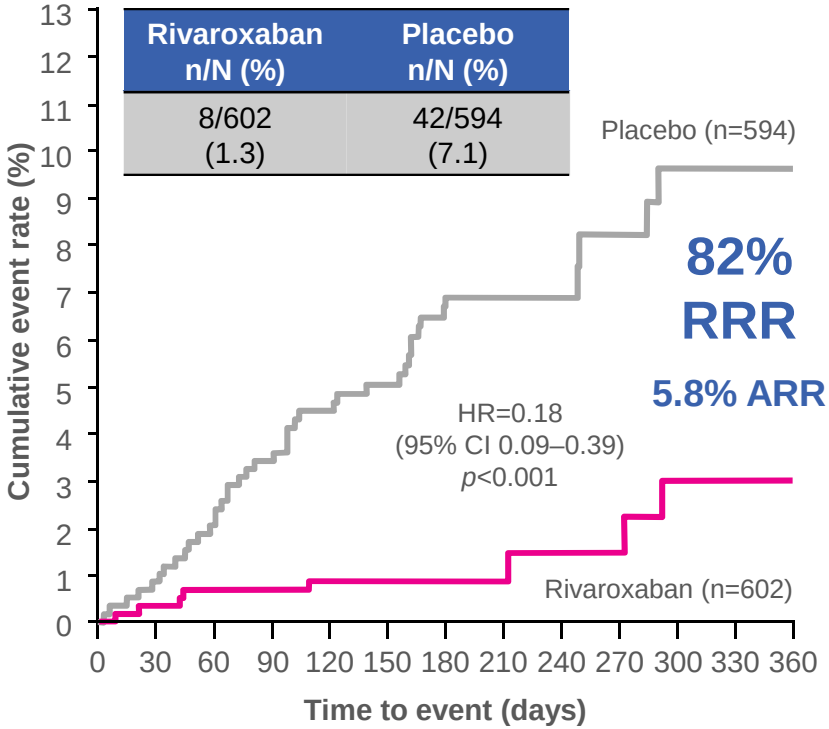
EINSTEIN EXT showed that an additional 6 or 12 months of rivaroxaban 20 mg od after prior anticoagulation therapy, significantly reduced VTE recurrence vs placebo, with comparable major bleeding risk

In patients at clinical equipoise regarding the need for continued treatment



Number of patients at risk													
Riva	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	555	522	468	444	164	138	133	110	93	85

NNT = 17

	Rivaroxaban (n=598)		Placebo (n=590)		
	n	%	n	%	
Major bleeding	**4**	**0.7***	**0**	**0**	***p*=0.11**
Bleeding contributing to death	**0**	**0**	**0**	**0**	
Bleeding in a critical site	0	0	0	0	
Associated with fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units	4	0.7	0	0	
Gastrointestinal bleeding	3	0.5	0	0	
Menorrhagia	1	0.2	0	0	

Safety population; **p*=0.11

NNH = 143

CRNM	**32**	**5,4**	**7**	**1,2**
major or CRNMB	**36**	**6.0**	**7**	**1.2 <0.00**

HR 5.19 (2.3–11.7)

Rivaroxaban 20mg réduit les récidives ETEV sans augmentation signifIcatif des saignements majeurs …mais avec une augmentation des CRNMB

irrent VTE measured in the ITT population; all analyses were based on the first event
EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

Rivaroxaban

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

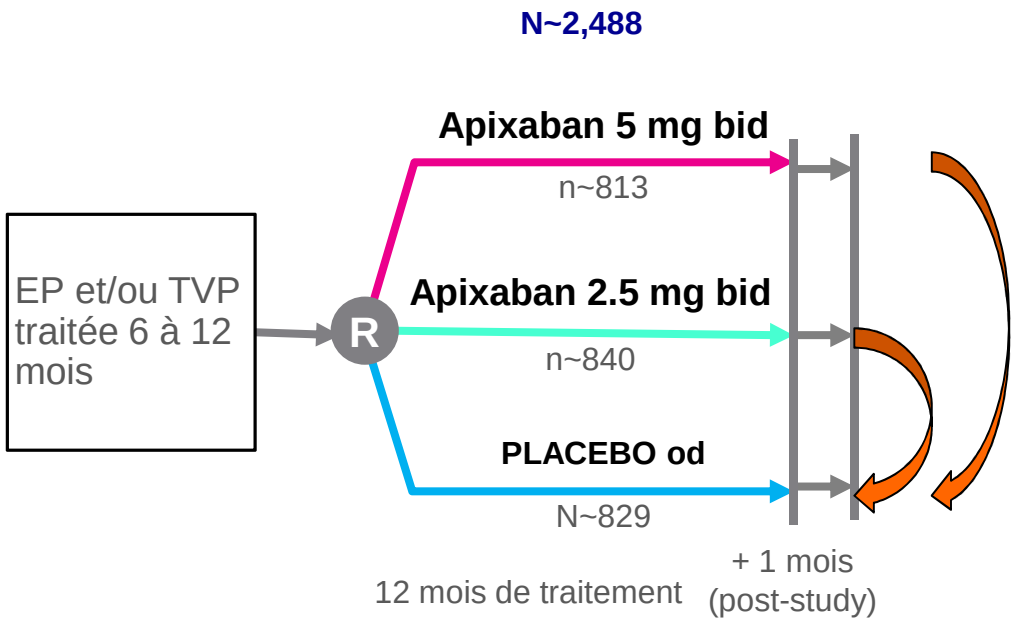
Avis

11 mai 2016

SMR	Le service médical rendu par XARELTO 15 mg et 20 mg : - reste important dans le traitement initial des TVP et EP et la prévention de leurs récidives jusqu'à 12 mois ; - est important dans le traitement prolongé au-delà de 12 mois en prévention des récidives d'EP et de TVP.
ASMR	XARELTO n'apporte pas d'amélioration du service médicale rendu (ASMR V) dans le traitement prolongé au-delà de 12 mois en prévention des récidives d'EP et de TVP chez l'adulte.
Place dans la stratégie thérapeutique	La Commission considère que, compte tenu de l'absence d'antidote et en l'absence de possibilité de mesure du degré d'anticoagulation en pratique courante, la prescription de XARELTO, comme celle d'ELIQUIS, dans le traitement des ETEV et la prévention de leurs récidives, n'est préconisée qu'en 2ème intention, à savoir dans les cas suivants • chez les patients sous AVK, mais pour lesquels le maintien de l'INR dans la zone cible (entre 2 et 3) n'est pas habituellement assuré malgré une observance correcte ; • chez les patients pour lesquels les AVK sont contre-indiqués ou mal tolérés, qui ne peuvent pas les prendre ou qui acceptent mal les contraintes liées à la surveillance de l'INR.

Extended treatment in patients at “equipoise” ?

“Amplify-Ext Study”



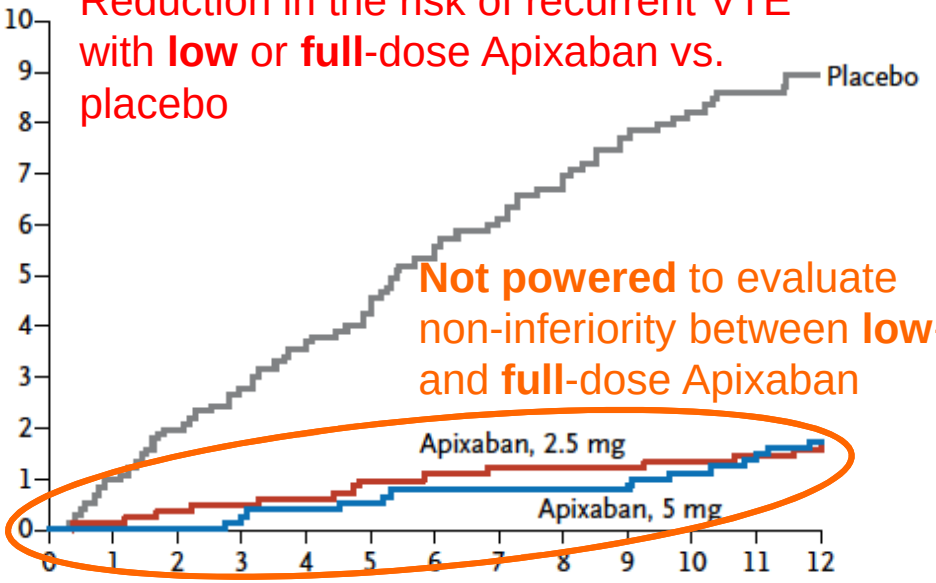
Short design: Multicentre, randomized, double-blind, double-blind, superiority study

AMPLIFY-EXT-investigators, NEJM 2013;368(8):699-708

F.Coutureau

Extended treatment in patients at “equipoise”with low-dose Apixaban? “Amplify-Ext Study”

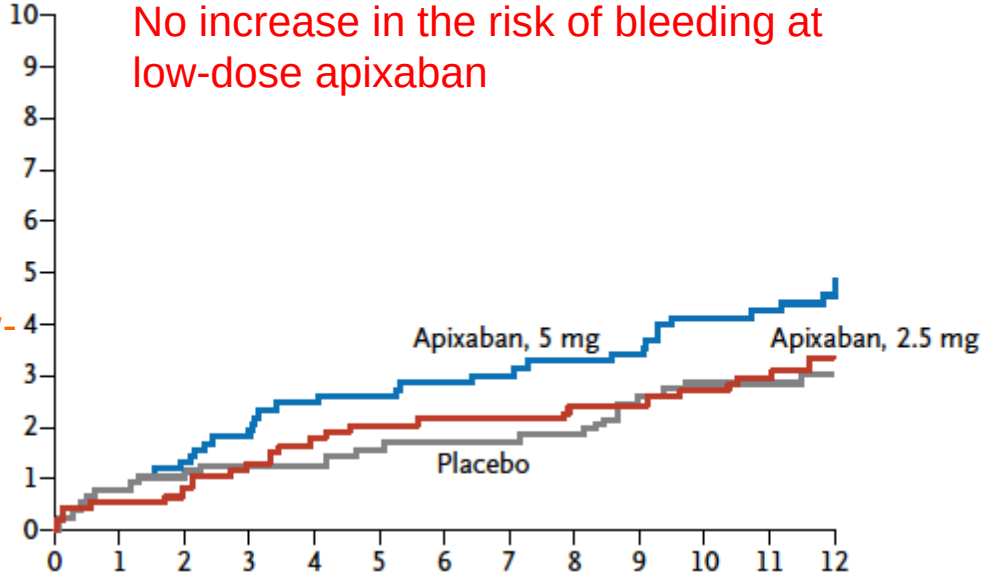
Reduction in the risk of recurrent VTE with **low** or **full**-dose Apixaban vs. placebo



Not powered to evaluate non-inferiority between **low**- and **full**-dose Apixaban

Primary end point of recurrent or fatal VTE or unexplained death

No increase in the risk of bleeding at low-dose apixaban



Major or clinically relevant bleeding event

Population à risque intérmédiaire (equipoise)
AOD demi-dose ou pleine dose plus efficace que placebo
Risques hémorragiques très faibles et non différents
Pas d’hétérogénéité sur les strates
Quelle dose optimale pour quelle population ?

AMPLIFY-EXT, NEJM 2013;

F.Coutureau

Extended treatment in patients at “equipoise”with low-dose Apixaban? “Amplify-Ext Study”

Quelle dose optimale pour quelle population ? 2,5mg au long cours RCP?

	Schéma d'administration	Dose maximale quotidienne
Traitement de la TVP ou de l'EP	10 mg deux fois par jour durant les 7 premiers jours	20 mg
	suivis de 5 mg deux fois par jour	10 mg
Prévention de la récidive de TVP et/ou d'EP à l'issue de 6 mois de traitement pour une TVP ou une EP	2,5 mg deux fois par jour	5 mg

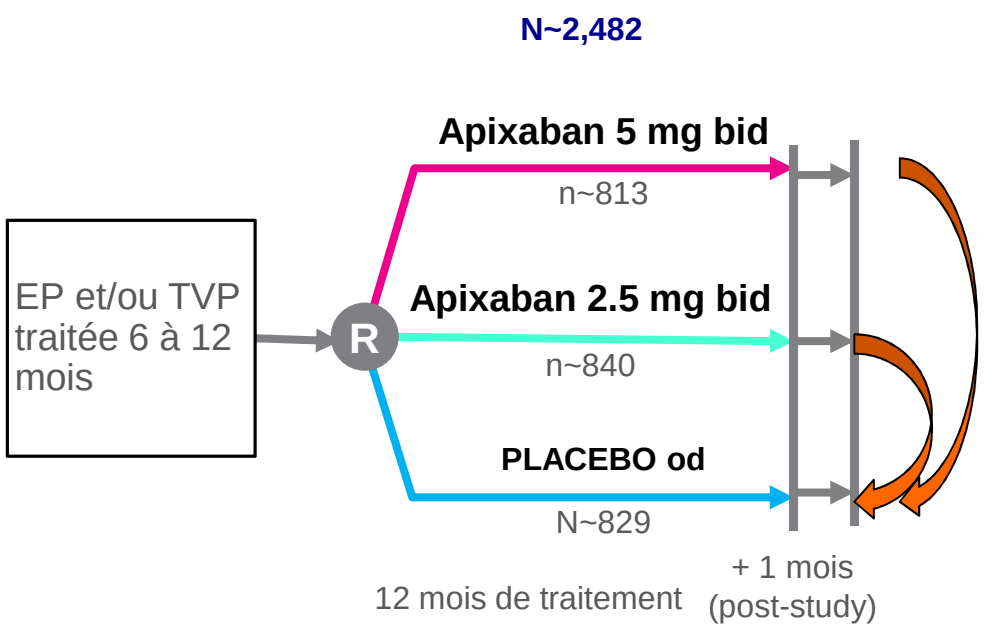
Pas d'hétérogénéité sur les strates

Quelle dose optimale pour quelle population ? 2,5mg au long cours RCP?

F.Coutureau

Extended treatment in patients at “equipoise”?

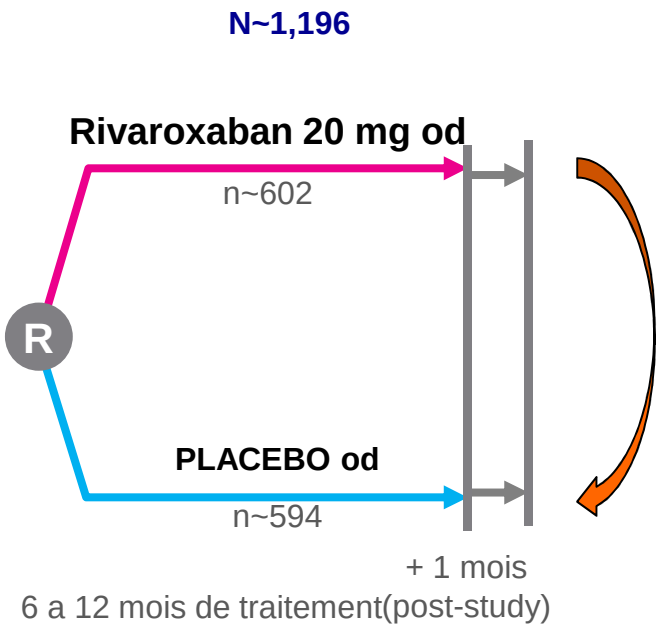
“Amplify-Ext Study”



Design: Multicentre, randomized, double-blind, superiority study

AMPLIFY-EXT-investigators, NEJM 2013;368(8):699-708

“Einstein Ext Study”



Design: Multicentre, randomized, double-blind, superiority study

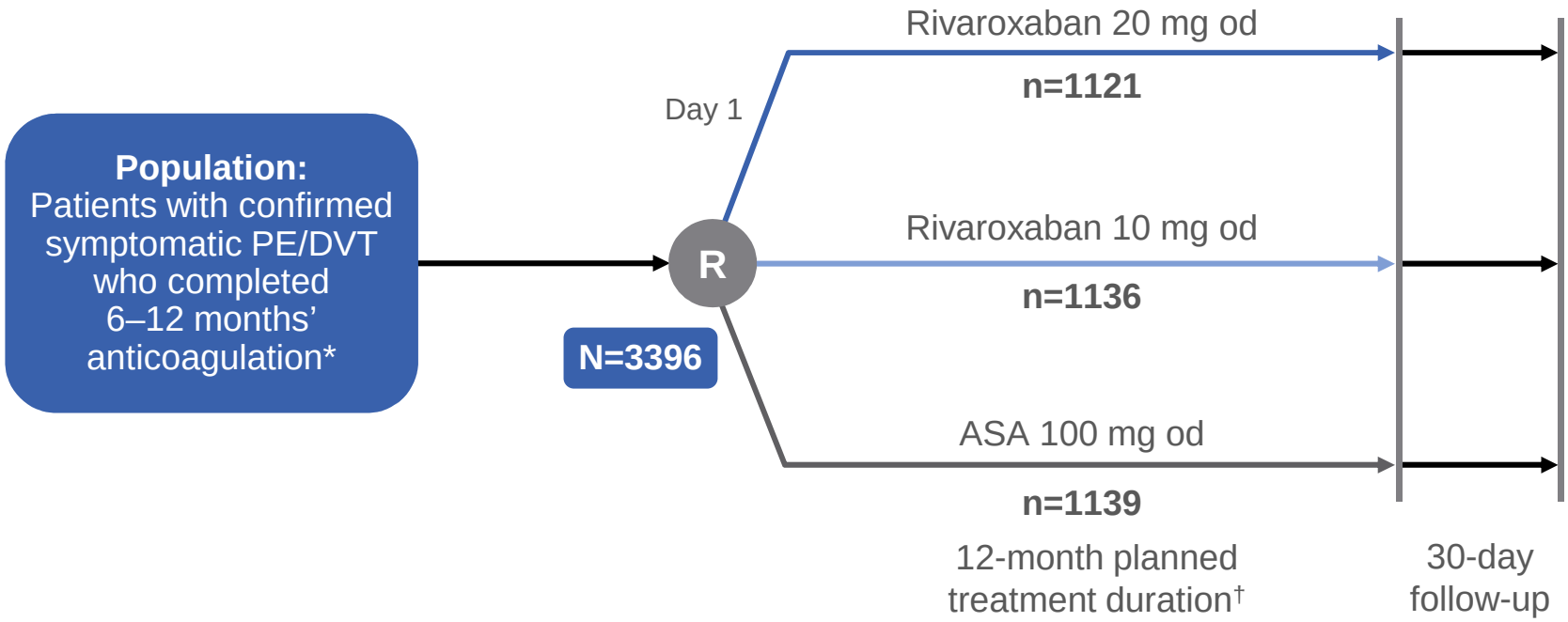
*www.clinicaltrials.gov/ct2/show/NCT02064439

F.Couturaud

EINSTEIN CHOICE Evaluated Rivaroxaban Versus ASA for Extended Treatment of VTE

Objectives: Compare the efficacy and safety of once daily rivaroxaban (20 or 10 mg) with aspirin (100 mg) in VTE patients who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation

Multicentre, randomized, double-blind, active-comparator, event-driven, superiority study



*Completed 6–12 months anticoagulation at randomization with no interruption of anticoagulation >1 week
†Patients randomized after the requisite number of primary efficacy outcomes was reached were treated for ≥6 months

Weitz JI *et al, Thromb Hemost* 2015;114:645–650;
Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

EINSTEIN CHOICE: Study Details

Primary endpoints

- Symptomatic recurrent VTE
- Major bleeding

Secondary endpoints

- MACE (symptomatic recurrent VTE, MI, ischaemic stroke, systemic non-CNS embolism)
- CRNM bleeding
- Composite of non-fatal symptomatic VTE and all-cause mortality
- Composite of major bleeding and recurrent VTE
- Composite of major bleeding, recurrent VTE, MI, ischaemic stroke and systemic non-CNS embolism

Key inclusion criteria

- Objectively confirmed DVT and/or PE
- Completed 6–12 months of treatment with apixaban, dabigatran, rivaroxaban or a vitamin K antagonist
- No therapy interruption >7 days pre-randomization
- No symptomatic recurrence during the treatment period

Key exclusion criteria

- Indication for therapeutic dose anticoagulants
- Indication for antiplatelet or NSAID
- CrCl <30 ml/min
- Active bleeding or high risk of bleeding
- Concomitant use of strong CYP450 3A4 or P-glycoprotein inhibitors
- Life expectancy <6 months

Weitz JI *et al*, *Thromb Haemost* 2015;114:645–650

◄ Slide Index

Primary and Secondary Study Outcomes

- Efficacy outcomes:
  - **Primary:** Recurrent VTE*
  - **Secondary:** Recurrent VTE, MI, ischaemic stroke and non-CNS SE
  - **Other efficacy outcomes**: MI, ischaemic stroke, venous thrombosis in locations other than the deep veins of the lower extremities, and all-cause mortality
- Safety outcomes
  - **Principal:** Major bleeding[#]
  - Clinically relevant non-major bleeding [#]
  - Major bleeding and clinically relevant non-major bleeding [#]
  - Non-major bleeding associated with study drug interruption for >14 days

*Fatal or non-fatal symptomatic recurrent DVT/PE including unexplained death where PE cannot be excluded; [#]defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Clinical Characteristics*

Outcome		Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)
Male, n (%)		602 (54.4)	620 (55.0)	643 (56.9)
Age, (mean years±SD)		57.9±14.7	58.8±14.7	58.8±14.7
Body mass index, n (%)	<30 kg/m^2	712 (64.3)	751 (66.6)	756 (66.8)
	≥30 kg/m^2	394 (35.6)	376 (33.4)	375 (33.2)
Creatinine clearance, n (%)	<30 ml/min	1 (0.1)	2 (0.2)	1 (0.1)
	30–<50 ml/min	40 (3.6)	49 (4.3)	63 (5.6)
	50–<80 ml/min	279 (25.2)	302 (26.8)	277 (24.5)
	≥80 ml/min	787 (71.1)	774 (68.7)	790 (69.8)

*Differences in baseline characteristics were not significant; SD, standard deviation

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

EINSTEIN CHOICE

Clinical Characteristics*

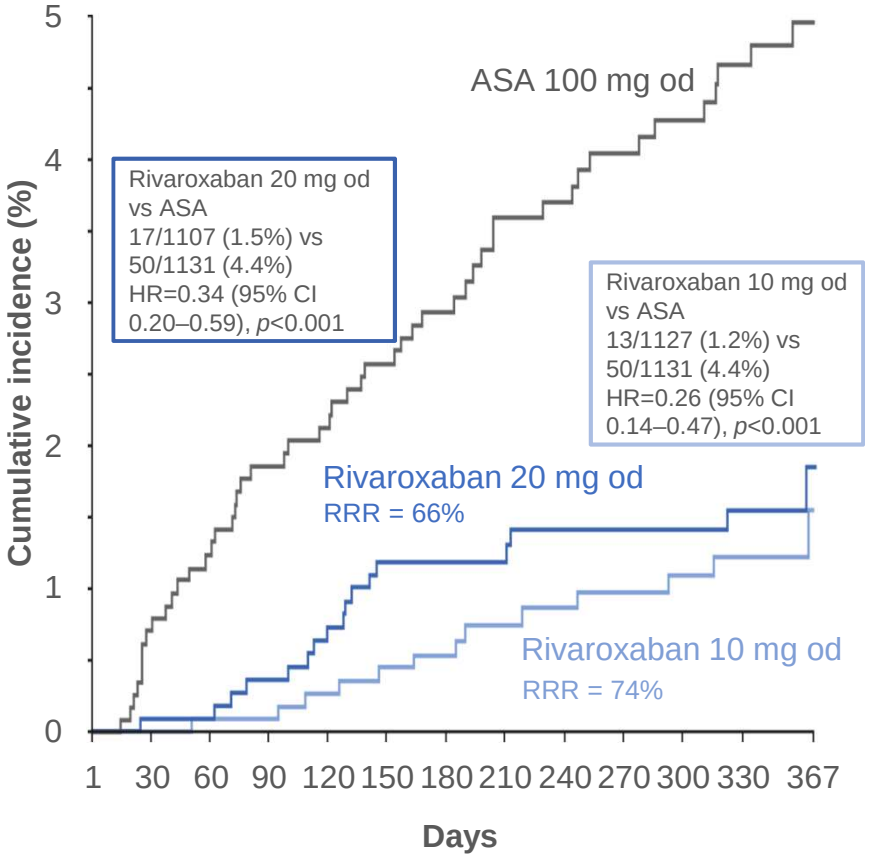
Outcome		Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)
Index event, n (%)	DVT	565 (51.0)	565 (50.1)	577 (51.0)
	PE	381 (34.4)	381 (33.8)	366 (32.4)
	Both	155 (14.0)	179 (15.9)	181 (16.0)
	Asymptomatic or unconf.	6 (0.5)	2 (0.2)	7 (0.6)
Classification of index VTE, n (%)	Unprovoked	441 (39.8)	480 (42.6)	468 (41.4)
	Provoked	666 (60.2)	647 (57.4)	663 (58.6)
History of prior VTE, n (%)		198 (17.9)	197 (17.5)	194 (17.2)
Known thrombophilia, n (%)		79 (7.1)	74 (6.6)	70 (6.2)
Active cancer, n (%)		25 (2.3)	27 (2.4)	37 (3.3)
Study drug duration (median days, IQR)		349 (189-362)	353 (190-362)	350 (186-362)

*Differences in baseline characteristics were not significant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; IQR, interquartile range

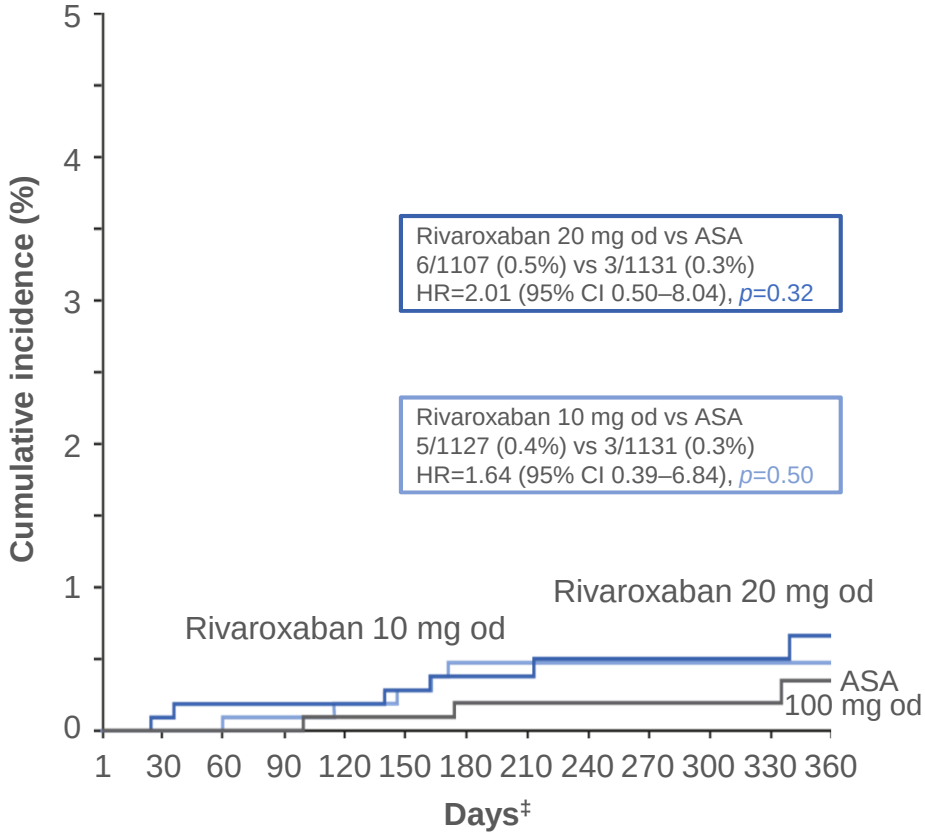
Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Both Rivaroxaban Doses Reduced Recurrent VTE Rates and Similar Risk of Bleeding Compared with ASA

Efficacy*
Symptomatic recurrent VTE



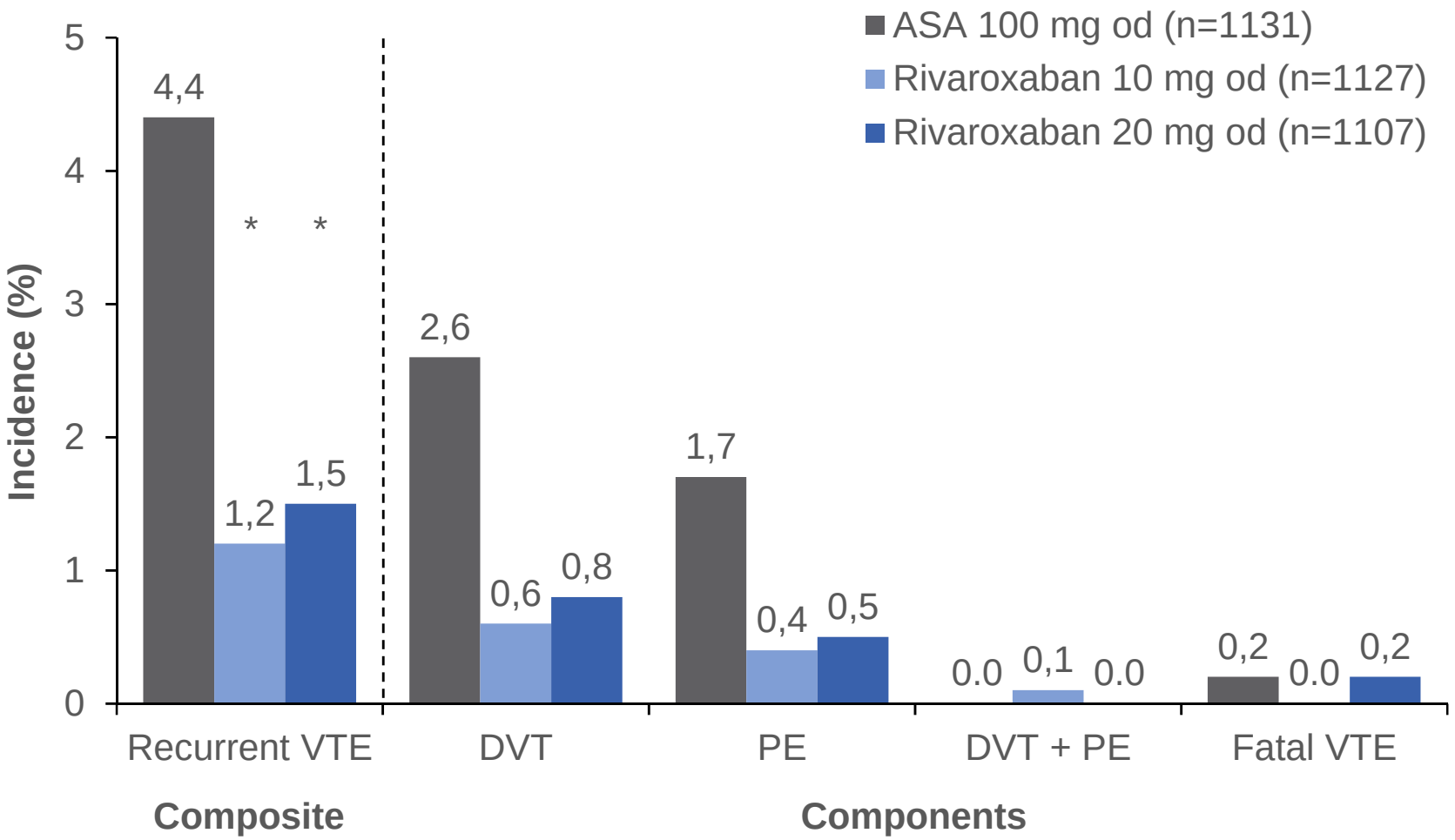
ISTH Major bleeding#



*Intention-to-treat analysis; #safety analysis; ‡no events after Day 360 up to Day 480
*Fatal or non-fatal symptomatic recurrent DVT/PE including unexplained death where PE cannot be excluded; #defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria
Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

EINSTEIN CHOICE

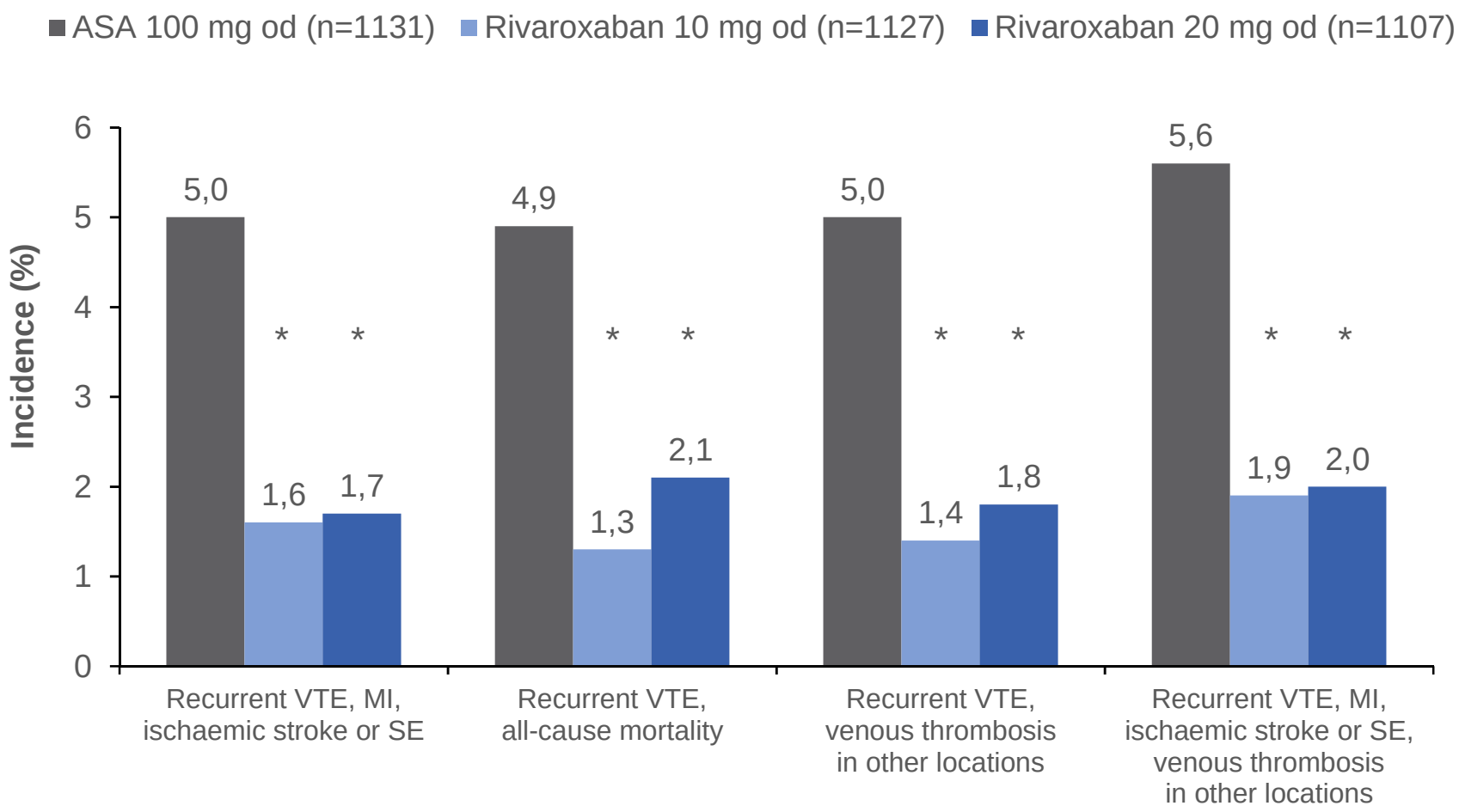
Primary Efficacy Outcome Results Components



Intention-to-treat analysis. *p<0.001 versus ASA 100 mg od

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Other Efficacy Endpoints Reduced with Both Rivaroxaban Doses Versus ASA



Intention-to-treat analysis. *p<0.001 versus ASA 100 mg od

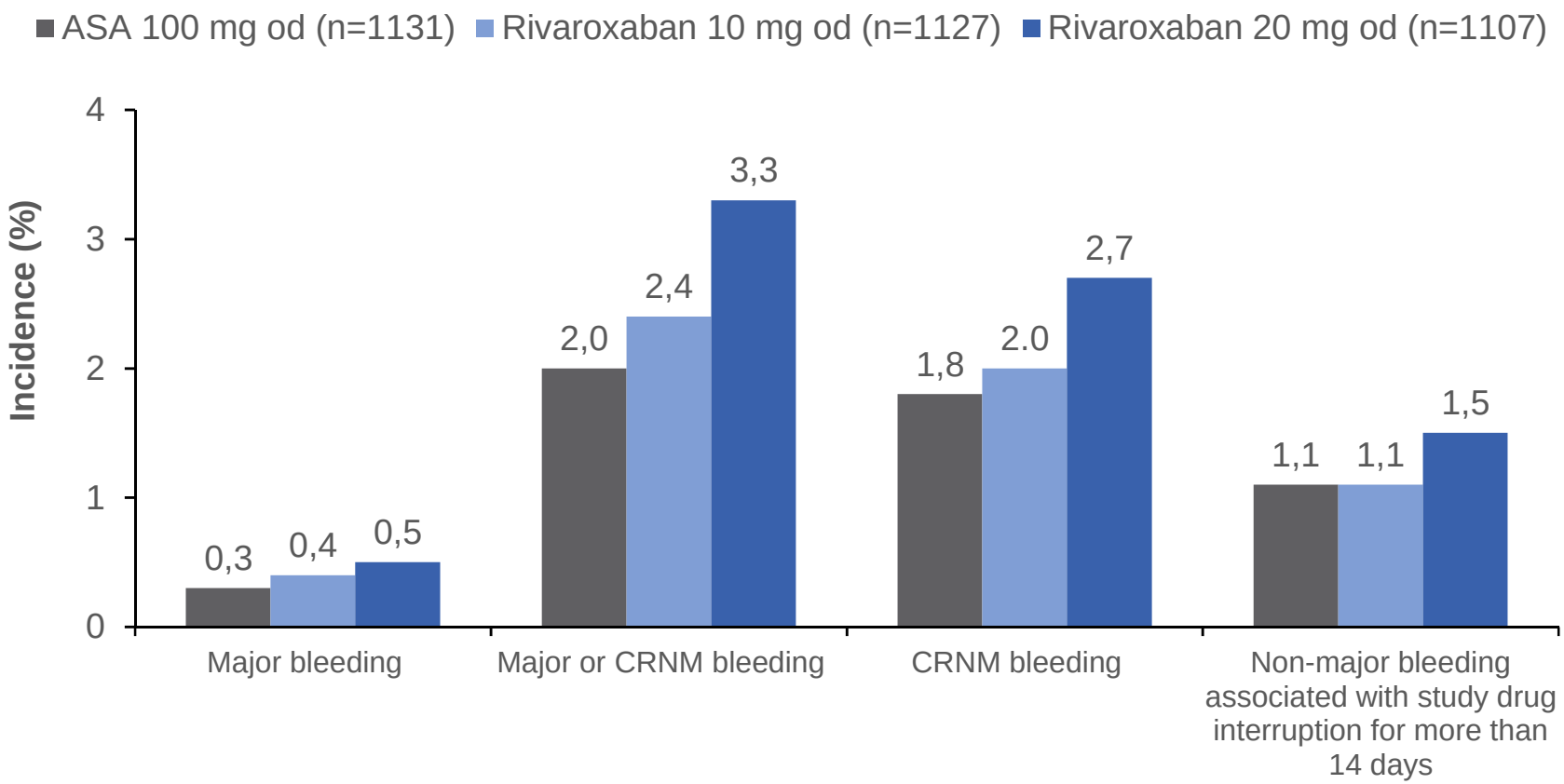
Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Both Rivaroxaban Doses Reduced VTE Recurrence Versus ASA in a Broad Spectrum of Patients

	Rivaroxaban 20 mg od (n=1107)	Rivaroxaban 10 mg od (n=1127)	ASA 100 mg od (n=1131)
Recurrent VTE, all patients, n/N (%)	17/1107 (1.5)	13/1127 (1.2)	50/1131 (4.4)
Risk profile, n/N (%)			
Unprovoked index event	8/441 (1.8)	7/480 (1.5)	26/468 (5.6)
Provoked index event	9/666 (1.4)	6/647 (0.9)	24/663 (3.6)
History of previous VTE, n/N (%)			
Yes	3/198 (1.5)	2/197 (1.0)	17/194 (8.8)
No	14/909 (1.5)	11/930 (1.2)	33/937 (3.5)
Duration of anticoagulation prior to randomization, n/N (%)			
<9 months	12/774 (1.6)	7/782 (0.9)	35/793 (4.4)
≥9 months	5/333 (1.5)	6/345 (1.7)	15/338 (4.4)

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Bleeding Outcome Analyses



Similar rates of bleeding were observed in the rivaroxaban and ASA treatment groups

Safety analysis. All treatment comparisons $p>0.05$

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

EINSTEIN CHOICE

Major Bleeding Rates Were Similar Across Different Patient Subgroups

	Rivaroxaban 20 mg od (n=1107)	Rivaroxaban 10 mg od (n=1127)	ASA 100 mg od (n=1131)
Major bleeding, all patients, n/N (%)	6/1107 (0.5)	5/1127 (0.4)	3/1131 (0.3)
Risk profile, n/N (%)			
Unprovoked index event	4/441 (0.9)	2/480 (0.4)	1/468 (0.2)
Provoked index event	2/666 (0.3)	3/647 (0.5)	2/663 (0.3)
History of previous VTE, n/N (%)			
Yes	2/198 (1.0)	0/197 (0.0)	1/194 (0.5)
No	4/909 (0.4)	5/930 (0.5)	2/937 (0.2)
Duration of anticoagulation prior to randomization, n/N (%)			
<9 months	3/774 (0.4)	3/782 (0.4)	3/793 (0.4)
≥9 months	3/333 (0.9)	2/345 (0.6)	0/338 (0)

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

EINSTEIN CHOICE

Provoked / Unprovoked subgroup
Primary Efficacy Outcome

Subgroups	HR (95% CI)	Rivaroxaban 20 mg od	ASA 100 mg od
RF profile index event			
Unprovoked		8/441 (1.8%)	26/468 (5.6%)
Provoked		9/666 (1.4%)	24/663 (3.6%)

Subgroups	HR (95% CI)	Rivaroxaban 10 mg od	ASA 100 mg od
RF profile index event			
Unprovoked		7/480 (1.5%)	26/468 (5.6%)
Provoked		6/647 (0.9%	24/663 (3.6%)

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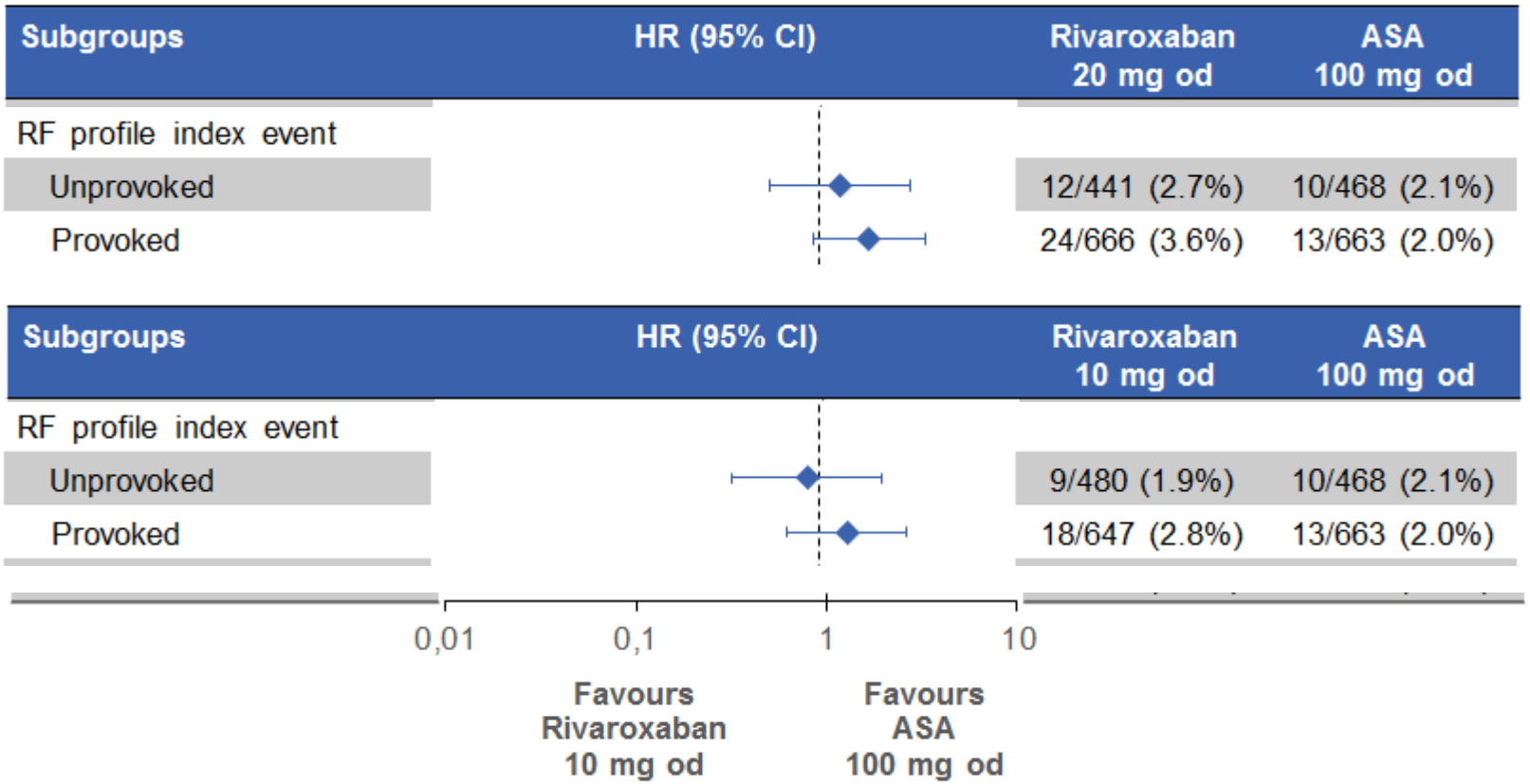
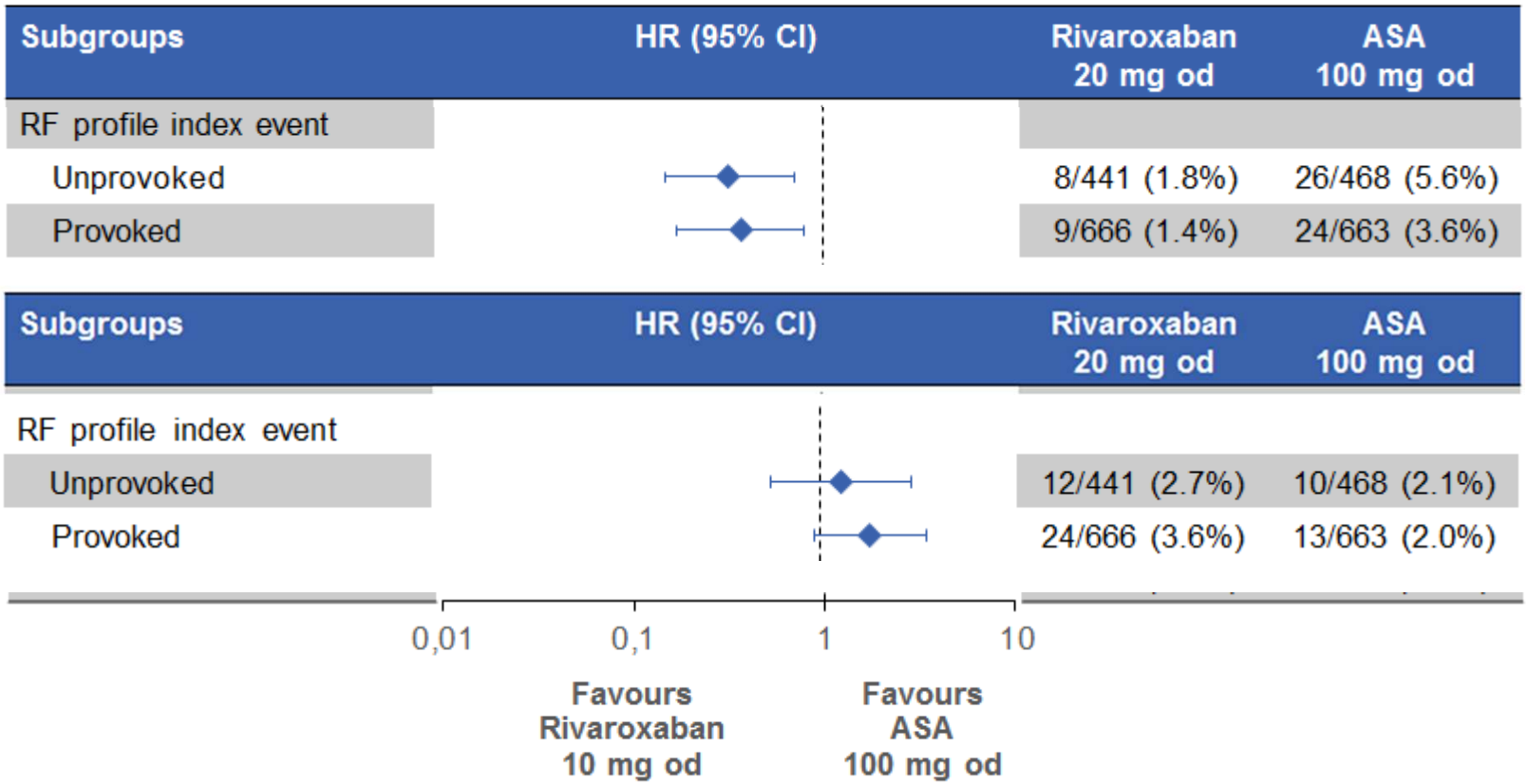
Provoked / Unprovoked subgroup
Composite of Treatment-Emergent MB or CRNMB



Rivaroxaban 20mg
Primary Efficacy Outcome/ MB or CRNMB

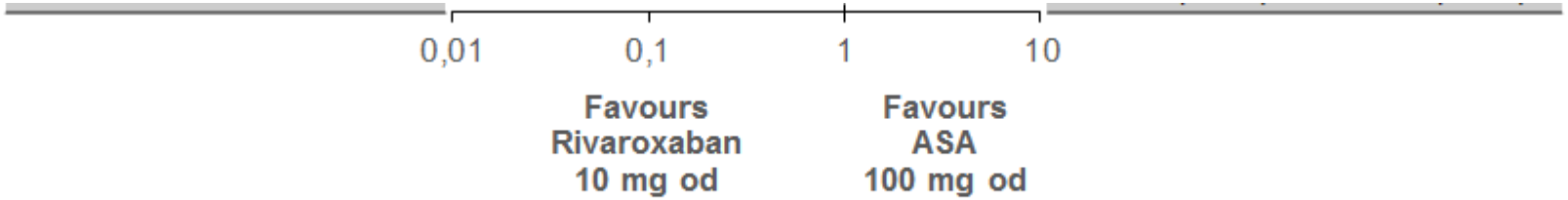


Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518 - Appendix

Rivaroxaban 10mg
Primary Efficacy Endpoint /MB or CRNMB

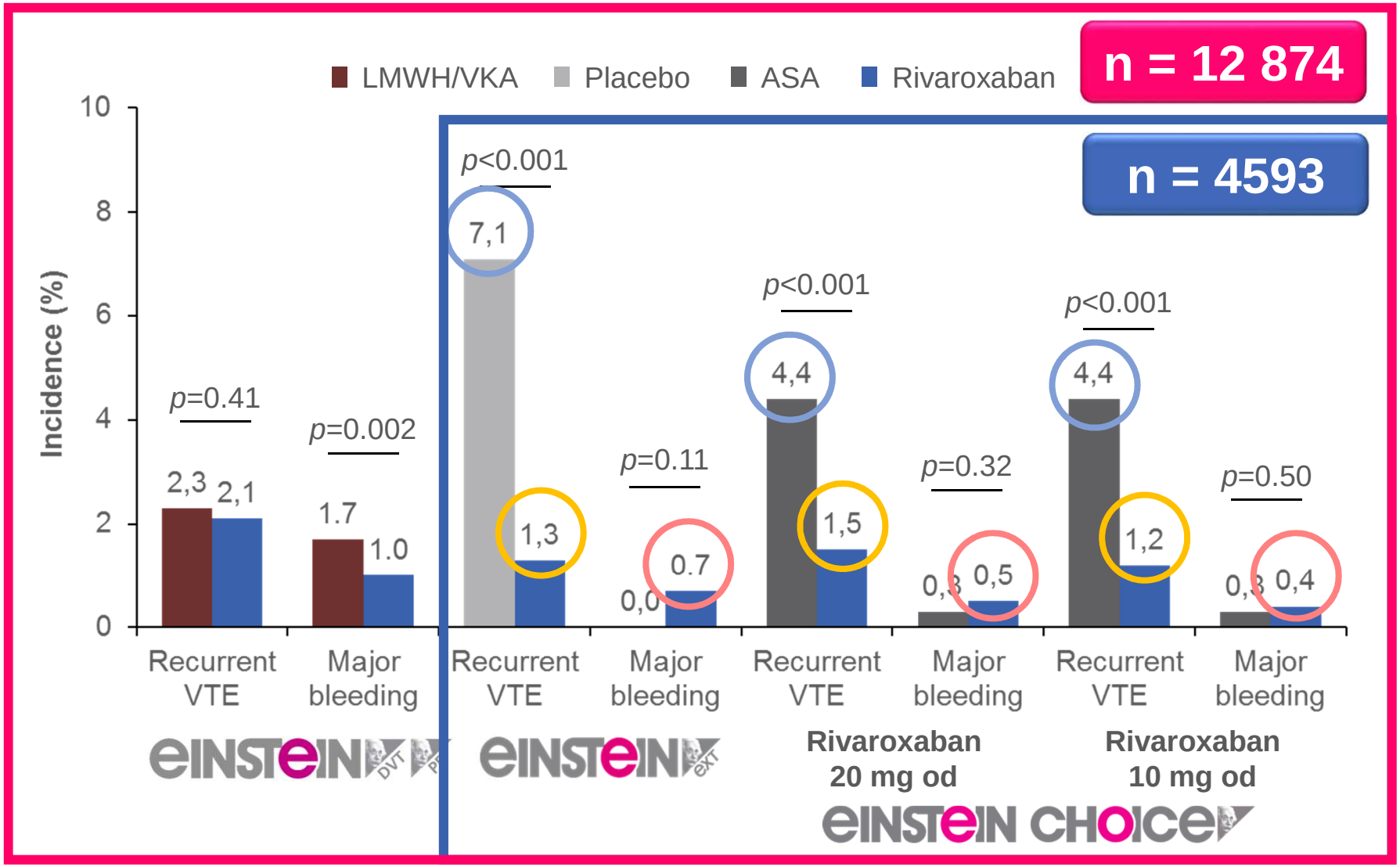
Subgroups	HR (95% CI)	Rivaroxaban 10 mg od	ASA 100 mg od
RF profile index event			
Unprovoked		7/480 (1.5%)	26/468 (5.6%)
Provoked		6/647 (0.9%	24/663 (3.6%)

Subgroups	HR (95% CI)	Rivaroxaban 10 mg od	ASA 100 mg od
RF profile index event			
Unprovoked		9/480 (1.9%)	10/468 (2.1%)
Provoked		18/647 (2.8%)	13/663 (2.0%)



Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518 - Appendix

Rivaroxaban Efficacy and Safety in the Initial, Continued and Extended Treatment of VTE (N=12,874)



1. Prins MH *et al, Thromb J* 2013;11:21 ; 2. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510;
3. Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

AOD en phase d'extension: caractéristiques

Indication à prolonger un traitement	Incertaine	Incertaine
	EINSTEIN-EXT (rivaroxaban)	**EINSTEIN-CHOICE (rivaroxaban)**
n	1197	3396
Hommes	58%	55%
Age (moy)	58	58
Poids	*<50 kg* 1%	*IMC<30* 64,5%
	50-100 kg 82%	*IMC≥30* 35,5%
	>100 kg 15%	
TVP	**64%**	50%
EP	36%	**50%**
Non provoqué	**73%**	40%
Provoqué	27%	**60%**
≥2 MVTE	**17%**	**17%**
Thrombophilie	**8%**	**6.5%**
Cancer actif	4,5%	2,5%

Schulman et al. NEJM 2013. Agnelli et al. NEJM 2013. Büller et al. NEJM 2010. Weitz et al NEJM 2017

AOD en phase d'extension: résultats

	EINSTEIN-EXT rivaroxaban		**EINSTEIN-CHOICE** rivaroxaban		
Bras	R.20	*Pl.*	R.20	R.10	*ASA*
Récidive TEV	**1.3**	***7.1***	**1.5**	**1.2**	***4.4***
Hém. Maj.	0.7	*0*	0.5	0.4	*0.3*
Hém. CP.	5.4	*1.2*	2.7	2.0	*1.8*
Hém. Maj. + CP.	6.0	*1.2*	3.3	2.4	*2.0*
Décès	0.2	*0.3*	0.7	0.2	*0.6*

Schulman et al. NEJM 2013, Agnelli et al. NEJM 2013, Büller et al. NEJM 2010, Weitz et al NEJM 2017

AOD en phase d'extension: caractéristiques

Indication à prolonger un traitement	Certaine	Incertaine	Incertaine	Incertaine
	REMEDY (dabigatran)	**AMPLIFY-EXT** (apixaban)	**EINSTEIN-EXT** (rivaroxaban)	**EINSTEIN-CHOICE** (rivaroxaban)
n	2856	2482	1197	3396
Hommes	60%	58%	58%	55%
Age (moy)	55	56	58	58
Poids	*Moy.* 86 kg	*<60 kg* 7% *≥60 kg* 93%	*<50 kg* 1% *50-100 kg* 82% *>100 kg* 15%	*IMC<30* 64,5% *IMC≥30* 35,5%
TVP	**65%**	**65%**	**64%**	50%
EP	35%	35%	36%	**50%**
Non provoqué	**93,5%**	**93%**	**73%**	40%
Provoqué	6,5%	7%	27%	**60%**
≥2 MVTE	**36%**	**12%**	**17%**	**17%**
Thrombophilie	**18%**	**4%**	**8%**	**6.5%**
Cancer actif	4,2%	1,8%	4,5%	2,5%

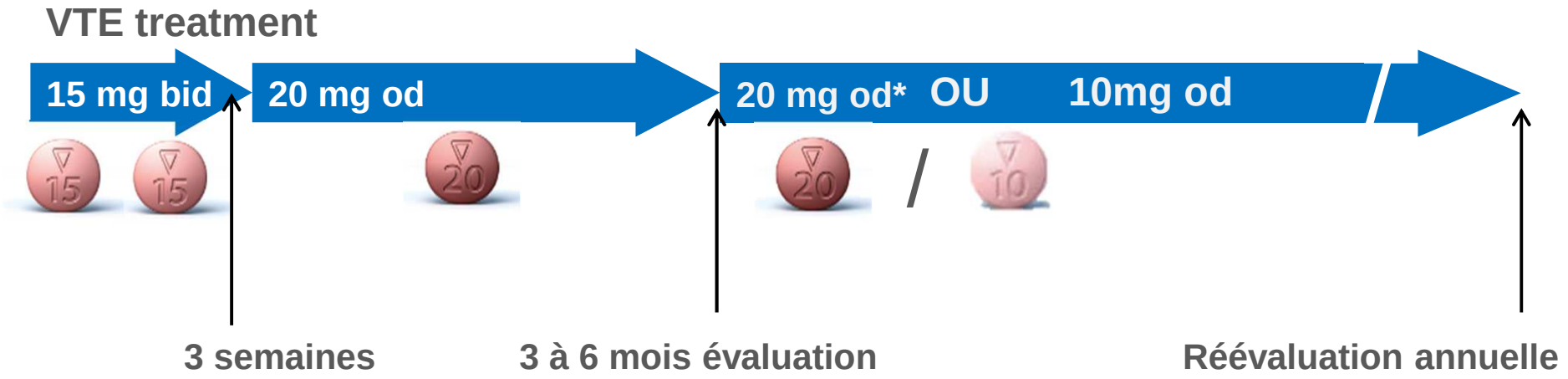
Schulman et al. NEJM 2013. Aanelli et al. NEJM 2013. Büller et al. NEJM 2010. Weitz et al NEJM 2017

AOD en phase d'extension: résultats

	REMEDY dabigatran		AMPLIFY-EXT apixaban			EINSTEIN-EXT rivaroxaban		EINSTEIN-CHOICE rivaroxaban			
Bras	Dab.	War.	A.5	A.2.5	*Pl.*	R.20	*Pl.*	R.20	R.10	*ASA*	
Récidive TEV	**1.8**	**1.3**	**1.7**	**1.7**	***8.8***	**1.3**	***7.1***	**1.5**	**1.2**	***4.4***	Sup
Hém. Maj.	0.9	1.8	0.1	0.2	*0.5*	0.7	*0*	0.5	0.4	*0.3*	
Hém. CP.			4.2	3.0	*2.3*	5.4	*1.2*	2.7	2.0	*1.8*	
Hém. Maj. + CP.	5.6	10.2	4.3	3.2	*2.7*	6.0	*1.2*	3.3	2.4	*2.0*	NS
Décès	1.2	1.3	0.5	0.8	*1.7*	0.2	*0.3*	0.7	0.2	*0.6*	

Schulman et al. NEJM 2013, Agnelli et al. NEJM 2013, Büller et al. NEJM 2010, Weitz et al NEJM 2017

RCP Rivaroxaban (mise à jour 19 Octobre 2017)



RCP (mise à jour 19 Octobre 2017):
« Lorsqu'une prévention prolongée des récidives de TVP et d'EP est indiquée (à l'issue d'un traitement d'au moins 6 mois pour les TVP et les EP), la dose recommandée est **de 10 mg en une prise quotidienne**.

Chez les patients pour lesquels le risque de récidive de TVP ou d'EP est jugé élevé, par exemple en présence de **comorbidités complexes** ou lorsqu'une **récidive de TVP ou d'EP** s'est produite au cours d'une prévention prolongée avec Xarelto 10 mg en une prise quotidienne, **la dose de 20 mg de Xarelto en une prise quotidienne doit être envisagée ».**

*15 mg if bleeding risk higher than thrombotic risk .

15 and 20 mg tablets must be taken with food

Prévention MTEV au long cours

Risque de récidive?

Quel antithrombotique ?

Quels patients ?

- évenements provoqués
- évenements non provoqués

Prévention MTEV au long cours

Risque de récidive?

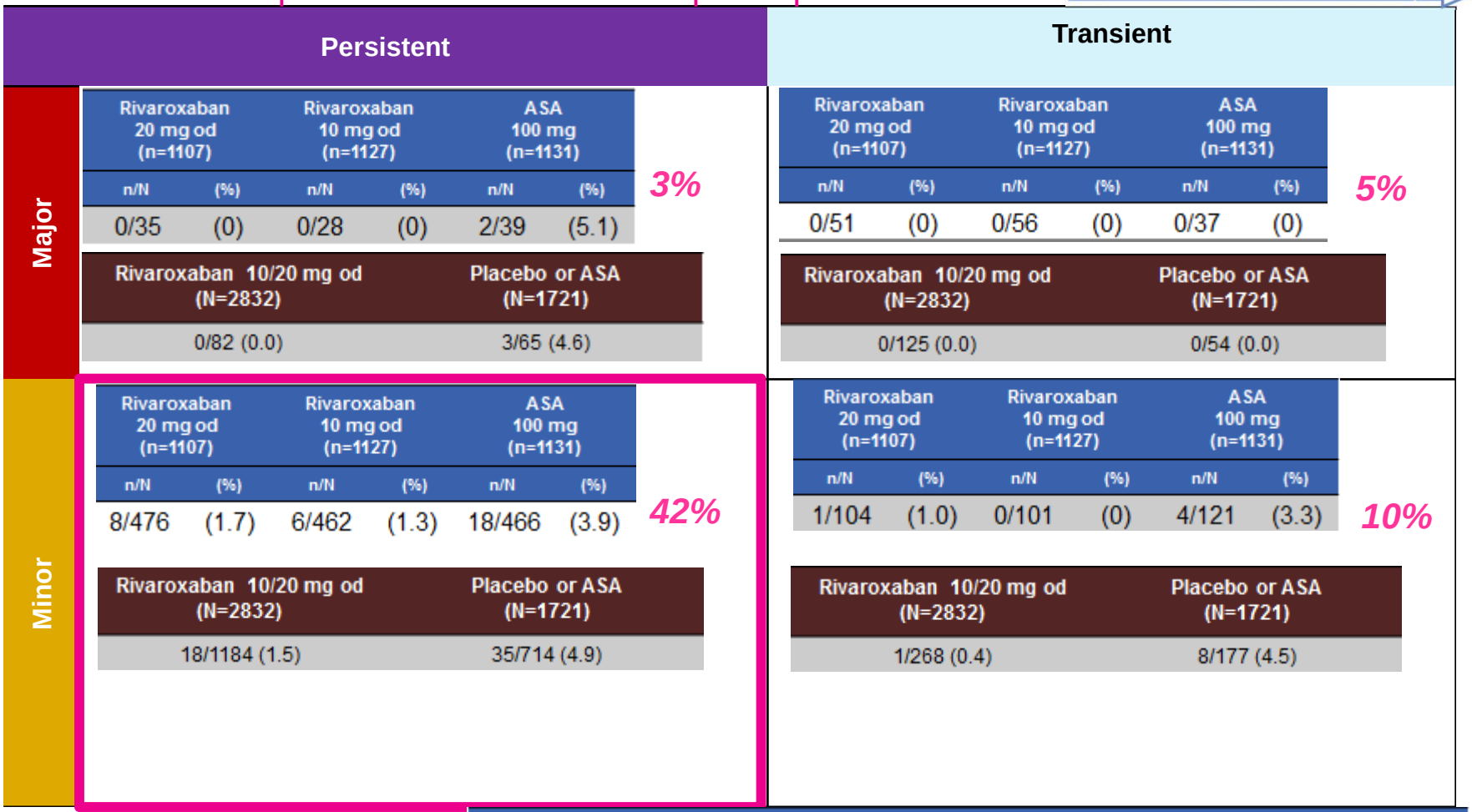
Quel antithrombotique ?

Quels patients ?

- évenements provoqués : Données
- évenements non provoqués

EINSTEIN Pooled et Einstein CHOICE Provoked VTE Can Be Categorized into Four Groups

Répartition en % des patients avec évènemens provoqués dans choice



Data presented at ISTH 2017. Abstract OC39.1

1st provoked VTE: duration of anticoagulant treatment

	• Persistent	• Transient
Major	• **Active cancer** (excluding basal-cell or squamous-cell skin carcinoma) • **APL syndrome, AT deficiency** Traitement Long	• Caesarean section • Major surgery • Major trauma • Hospitalization ≥ 3d • **Use of oestrogen therapy** 3 mois
Minor	• BMI over 30 kg/m^2 • Congestive heart failure • Creatinine clearance <50 mL/min • Family history of VTE • **Other major** Hereditary thrombophilia • Inflammatory bowel disorders • Paralysis/paresis of a lower extremity Traitement Plûtot long ½ dose AOD?	• Immobilization ≥ 3d • Hospitalization < 3d • Minor surgery • Leg injury with impaired mobility ≥ 3d • Pregnancy/puerperium • Travel >8 hours 3 - 6 mois

All Rivaroxaban (10 & 20 mg)	All comparator ASA+placebo
18/1184(1.5%)	35/714(4.9%)

All Rivaroxaban (10 & 20 mg)	All comparator ASA+placebo
1/268 (0.4%)	8/177 (4.5%)

Prévention MTEV au long cours

Risque de récidive?

Quel antithrombotique ?

Quels patients ?

- évenements provoqués
- évenements non provoqués

1st unprovoked VTE:duration of anticoagulant treatment

- i.e. VTE that was not provoked by a major transient risk factor in the absence of persistent major risk factor

- Women with HERDOO2 score ≤ 1: **6 months**

- All men and women with HERDOO2 > 1
  - DOAC full dose
  - DOAC ½ dose
  - VKA (INR 2-3)

6 months
Or extended
If extended:
DOAC full dose
DOAC ½ dose
VKA (INR 2-3)

Reverse-II results

“Men Continue and HERDOO2”

HERDOO2[1]	
HOMME **ou** **FEMME + ≥ 2 items:** **- Âge ≥ 65** **- DD ≥ 250 avec anticoagulants** **- PTS** **- BMI≥30**	
FEMME HERDOO2 ≤ 1	3%
FEMME HERDOO2 ≥ 2 ou HOMME	7% à 8%

Rodger M, et al. BMJ 2017

HERDOO Points in ♀

+1	**H**yperpigmentation **E**dema or **R**edness **(HER)** in either leg
+1	**D**-Dimer (Vidas) >250ug/L
+1	**O**besity, BMI ≥ 30
+1	**O**lder age ≥ 65
=___	**HERDOO points**

Rodger, CMAJ, 2008

Prévention MTEV au long cours

Risque de récidive?

Quel antithrombotique ?

Quels patients ?

Recommandations /HAS

2016 ACCP Guidelines and 2014 ESC Guidelines for Antithrombotic Therapy in VTE

- **Rivaroxaban** (20 mg once daily), **dabigatran** (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) or **apixaban** (2.5 mg twice daily) **should be considered as an alternative to VKA** (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary[2]
- **In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis[2]**

- **In patients with DVT of the leg or PE and no cancer,** as long-term anticoagulant therapy (first 3 months), **we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy (all Grade 2B)[1]**
- In patients with DVT of the leg or PE who receive extended therapy, we suggest that **there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C)[1]**
- **In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B)[1]**

1. Kearon C *et al*, *Chest* 2016;149:315–352; 2. Konstantinides SV *et al*, *Eur Heart J* 2014;35:3033–3069

Avis de CT 24 janvier 2018: Préviscan et Pradaxa ont un SMR dégradé MTEV

	SMR	ASMR	Place dans stratégie thérapeutique	Taux de remboursement
Préviscan	Modéré dernière intention parmi les AVK	V	1ere intention	30%
Coumadine	Important	V	1ere intention	65%
Sintron	Important	V	1ere intention	65%
Rivaroxaban	Important	V	1ere intention	65%
Apixaban	Important	V	1ere intention	65%

Avis de CT 24 janvier 2018
Xarelto® MTEV : traitement prolongé

HAUTE AUTORITÉ DE SANTÉ

Page	Passage de l'avis CT	Commentaires
p 3/5	XARELTO est un traitement de **1ère intention dans cette indication.**	Principal changement : passage d'une 2ème intention à une 1ère intention de traitement
p 3/5	En conséquence, la Commission considère que le service médical rendu par XARELTO 15 et 20 mg reste important dans le traitement des TVP et EP **et la prévention de leurs récidives, y compris en cas de traitement prolongé.**	L'utilisation de Xarelto au long cours est une nouvelle fois reconnue par les autorités

Avis de CT 24 janvier 2018
Xarelto® MTEV : Patients cancéreux

Cas des patients ayant un cancer

Pour le traitement initial et jusqu'à 10 jours de traitement, tous les médicaments antithrombotiques injectables ayant l'AMM peuvent être utilisés, notamment HBPM à dose curative, HNF, fondaparinux. Au-delà des 10 premiers jours, des recommandations françaises et internationales préconisent de poursuivre le traitement par HBPM à dose curative pendant une durée optimale de 6 mois, ou à défaut 3 mois minimum. Seules la daltéparine et la tinzaparine ont l'AMM dans le traitement prolongé de la MTEV symptomatique et la prévention de ses récidives, chez les patients atteints d'un cancer en évolution et/ou en cours de chimiothérapie.

La Commission n'est pas favorable à l'utilisation des différents AOD chez ces patients, car peu représentés dans les études.

Rivaroxaban (XARELTO)

Depuis le dernier avis de réévaluation de 2014, les principales modifications de RCP apportées ont concerné les rubriques :

- Précaution d'emploi et mise en gardes et effets indésirables: ajout du risque de syndrome de Stevens-Johnson et de nécrolyse épidermique toxique.
- Propriétés pharmacodynamiques : ajout des résultats des études XALIA (indication TVP et EP) et XANTUS (indication FANV).

Il est à noter qu'après examen des données cliniques chez les patients cancéreux dans les indications traitement de la TVP et de l'EP, le CHMP n'a pas souhaité l'ajout d'une précaution d'emploi de XARELTO dans cette population, à la différence des autres AOD. Cette décision a été prise considérant l'effectif des patients ayant un cancer évolutif au regard de l'effectif total des études et la diversité des patients (différentes formes et sévérités des cancers). Selon le CHMP, la décision du traitement par rivaroxaban chez le patient cancéreux est laissée à la discrétion du médecin traitant (décision CHMP du 26 mars 2015).

RCP Xarelto: Contre-indication : *Lésion ou maladie, si considérée comme étant à risque significatif de saignement majeur,* dont *la présence de tumeurs malignes à haut risque de saignements*

Avis de transparence HAS (24/01/2018) – cf p,98 (Cas des patients ayant un cancer) et p.58 (Rivaroxaban / patients cancéreux)

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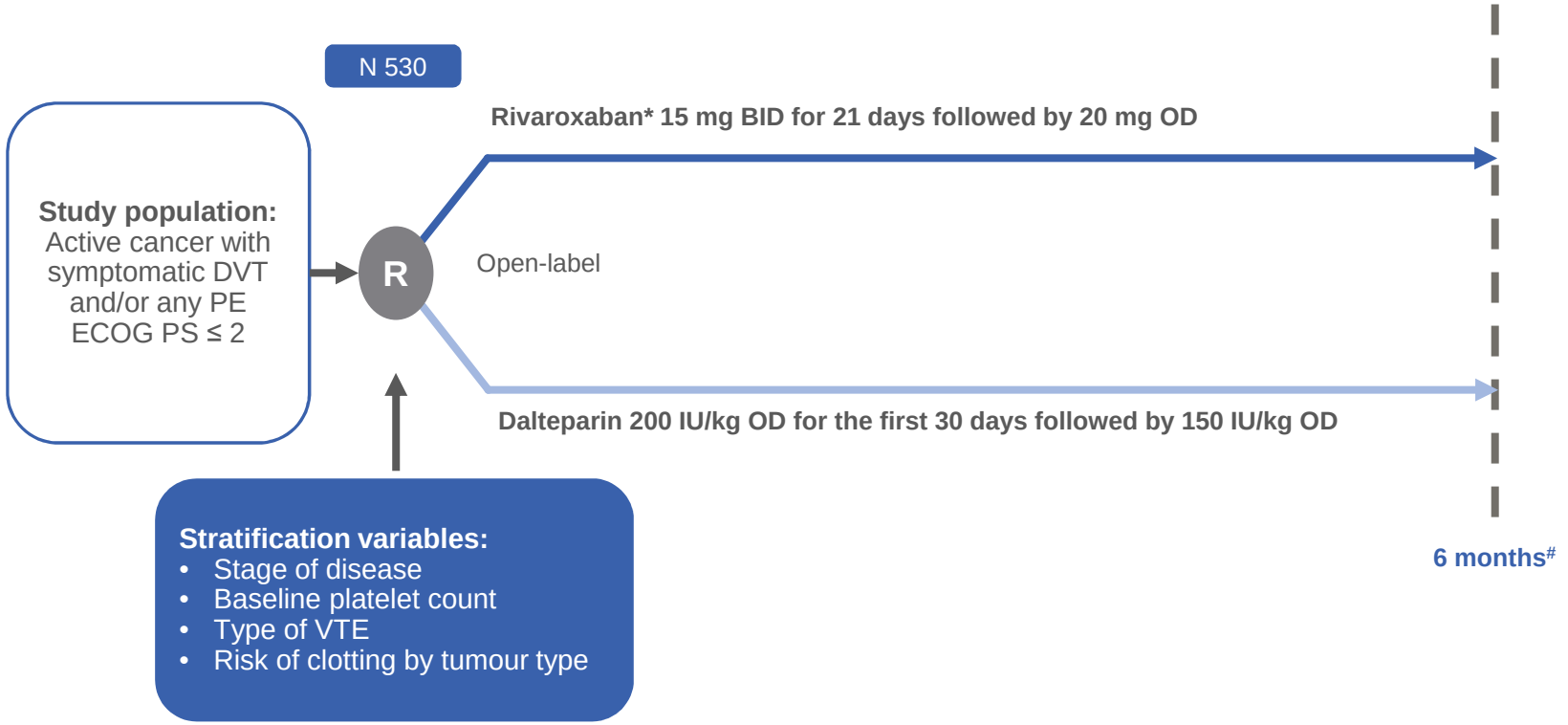
Back up slides

Premieres données Cancer

AOD/HBPM

select-D: Phase III Pilot Study Comparing Rivaroxaban versus Dalteparin for the Treatment of Cancer Associated Thrombosis

Study design: Prospective, randomized, open-label, multicentre pilot phase III study



*For patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; #The second randomization phase for extended treatment of VTE from 6 to 12 months for patients with PE as an index event or patients with Residual DVT at 5 month assessment was closed due to low recruitment. Sample size reduced from 530 to 400 patients for main trial comparison (95% CI for VTE recurrence +/-4.5%)

Young A *et al*, *Thromb Res* 2016;140:S172–S173; EudraCT number: 2012-005589-37; Bach M *et al*, *Thromb Haemost* 2016;116:S24–S32; Data on File

select-d: Outcomes, Inclusion and Exclusion Criteria

Primary outcome

- To assess VTE recurrence rates* (including symptomatic VTE and incidental PE)

Key secondary outcomes

- Major bleeding and clinically relevant non-major bleeding[#]
- Feasibility to evaluate extended anticoagulation treatment beyond 6 months in selected patients
- Acceptability and compliance
- Treatment satisfaction (ACTS)
- QoL (EuroQol [EQ-5D-5L] and SF36® health survey questionnaire)

Key inclusion criteria

- Active cancer
- Objectively confirmed VTE (symptomatic lower extremity proximal DVT or symptomatic/incidental PE)
- ECOG performance status score ≤2
- Adequate haematological function[‡]
- Adequate renal and hepatic function[§]

Key exclusion criteria

- >72 hours' pretreatment with anticoagulant prior to randomization[¶]
- Previous history of VTE
- Requirement for antiplatelet therapy**
- Bacterial endocarditis
- SBP >180 mmHg or DBP >110 mmHg[##]
- Bodyweight <40 kg at time of VTE
- Contraindications according to EU label

*Investigator-reported recurrent VTE; [#]all bleeding outcomes were independently adjudicated; [‡]recommended levels: haemoglobin >100 g/l, white cell count >2×10^9/l, platelets >100×10^9/l; [§]liver enzymes <3 × ULN; CrCl ≥30 ml/min; [¶]this can be extended to 96 hours if required; **other than ASA ≤75 mg daily; [##]control of blood pressure using anti-hypertensive drugs is permitted

Young A *et al*, *Thromb Res* 2016;140:S172–S173; EudraCT number: 2012-005589-37; Bach M *et al*, *Thromb Haemost* 2016;116:S24–S32

select-d: Patients Baseline Characteristics

Baseline characteristics

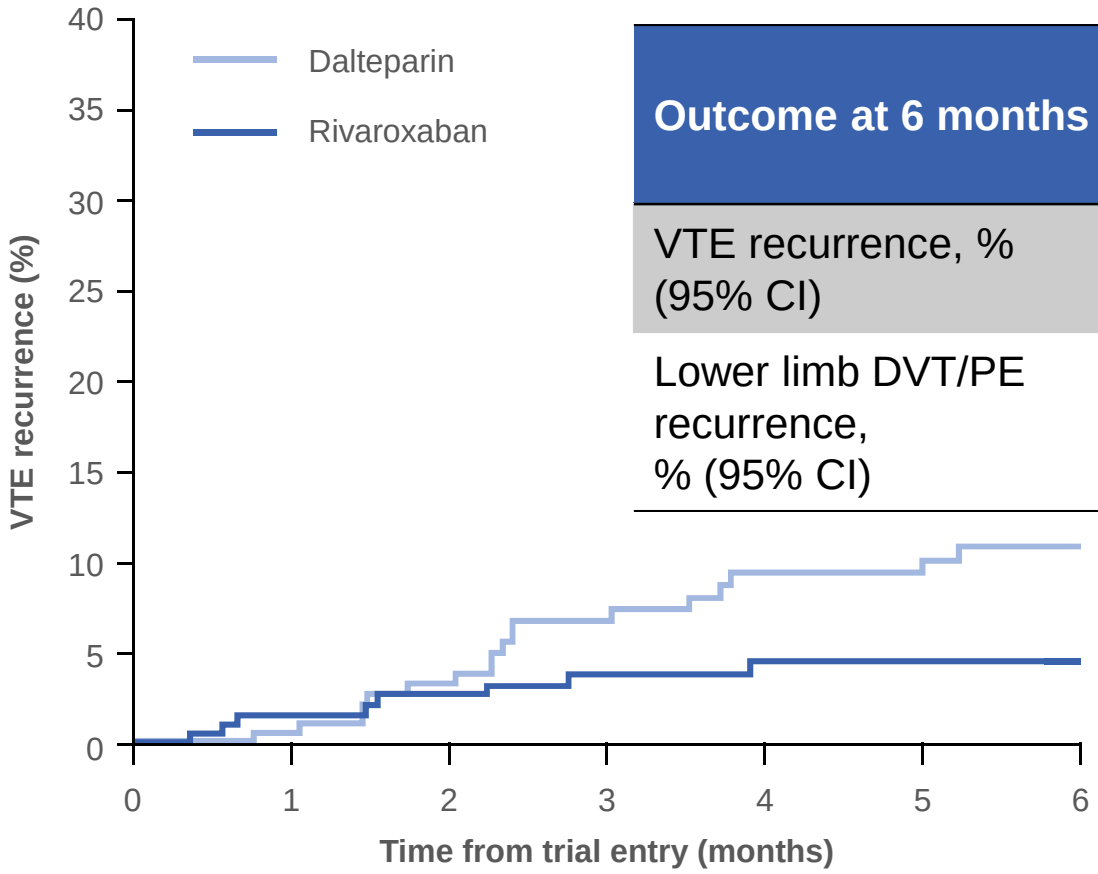
	Rivaroxaban (n=203)	Dalteparin (n=203)
Age, years, median (range)	67 (22–87)	67 (34–87)
Gender male, %	54	48
Metastatic cancer, %	59	59
ECOG performance status, % 0 or 1 2	 72 26	 76 21
Qualifying VTE, % Symptomatic VTE Incidental PE	 46 54	 48 52

Primary tumour type

Tumour type, %	Rivaroxaban (n=203)	Dalteparin (n=203)
Colorectal	27	23
Lung	11	12
Breast	9	10
Ovarian	5	9
Pancreatic	9	5
Lymphoma	5	6
Oesophageal/ gastro-oesophageal	5	9
Prostate	6	3
Bladder	5	2
Other	18	21

Young A *et al*, ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/

Select-d Primary Outcome: Lower Incidence of VTE Recurrence Events with Rivaroxaban Versus Dalteparin

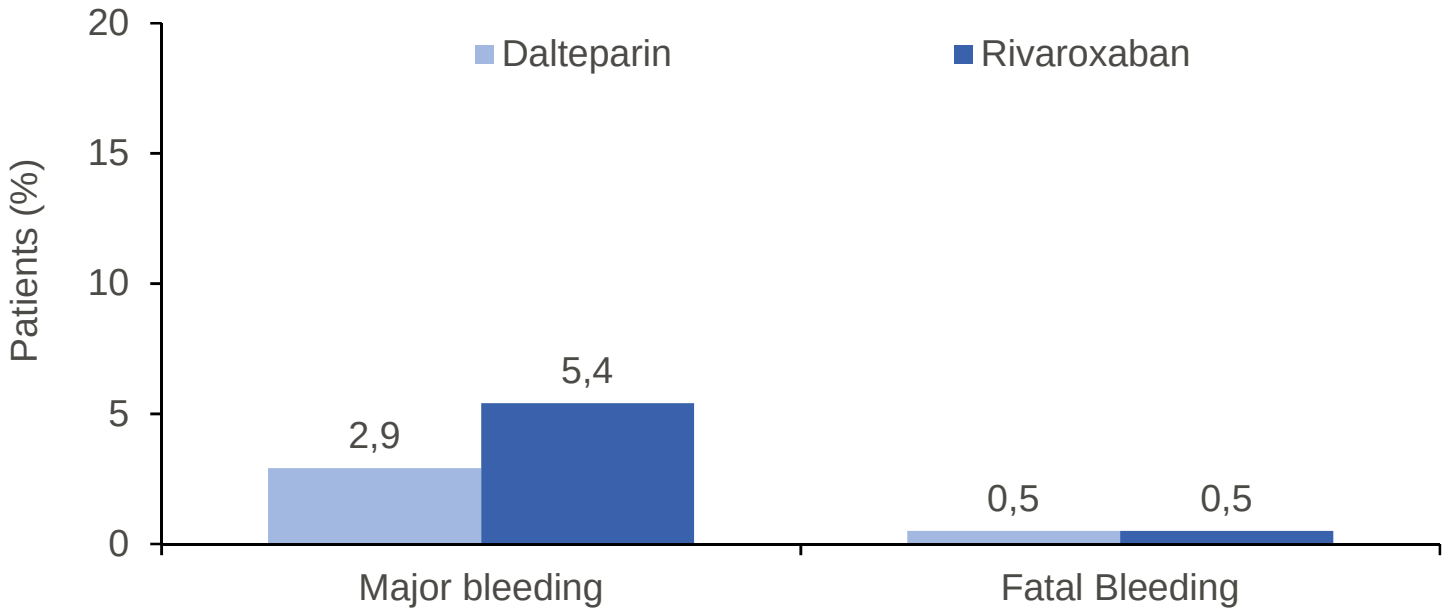


Outcome at 6 months	Rivaroxaban (n=203)	Dalteparin (n=203)
VTE recurrence, % (95% CI)	4 (2–9)	11 (7–16)
Lower limb DVT/PE recurrence, % (95% CI)	3 (1-7)	9 (6-15)

Number at risk				
Dalteparin	203	171	139	115
Rivaroxaban	203	174	149	134

Young A *et al.* ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/

Select-d Secondary Outcome: Low Incidence of Major Bleedings in Both Arms with Similar Rate of Fatal Bleeding

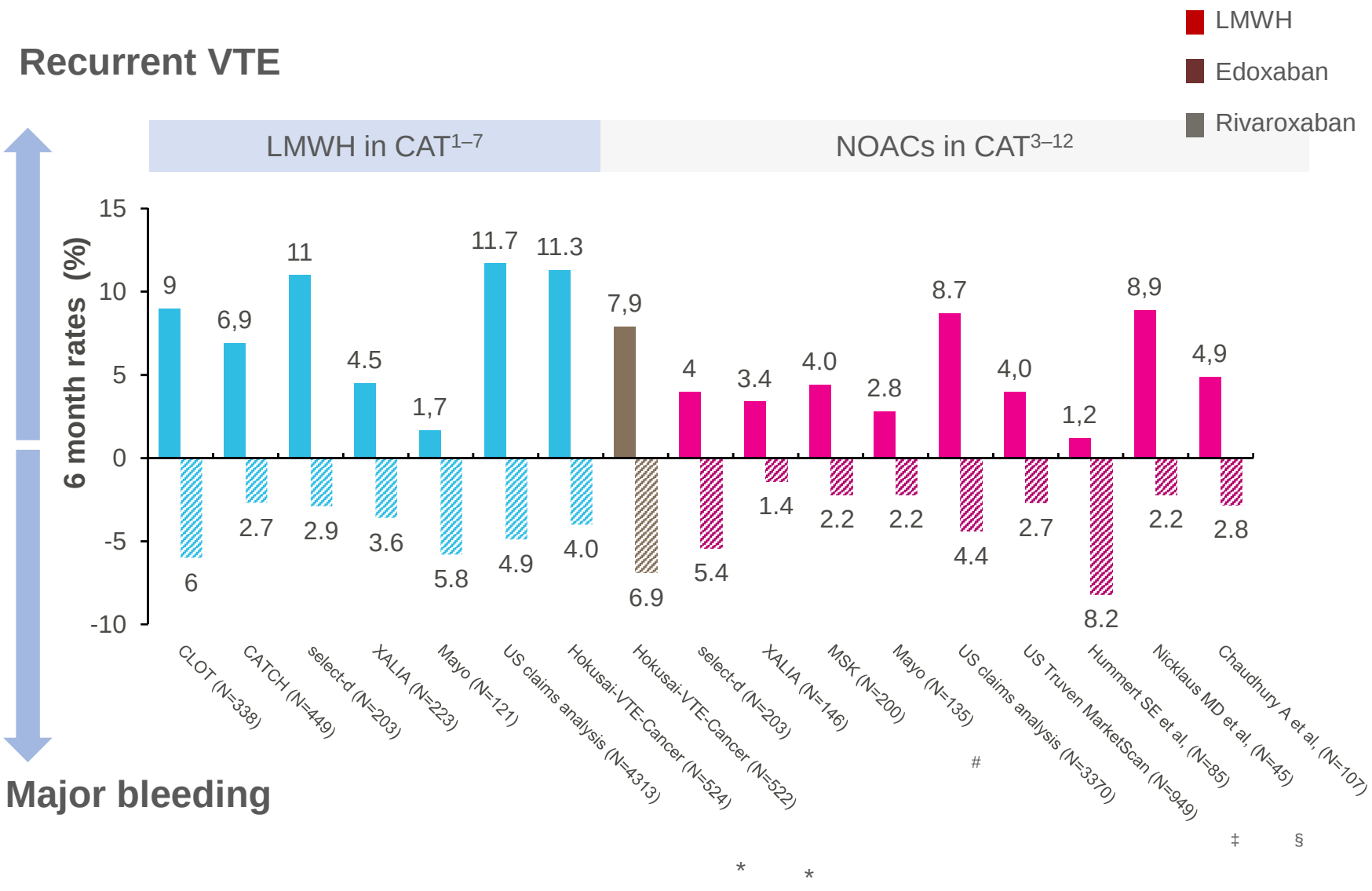


Most Major Bleedings events were Gastrointestinal Bleedings*. No Central Nervous System Bleeding was observed in rivaroxaban and dalteparin groups.

*All bleedings events were adjudicated. Clinical Major Bleedings in rivaroxaban group was 12.3% vs. 2.9% in the daltaparin group. Overall survival at 6 months was 70%(63-76%) in the rivaroxaban group and 75%(69-81%) in the dalteparin group.

Young A *et al*, ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/

Effectiveness and Safety of Anticoagulants in Patients with Active Cancer and VTE



*12 month VTE recurrence rates; Results reported during: #7.2 months, ‡5.6 months and §7.1 months follow-up period