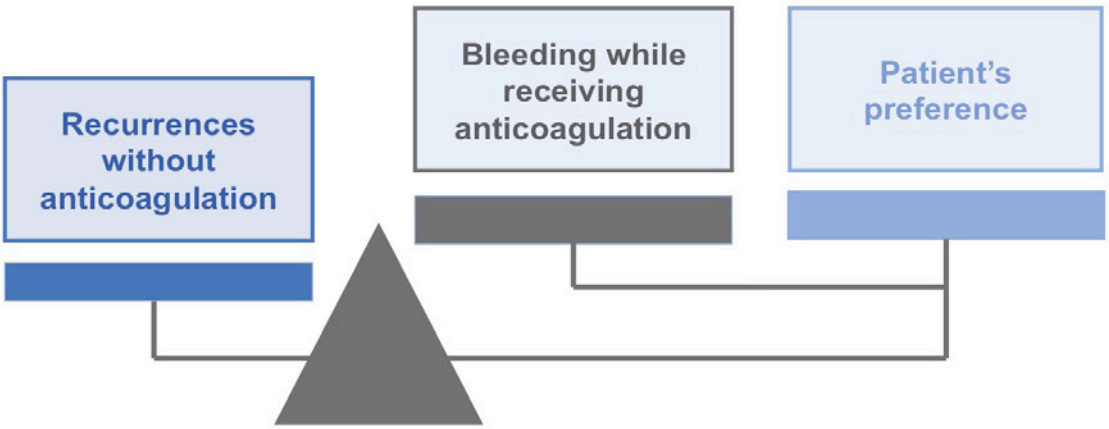
Paolo Prandoni, MD, PhD

Estensione della terapia anticoagulante in pazienti con TEV
Bilancio tra il rischio di recidiva e quello emorragico

fondazione arianna ANTICOAGULAZIONE

Index

Balancing the Risk of Recurrent VTE Versus Bleeding Is Critical for Deciding to Extend Treatment



Original Article

The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients

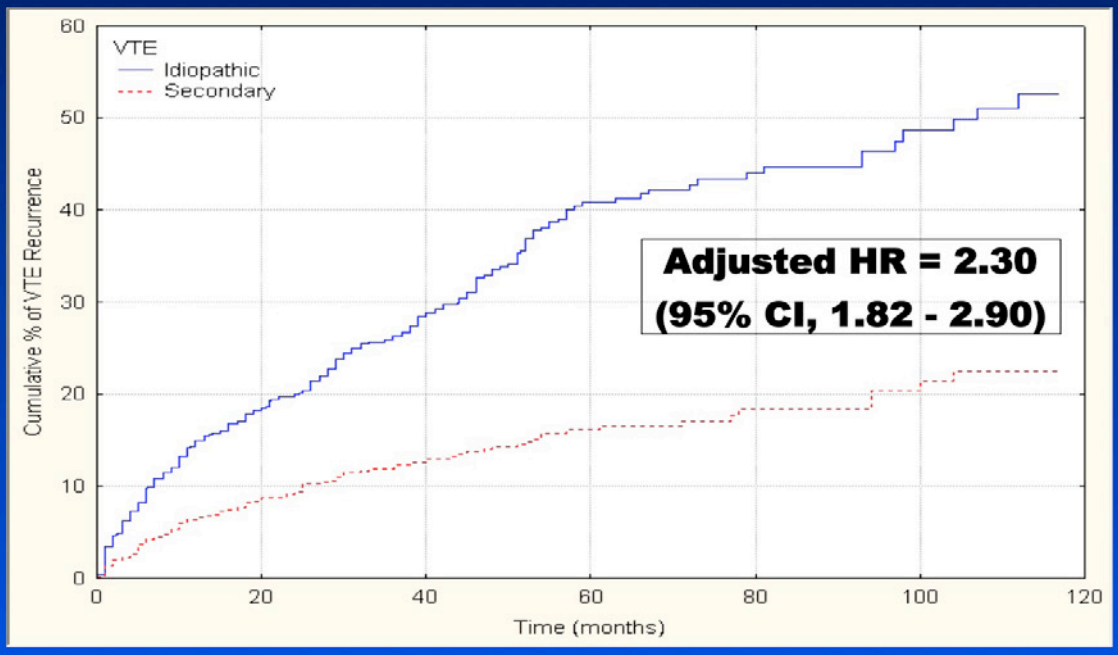
Paolo Prandoni, Franco Noventa, Angelo Ghirarduzzi, Vittorio Pengo, Enrico Bernardi, Raffaele Pesavento, Matteo Iotti, Daniela Tormene, Paolo Simioni, Antonio Pagnan

Haematologica 2007; 92: 199-205

The clinical course of 1626 patients with DVT and/or PE

Patients (number)	**1626**
Age (median, range)	**66 (16,96)**
Gender (n., % males)	**735 (45.2)**
Modality of clinical presentation	
- DVT alone	**1073 (66.0)**
- DVT + PE	**292 (18.0)**
- PE alone	**261 (16.0)**
Patients categories	
- Unprovoked	**864 (53.1)**
- Secondary to acquired risk factors	**762 (46.9)**
Risk factors for thrombosis	
- Recent trauma or surgery	**553 (72.6)**
- Hormonal treatment, pregnancy or puerperium	**109 (14.3)**
- Medical diseases	**100 (13.1)**
Thrombophilic abnormalities	**229/953 (24.0)**
Duration of oral anticoagulation	
- Three months or less	**540 (33.2)**
- Between three and six months	**811 (49.9)**
- Between six and twelve months	**196 (12.0)**
- Between one and two years	**67 (4.1)**
- Between two and three years	**12 (0.7)**

The clinical course of 1626 patients with DVT and/or PE



Prandoni, Hematologica 2007

Provoked VTE and risk of recurrent events

Factors	CI (95% CI)
Medical diseases	31.8 (18.2-45.3)
Women-specific risk factors	20.3 (8.9-31.7)
Recent trauma/surgery	11.4 (4.7-18.0)

Prandoni et al, Haematologica 2007

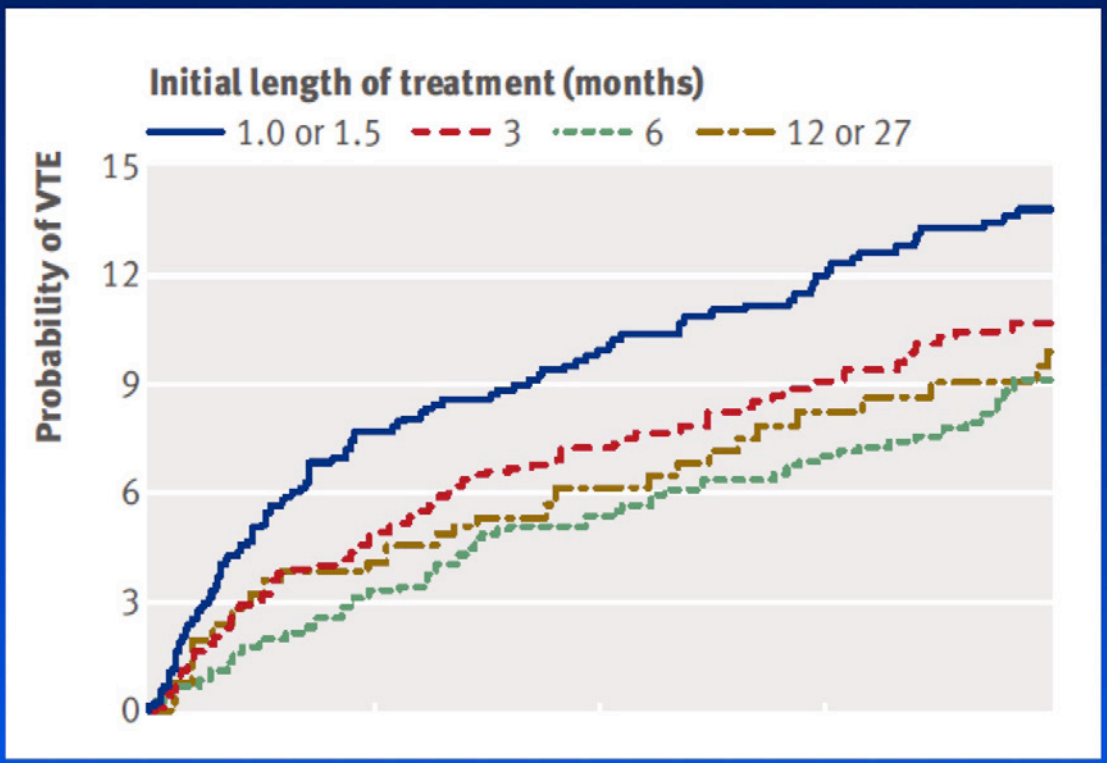
BMJ

2011, online first

RESEARCH

Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials

Florent Boutitie, statistical investigator,[1] Laurent Pinede, investigator,[2] Sam Schulman, professor,[3,4] Giancarlo Agnelli, professor,[5] Gary Raskob, professor,[6] Jim Julian, statistical investigator,[7] Jack Hirsh, professor emeritus,[4] Clive Kearon, professor[4]



Original Investigation

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD; Elisabeth Duhamel, MD; Karine Provost, MD; Claire Bal dit Sollier, MB; Emilie Presles, MS; Philippe Castellant, MD; Florence Parent, MD; Pierre-Yves Salaun, MD, PhD; Luc Bressollette, MD, PhD; Michel Nonent, MD, PhD; Philippe Lorillon, PharmD; Philippe Girard, MD; Karine Lacut, MD, Marie Guégan, MS; Jean-Luc Bosson, MD, PhD; Silvy Laporte, MS, PhD; Christophe Leroyer, MD, PhD; Hervé Décousus, MD; Guy Meyer, MD; Dominique Mottier, MD; for the PADIS-PE Investigators

Table 1. Baseline Characteristics of Study Participants[a]

	Warfarin (n = 184)	Placebo (n = 187)
Age, mean (SD), y	58.7 (17.9)	57.3 (17.4)
>65 y, No. (%)	74 (40.2)	70 (37.4)
Women, No. (%)	106 (57.6)	84 (44.9)
Body mass index, mean (SD)	27.8 (5.9)	27.1 (5.1)
≥30, No. (%)	53 (28.8)	39 (20.9)
Creatinine clearance category, mL/min, No. (%)[b]		
<30	0	0
≥30-<50	16 (8.9)	7 (3.9)
≥50	164 (91.1)	173 (96.1)
Medical conditions, No. (%)		
Previous cancer[c]	8 (4.3)	6 (3.2)
Previous distal deep-vein thrombosis or superficial-vein thrombosis	17 (9.2)	14 (7.5)
Chronic heart failure	4 (2.2)	9 (4.8)
Chronic respiratory failure	40 (21.7)	35 (18.7)
Method used to diagnose the incident pulmonary embolism, No. (%)		
High-probability ventilation/perfusion lung scanning	47 (25.5)	39 (20.9)
Spiral computed tomography angiography	137 (74.5)	148 (79.1)
Associated proximal deep-vein thrombosis at diagnosis, No. (%)	56 (31.1)	56 (31.6)

The JAMA Network

From: **Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial**

JAMA. 2015;314(1):31-40. doi:10.1001/jama.2015.7046

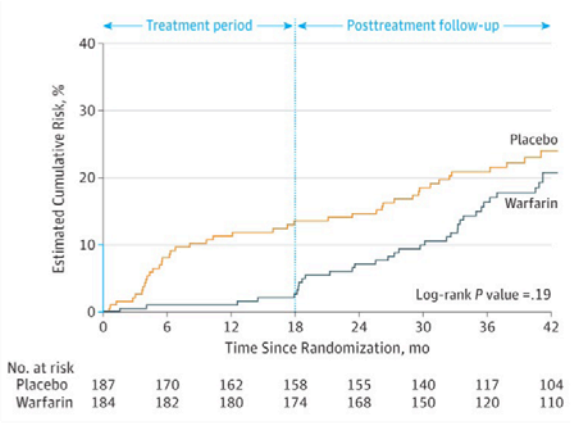


Figure Legend:

Probability of the Composite Outcome of Recurrent Venous Thromboembolism and Major Bleeding Throughout the Study PeriodThe unadjusted hazard ratios for warfarin-placebo were 0.23 (95% CI, 0.09-0.55) during the treatment period and 0.74 (95% CI, 0.47-1.17) for the entire study period. The y axis that is shown in blue indicates the range of estimated cumulative risk from 0% to 10%.

Extension of anticoagulant treatment beyond 3 to 6 months for VTE with the VKA

For 1,000 patient-years

Death by PE recurrence
80 VTE recurrences
Case-fatality rate 4%
3 – 10 deaths

Death by major bleed
20 – 60 bleeds
Case-fatality rate 11%
2 – 6 deaths

Douketis JD, et al. *Ann Intern Med* 2007
Linkins LA, et al. *Ann Intern Med* 2003

Durata fissa della terapia anticoagulante

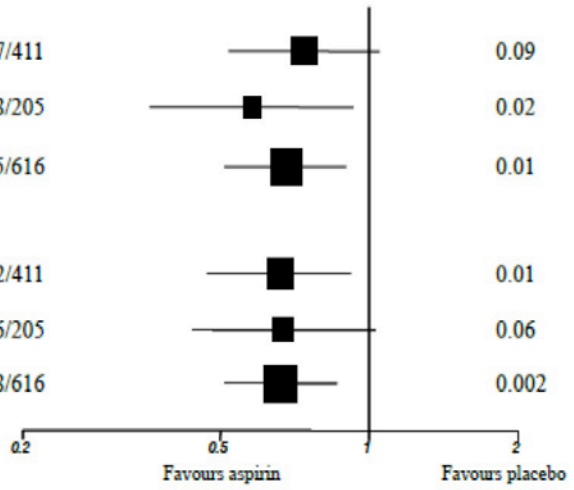
Terapia indefinita con i VKA

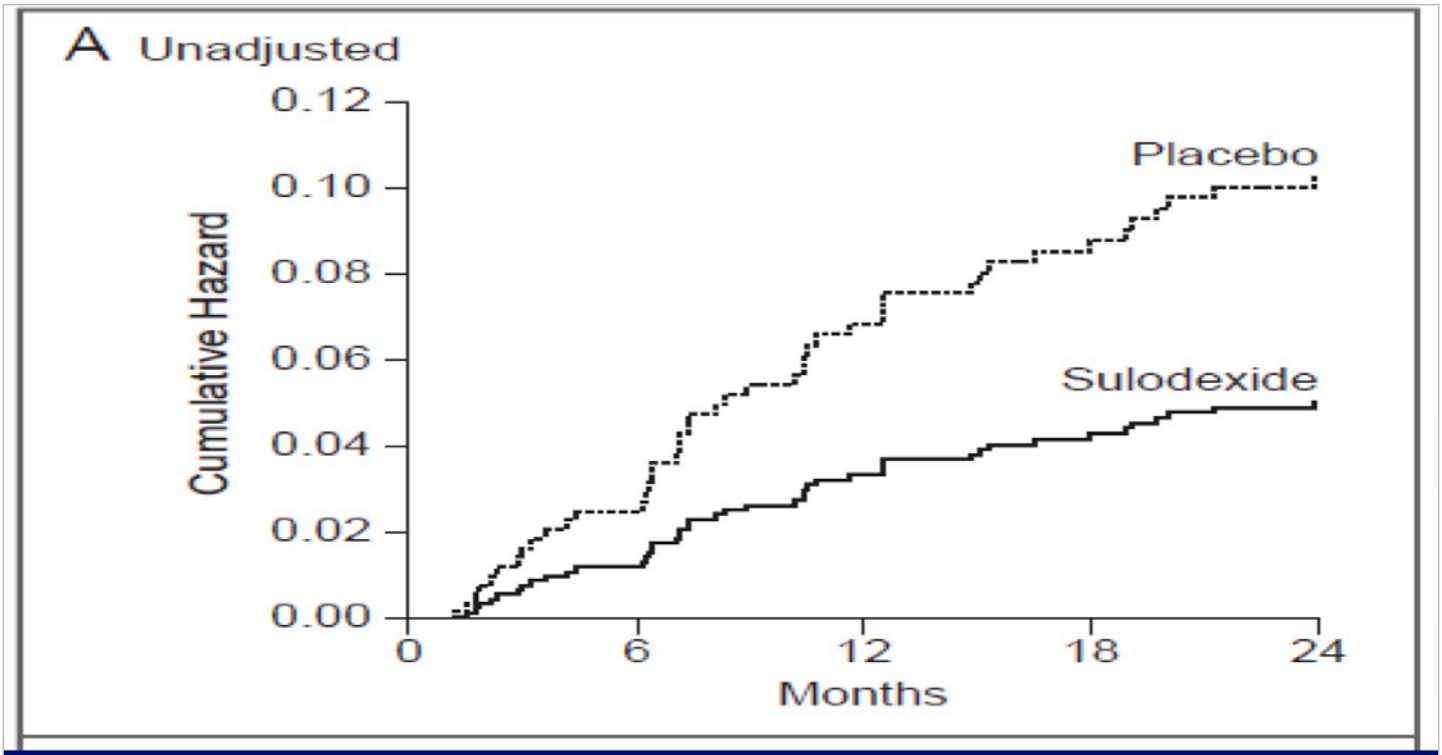
Scenari alternativi

1. Aspirina a basse dosi
2. Sulodexide 500 mg x 2
3. Basse dosi dei DOAC
4. Identificazione dei pazienti a basso rischio

Meta-analysis of the WARFASA and ASPIRE studies

Outcome and study	Placebo Events/*n*	Aspirin Events/*n*	Hazard Ratio (95% CI)	*P*	*P* heterogeneity
VTE					
Aspire	73/411	57/411		0.09	
Warfasa	43/197	28/205		0.02	0.42
Pooled	116/608	85/616		0.01	
Major vascular events					
Aspire	88/411	62/411		0.01	
Warfasa	48/197	36/205		0.06	0.96
Pooled	136/608	98/616		0.002	





Andreozzi et al, Circulation 2015

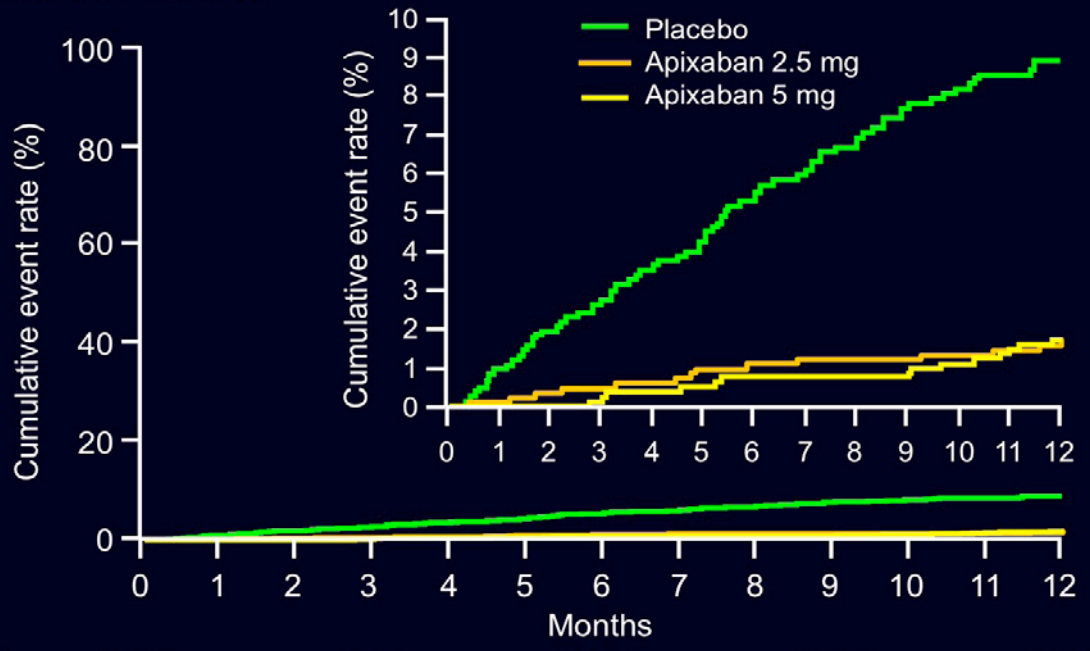
Benefit/risk of low-dose aspirin and sulodexide

RISK
No increase in major bleeding

BENEFIT
30-50% RRR over placebo of recurrent VTE

Amplify Extension

Kaplan–Meier:
Non-fatal and fatal VTE



No. at risk	Baseline	Month 3	Month 6	Month 9	Month 12
Apixaban 2.5 mg	840	836	825	818	533
Apixaban 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

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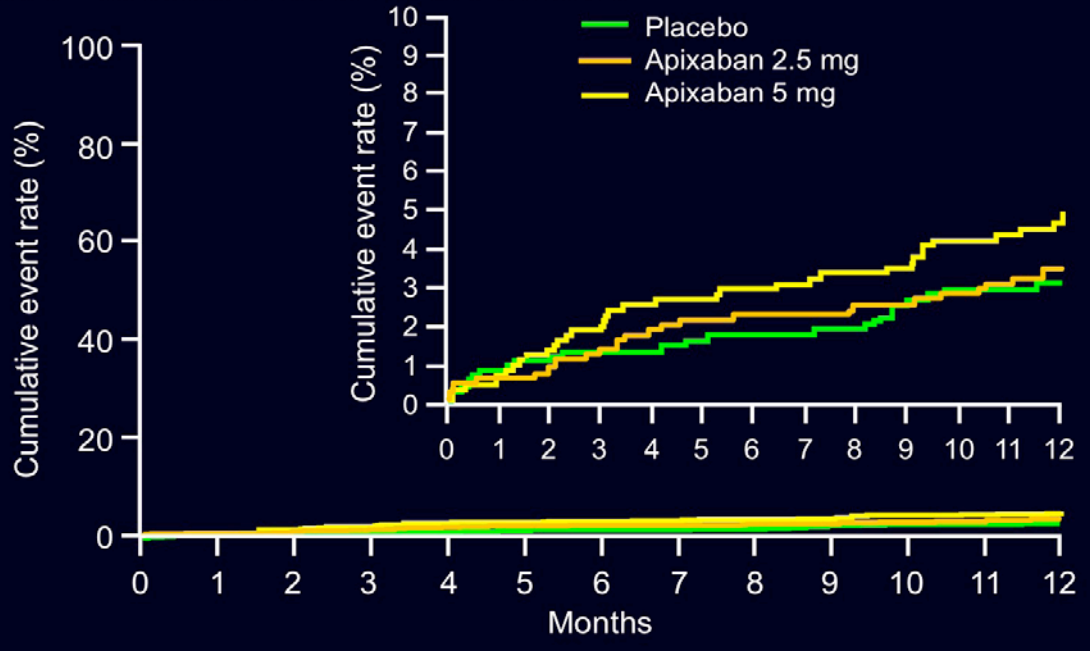
Kaplan–Meier:
Major or Clinically relevant non major bleeding



No. at risk	Baseline	Month 3	Month 6	Month 9	Month 12
Apixaban 2.5 mg	840	786	759	737	354
Apixaban 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

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EINSTEIN CHOICE

Reduced dose rivaroxaban and standard dose rivaroxaban versus aspirin in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism

Status 20.12.2016

EINSTEIN CHOICE

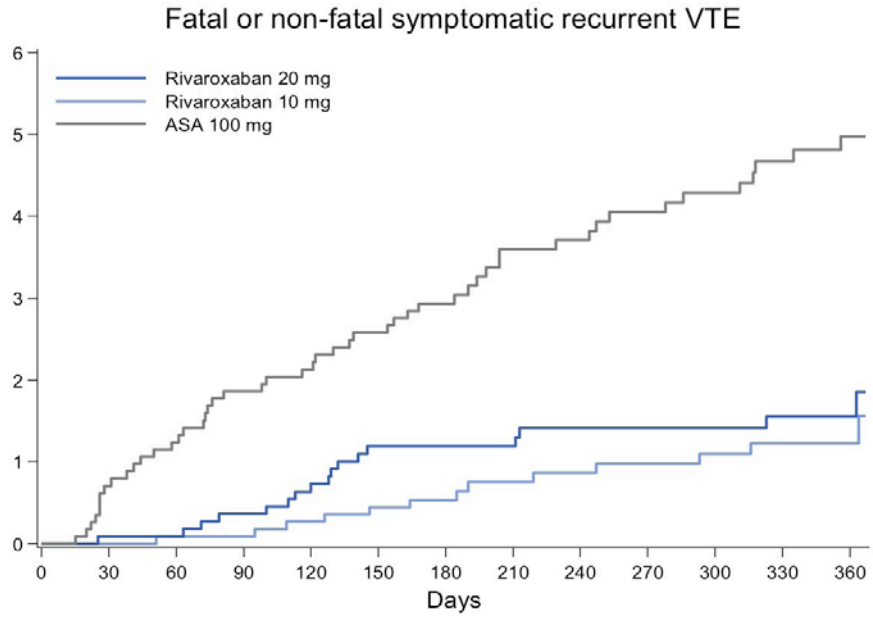
Demographics and Clinical Characteristics

		Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)
Male sex, n (%)		602 (54.4%)	620 (55.0%)	643 (56.9%)
Mean age, year (SD)		57.9 ± 14.7	58.8 ± 14.7	58.8 ± 14.7
Weight, n (%)	≤70 kg 70–≤90 kg >90 kg	276 (24.9%) 471 (42.5%) 360 (32.5%)	283 (25.1%) 480 (42.6%) 364 (32.3%)	277 (24.5%) 508 (44.9%) 346 (30.6%)
Body mass index	<30 kg/m² ≥30 kg/m²	712 (64.3%) 394 (35.6%)	751 (66.6%) 376 (33.4%)	756 (66.8%) 375 (33.2%)
Creatinine clearance, n (%)	<30 mL/min 30–<50 mL/min 50–<80 mL/min ≥80 mL/min	1 (< 0.1%) 40 (3.6%) 279 (25.2%) 787 (71.1%)	2 (0.2%) 49 (4.3%) 302 (26.8%) 774 (68.7%)	1 (<0.1%) 63 (5.6%) 277 (24.5%) 790 (69.8%)
Index event, n (%)	DVT PE PE+DVT No symptomatic event	565 (51.0%) 381 (34.4%) 155 (14.0%) 6 (0.5%)	565 (50.1%) 381 (33.8%) 179 (15.9%) 2 (0.2%)	577 (51.0%) 366 (32.4%) 181 (16.0%) 7 (0.6%)
Cause of VTE, n (%)	Unprovoked Provoked	441 (39.8%) 666 (60.2%)	480 (42.6%) 647 (57.4%)	468 (41.4%) 663 (58.6%)
Hormonal therapy, n (%) - Estrogens - Progestins	At randomization and during study	8 (0.7%) 19 (1.7%)	5 (0.4%) 22 (2.0%)	8 (0.7%) 25 (2.2%)
Active cancer, n (%)		25 (2.3%)	27 (2.4%)	37 (3.3%)
Known thrombophilia, n (%)		79 (7.1%)	74 (6.6%)	70 (6.2%)
Previous DVT or PE, n (%)		198 (17.9%)	197 (17.5%)	194 (17.2%)
Anatomical extent of DVT/ PE, n (%)	Limited Intermediate Extensive Non-evaluable, not confirmed, asymptomatic	190 (17.2%) 417 (37.7%) 492 (44.4%) 8 (0.7%)	189 (16.8%) 423 (37.5%) 512 (45.4%) 3 (0.3%)	197 (17.4%) 406 (35.9%) 520 (46.0%) 8 (0.7%)

Table

EINSTEIN CHOICE

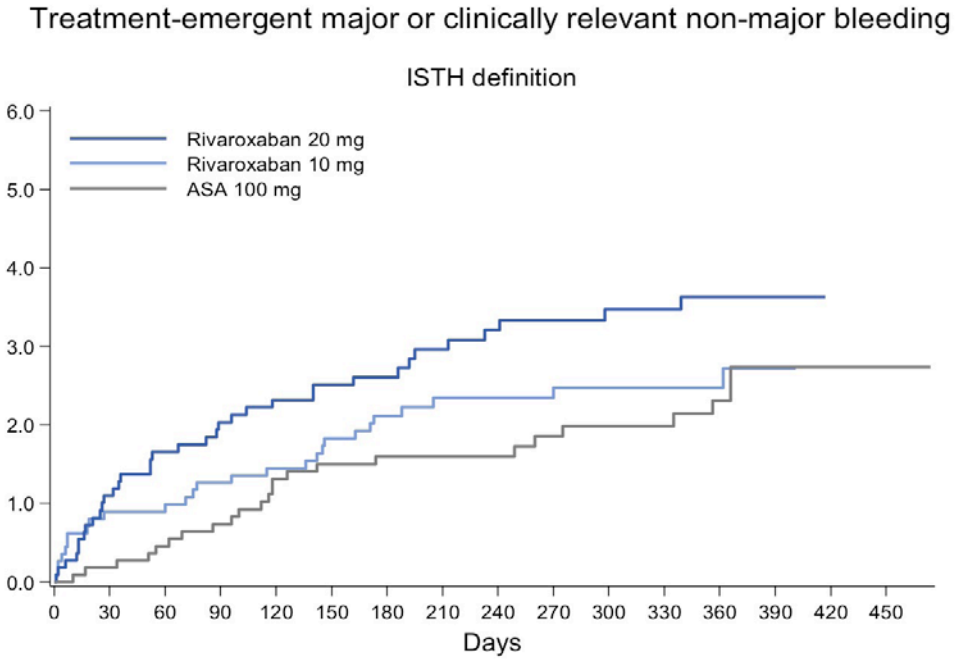
Primary Efficacy Outcome – Cumulative Incidence



Table

EINSTEIN CHOICE

Major or CRNM bleeding (ISTH)



Treatment-emergent: onset during study treatment up to 2 days after stop of study treatment

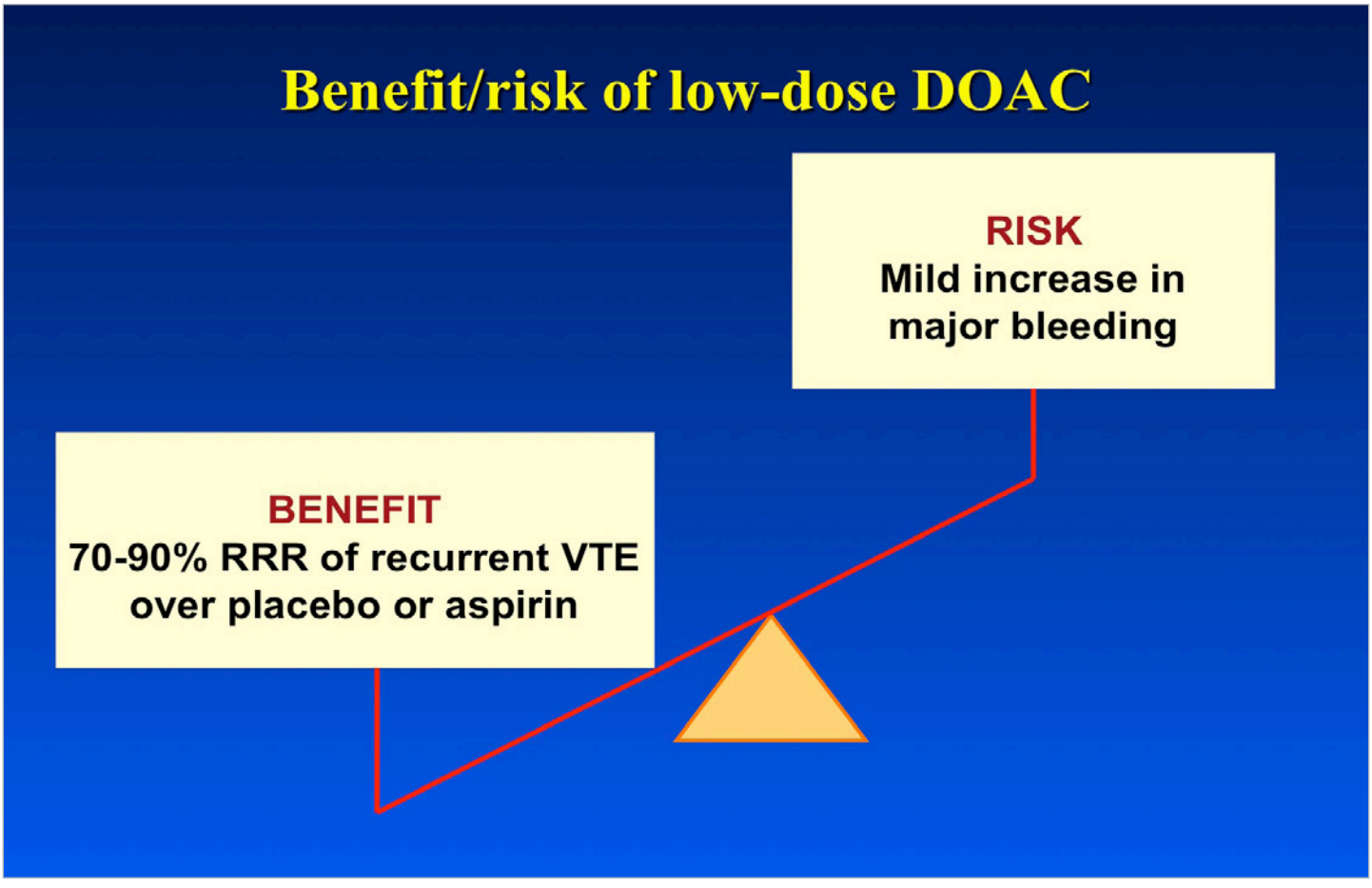
EINSTEIN CHOICE

Recurrent VTE by Risk Factor Profile

	Rivaroxaban 20 mg (n=1107)		Rivaroxaban 10 mg (n=1127)		Aspirin 100 mg (n=1131)	
	n	(%)	n	(%)	n	(%)
Risk factor profile for index event, n (%)						
Unprovoked VTE	8/441	1.8%	7/480	1.5%	26/468	5.6%
Persisting major risk factor	0/35	0	0/28	0	2/39	5.1%
Persisting minor risk factor	8/476	1.7%	6/462	1.3%	18/466	3.9%
Transient minor risk factor	1/104	1.0%	0/101	0	4/121	3.3%
Major transient risk factor	0/51	0	0/56	0	0/37	0
Risk for recurrent VTE during anticoagulation at randomization, n (%)						
High risk	0/65	0	0/74	0	5/95	5.3%
Low risk	17/1042	1.6%	13/1053	1.2%	45/1036	4.3%
History of previous VTE						
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%

Table

EINSTEIN CHOICE



Models to predict recurrent VTE

	Men continue and HER D002	Vienna Prediction Model	DASH-score	DAMOVES score
Study design	Prospective cohort	Prospective cohort	Patient level meta-analysis	Prospective cohort
Patients	646	929	1818	398
Predictive variables	Men: none Women: - age ≥ 60 years - signs of PTS - BMI ≥ 30 kg/m^2 - D-dimer > 250 µg/l during anticoagulation	- Sex - Location of first VTE - D-Dimer after anticoagulation	- Abnormal D-dimer after anticoagulation - Age < 50 years - Male sex - Hormonal therapy	- Age - Sex - Obesity - D-dimer during anticoagulation - F VIII - Thrombophilia - Varicose veins
Increased risk of recurrent VTE	>1 point	> 180 points (according to a nomogram)	> 1 point	> 11.5 (according to a nomogram)
Recurrence rate in patients at low risk	1.6% (95% CI, 0.3-4.6)	4.4% (95% CI, 2.7-6.2)	3.1% (95% CI, 2.3-3.9)	2.9% (95% CI, 2.13-4.35)

Validation of the HERDOO2

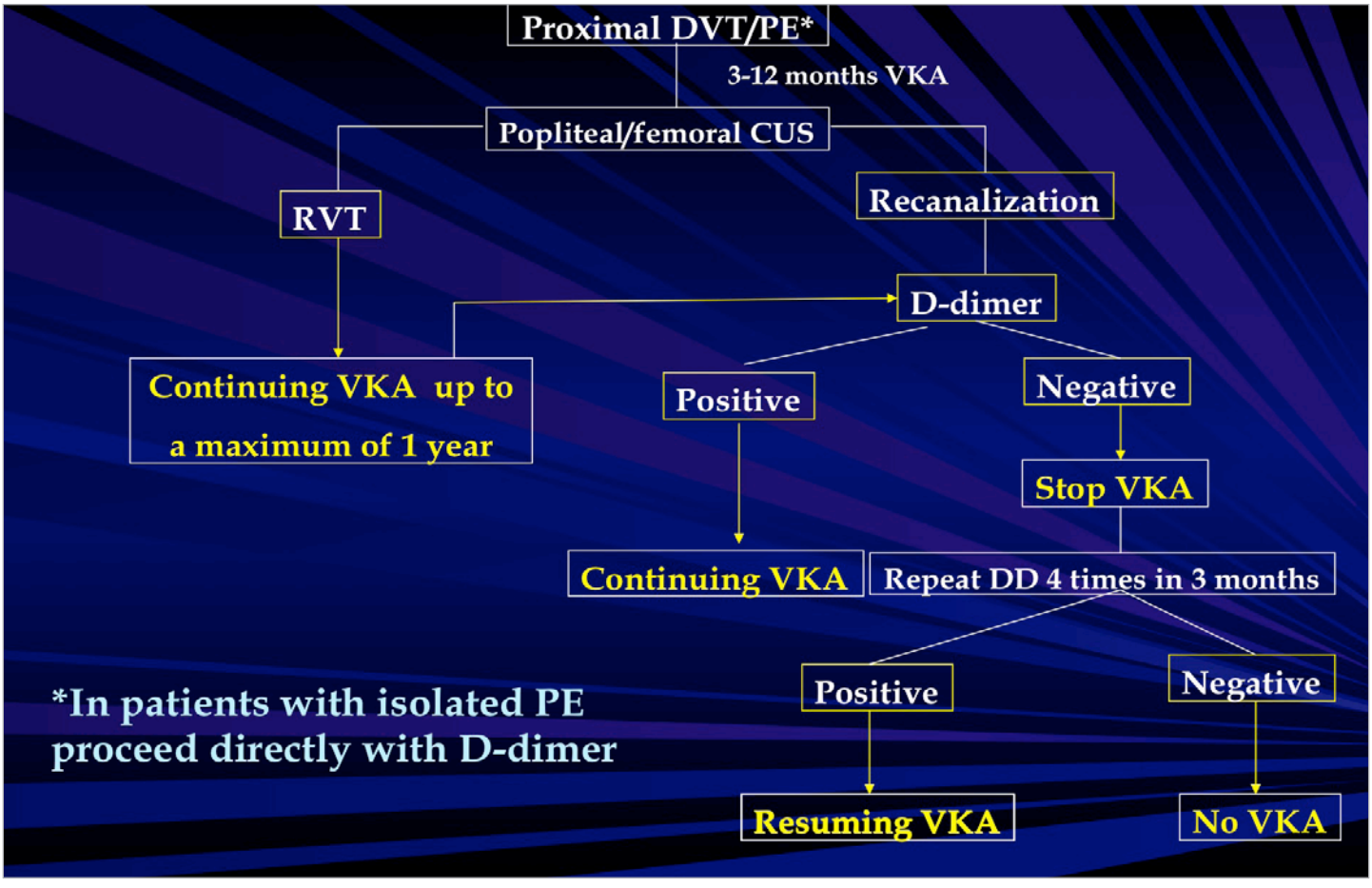
Groups	Low risk women* who discontinued oral anticoagulants (n=591)	Men and high risk women*		High risk* women who discontinued oral anticoagulants (n=101)
		Discontinued oral anticoagulants (n=323)	Continued oral anticoagulants (n=1802)	
Primary outcome:				
Risk of recurrent major† VTE	3.0 (1.8 to 4.8)	8.1 (5.2 to 11.9)	1.6 (1.1 to 2.3)	7.4 (3.0 to 15.2)
Secondary outcomes:				
Risk of major‡ bleed	0.2 (0 to 1.0)	0.6 (0 to 2.3)	1.2 (0.8 to 1.8)	2.1 (0.3 to 7.6)
Recurrent PE death	0	0	0.1 (0 to 0.3)	0
Non-PE death	0.2 (0 to 1.0)	0.1.0 (0.2 to 2.8)	0.4 (0.2 to 0.8)	2.1 (0.3 to 7.6)

Rodger MA et al, BMJ 2017

D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism
A management study

Palareti G, Cosmi B, Legnani C, Antonucci E, Erba N, Ghirarduzzi A, Poli D, Testa S, Tosetto A, Pengo V, Prandoni P

Blood 2014



Main Study Results

- Proportion of subjects with persistently negative D-Dimer among eligible patients 51.2%

- Annual incidence of recurrent VTE in this patients' group (mean f-up, 2 years) 3.0%

G.B. Morgagni

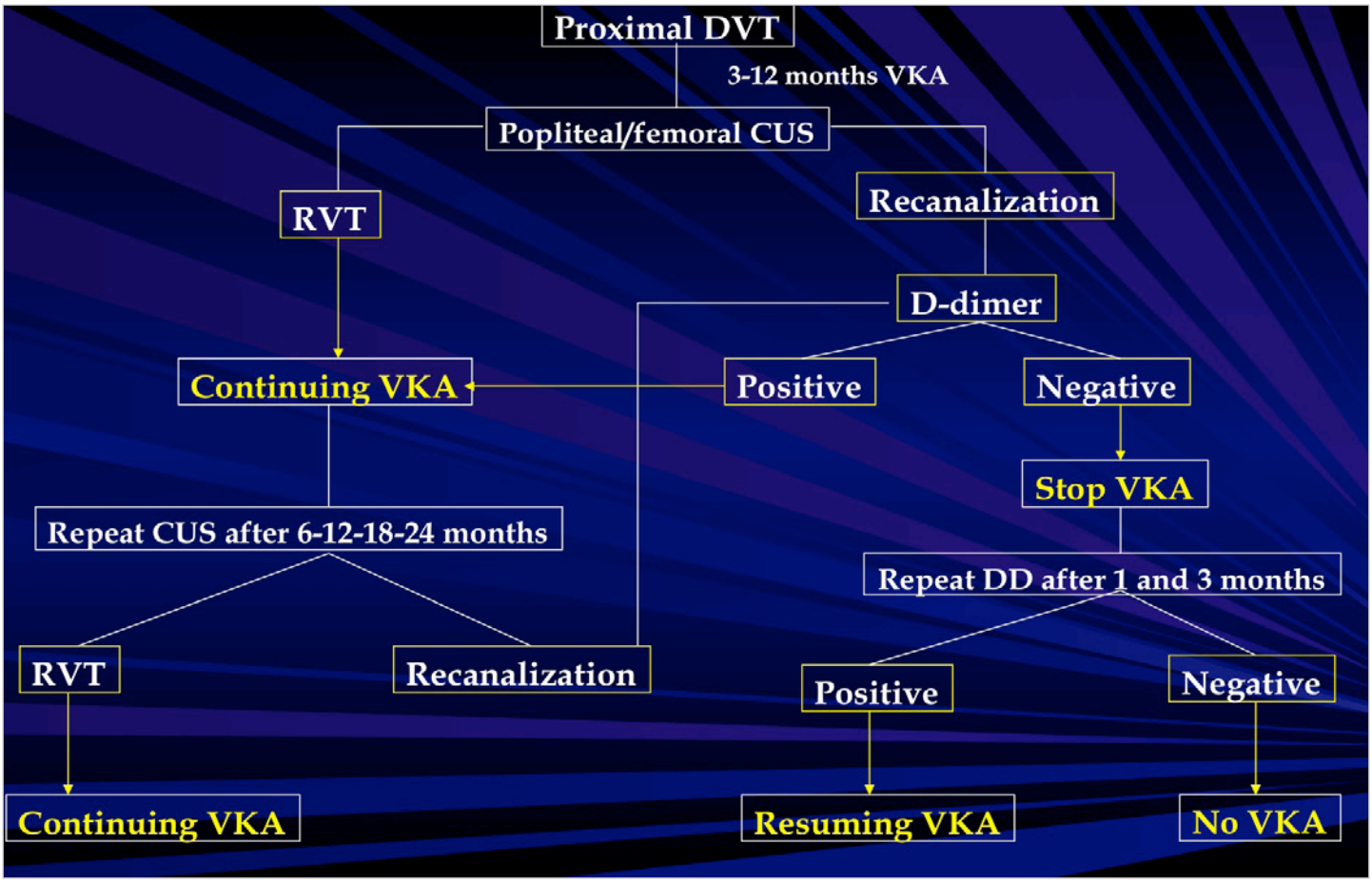
Paolo Prandoni

on behalf of the Morgagni Investigators

[19 Italian centers]

Residual vein thrombosis and serial D-dimer for the long-term management of patients with deep venous thrombosis

Thromb Res 2017

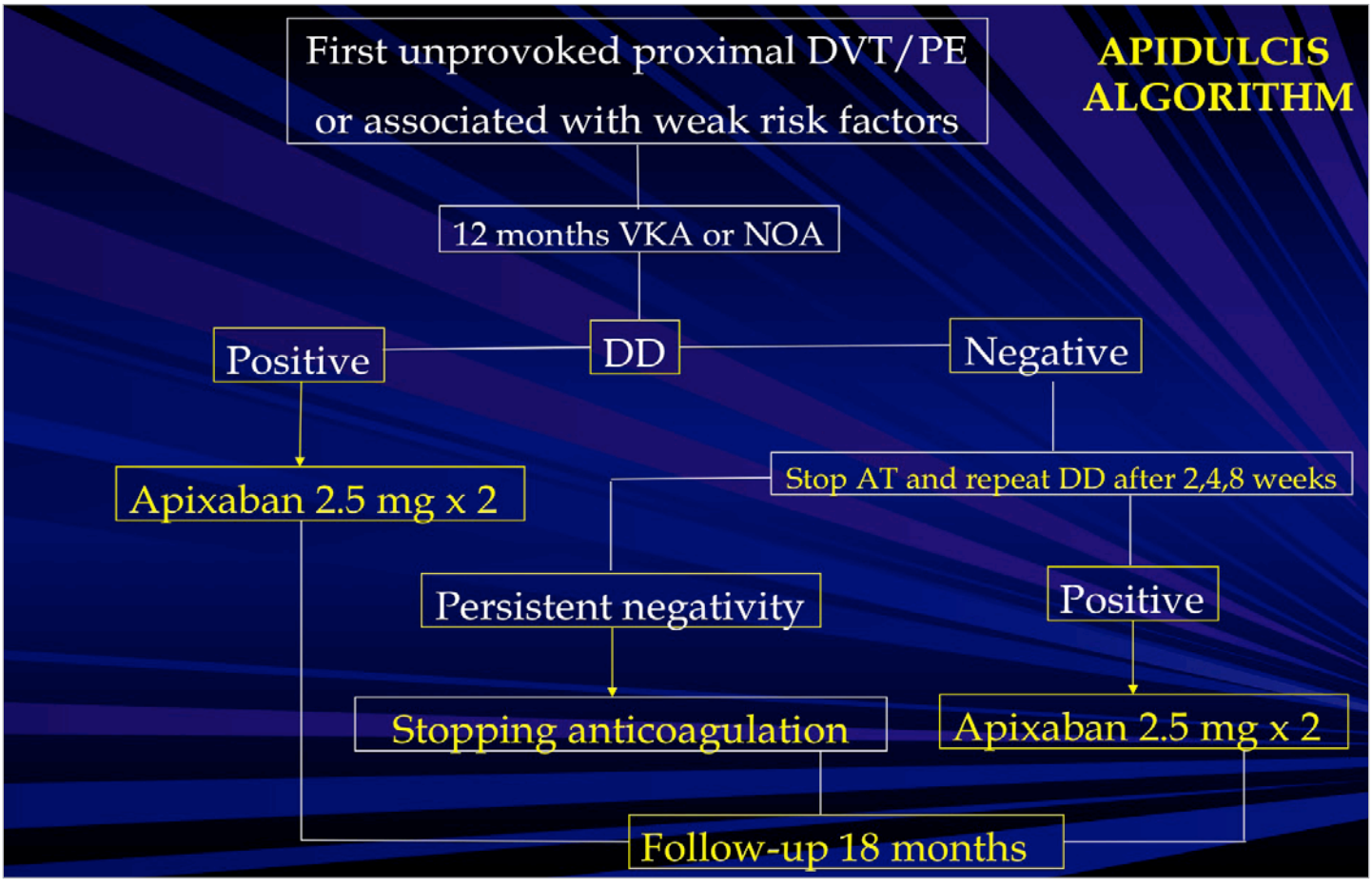


Main Study Results

Proportion of subjects meeting the Morgagni criteria among all eligible patients 65.0%

Annual incidence of recurrent VTE in this patients' group 3.6%

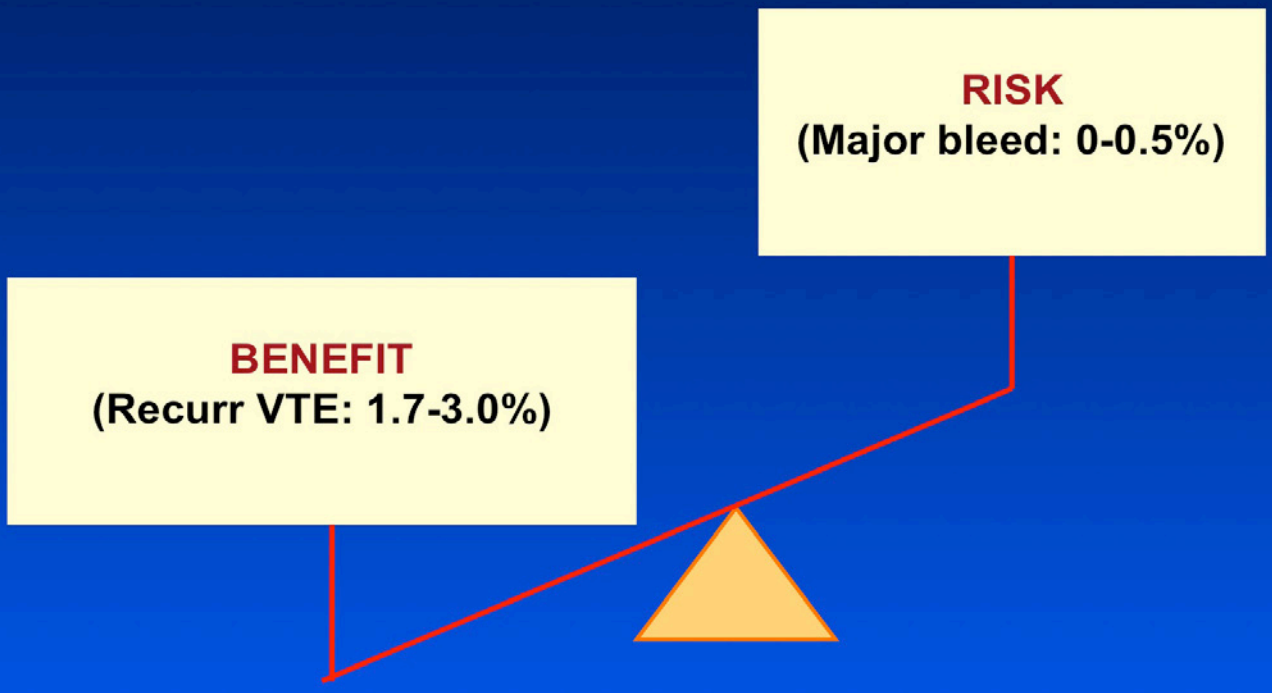
Apidulcis


APIDULCIS ALGORITHM
First unprovoked proximal DVT/PE or associated with weak risk factors
12 months VKA or NOA
DD
Positive
Negative
Apixaban 2.5 mg x 2
Stop AT and repeat DD after 2,4,8 weeks
Persistent negativity
Positive
Stopping anticoagulation
Apixaban 2.5 mg x 2
Follow-up 18 months

Expected benefit/risk of the Apidulcis study

Procedures	Expected annual rate of recurrent VTE	Expected annual rate of major bleeding
Apixaban 2.5 mg t.i.d	1.7%	0.5%
Stopping anticoagulation	3.0%	0%

Benefit/risk of the Apidulcis procedure



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(Prof. Paolo Prandoni facebook)

Grazie!