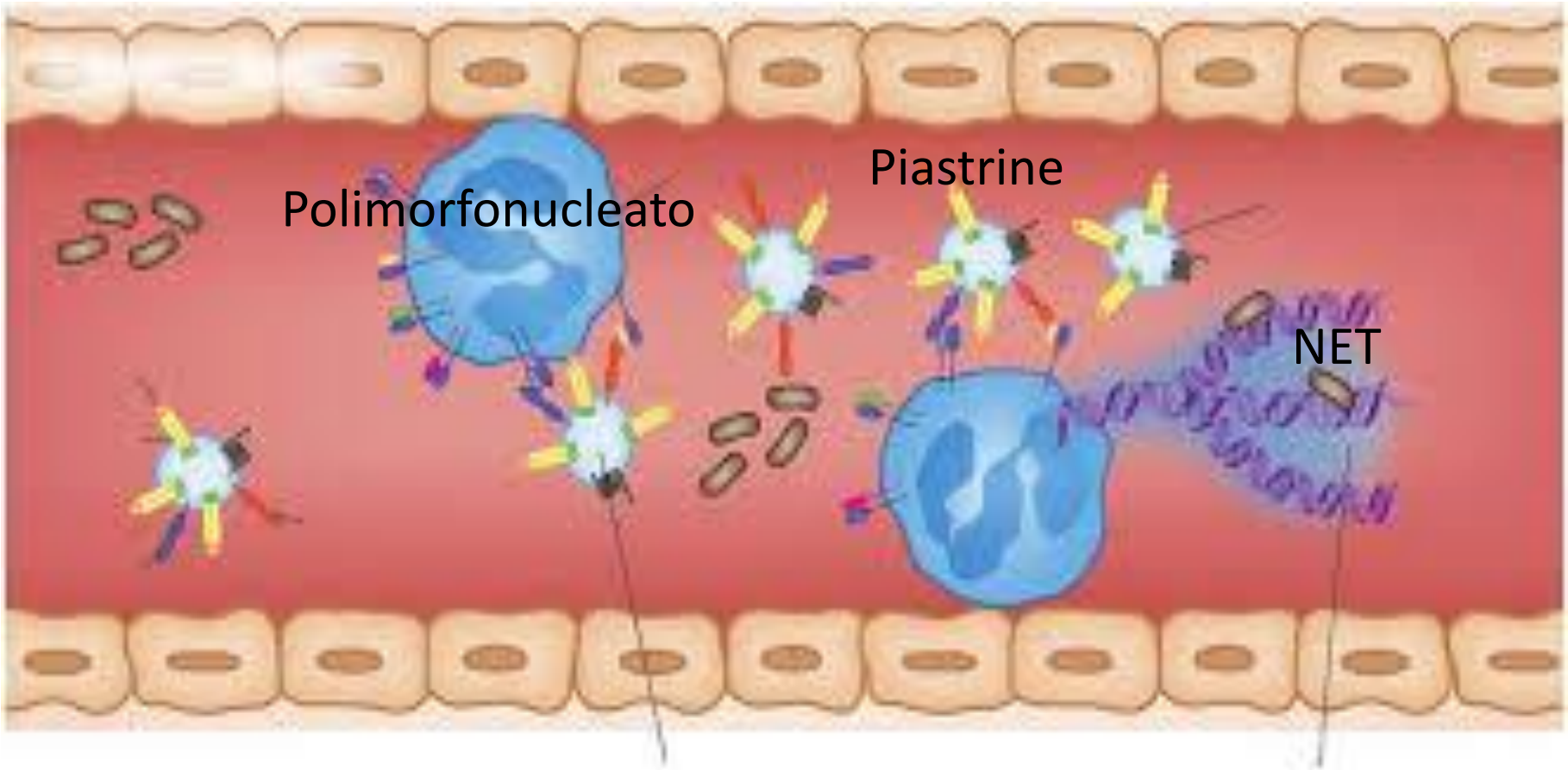
Indicazioni all'ASA dopo la TAO

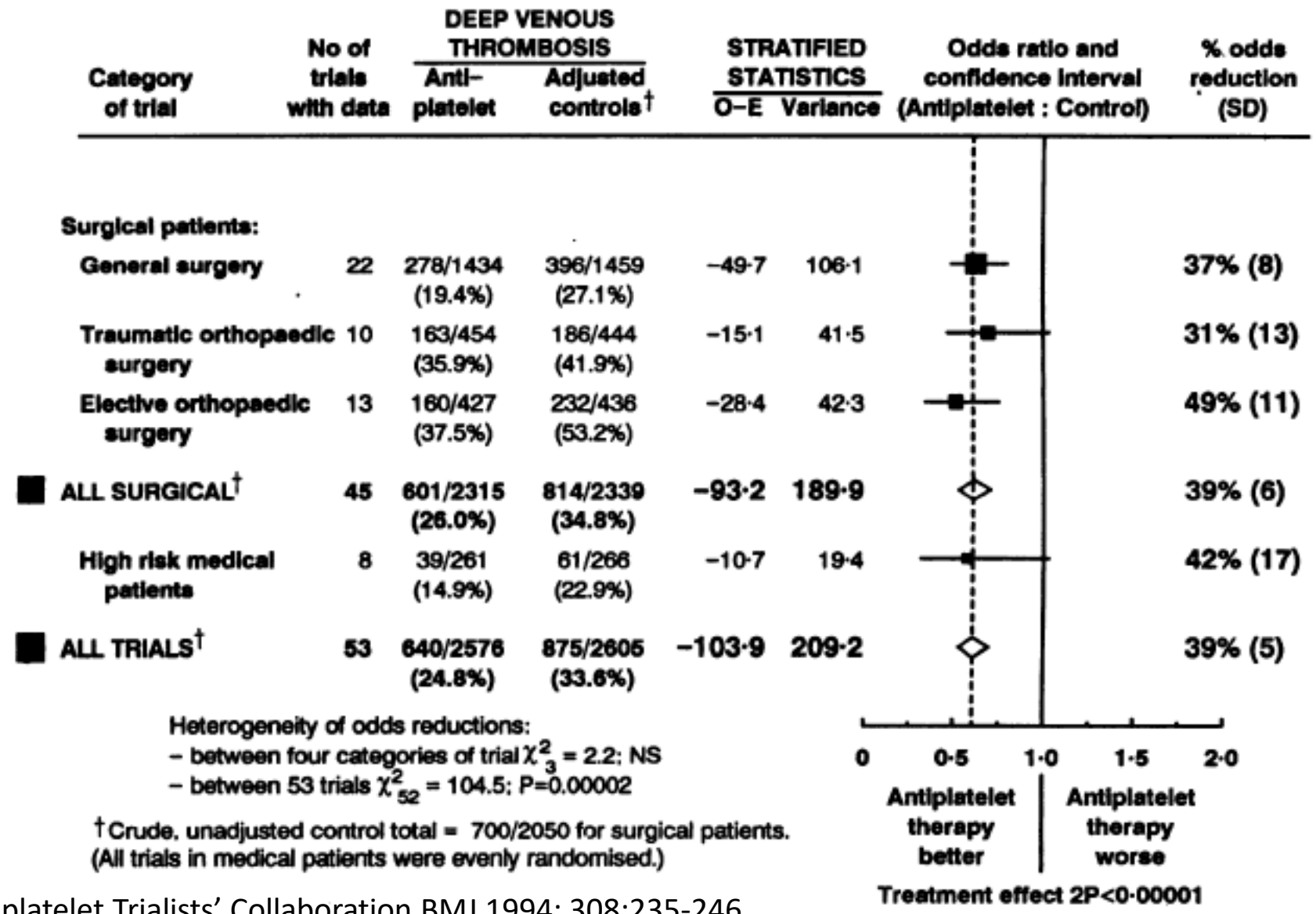
Cimminiello C. - Milano

Il razionale biologico per l'impiego di ASA nel TEV

Il ruolo delle piastrine nell'attivazione dei neutrofili



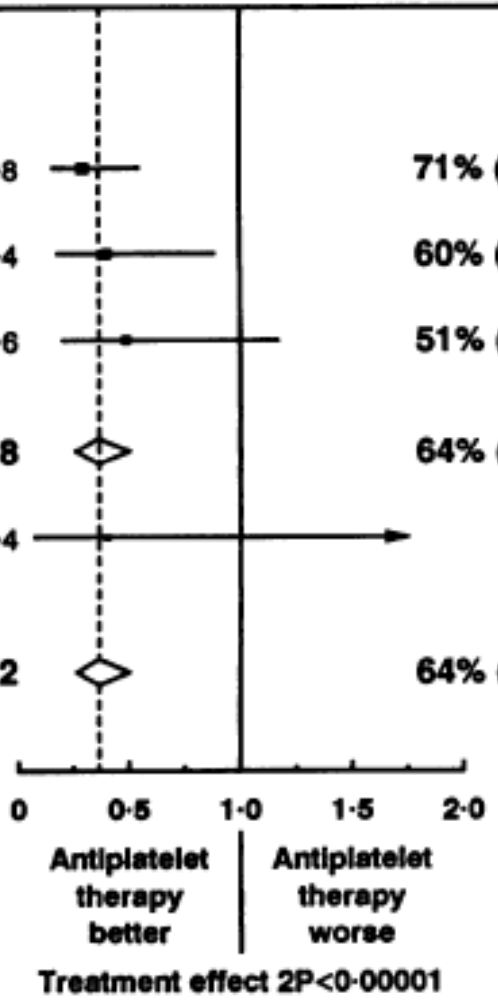
Indicazioni all'ASA dopo la TAO



Antiplatelet Trialists' Collaboration BMJ 1994; 308;235-246

Indicazioni all'ASA dopo la TAO

Category of trial	No of trials with data	PULMONARY EMBOLISM: Anti-platelet	PULMONARY EMBOLISM: Adjusted controls †	STRATIFIED STATISTICS: O–E	STRATIFIED STATISTICS: Variance	Odds ratio and confidence interval (Antiplatelet : Control)	% odds reduction (SD)
Surgical patients:							
General surgery	26	16/3408 (0.5%)	58/3419 (1.7%)	−20·7	16·8		71% (14)
Traumatic orthopaedic surgery	11	14/504 (2.8%)	34/494 (6.9%)	−9·5	10·4		60% (20)
Elective orthopaedic surgery	16	14/529 (2.6%)	29/537 (5.4%)	−6·2	8·6		51% (24)
■ **ALL SURGICAL†**	**53**	**44/4441 (1.0%)**	**121/4450 (2.7%)**	**−36·4**	**35·8**		**64% (10)**
High risk medical patients	9	3/275 (1.1%)	8/280 (2.9%)	−2·2	2·4		
■ **ALL TRIALS†**	**62**	**47/4716 (1.0%)**	**129/4730 (2.7%)**	**−38·5**	**38·2**		**64% (10)**



Heterogeneity of odds reductions:
– between four categories of trial $\chi^2_3 = 1.7$: NS
– between 62 trials $\chi^2_{37} = 37.5$: NS

†Crude, unadjusted control total = 109/3936 for surgical patients.
(All trials in medical patients were evenly randomised.)

Antiplatelet Trialists' Collaboration BMJ 1994; 308;235-246

Indicazioni all'ASA dopo la TAO

Pulmonary embolism

Only 32 trials planning to record symptomatic pulmonary embolism had recorded at least one non-fatal event, and among them antiplatelet therapy significantly reduced the risk of fatal or non-fatal pulmonary embolism (150/32 777 (0.46%) antiplatelet *v* 200/32 758 (0.61%) adjusted control; odds reduction 25% (10%); $P<0.01$). In both the treatment group and the control group, about half of those who had a pulmonary embolism survived to the end of the trial. Hence, the risk reduction was about one quarter in both cases (although with wide confidence intervals).

Antithrombotic Trialists' Collaboration BMJ 2002; 324;71-86

Indicazioni all'ASA dopo la TAO

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

2.1.1. In patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA), we recommend use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose vitamin K antagonist (VKA), aspirin (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C).

Long Term Treatment

Recommendations	Class [a]	Level [b]
▪ For patients with PE secondary to a transient (reversible) risk factor, treatment with a VKA is recommended for 3 months	I	A
▪ For patients with unprovoked PE, treatment with a VKA is recommended for at least 3 months	I	A
▪ Patients with a first episode of unprovoked PE and low bleeding risk, and in whom stable anticoagulation can be achieved, may be considered for long-term oral anticoagulation	IIb	B
▪ For patients with a second episode of unprovoked PE, long-term treatment is recommended	I	A
▪ In patients who receive long-term anticoagulant treatment, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals	I	C
▪ For patients with PE and cancer, LMWH should be considered for the first 3 to 6 months after this period, anticoagulant therapy with VKA or LMWH should be continued indefinitely, or until the cancer is considered cured	IIa I	B C
▪ In patients with PE, the dose of VKA should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) regardless of treatment duration	I	A

Indicazioni all'ASA dopo la TAO

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Treatment beyond Acute Period

- Surgery-associated DVT/PE: recommend 3 months. (1B)
- Non-surgical transient risk factor: recommend 3 months over 6 or more months. (1B)
- Unprovoked DVT/PE and low/intermediate risk for bleeding: suggest extended anticoagulation (2B). High bleeding risk: 3 months (1B).
- Cancer patient with DVT/PE: recommend/suggest extended therapy. LMWH rather than VKA (2C).

Kearon C et al. Chest 2012;141(2)(Suppl):e419S-e494S]

Definitions for 'VTE provoked by a transient risk factor', 'VTE provoked by a persistent risk factor' and 'unprovoked VTE' Guidance from SSC of ISTH

VTE PROVOKED BY A TRANSIENT RISK FACTOR

Minor (yet important) transient risk factor during the 2 months before diagnosis of VTE

A risk factor is considered 'minor' if it has been shown to be associated with:

(1) half the risk of recurrent VTE after stopping anticoagulant therapy (compared with if there was no transient risk factor), when the risk factor occurred up to 2 months before the VTE†; or

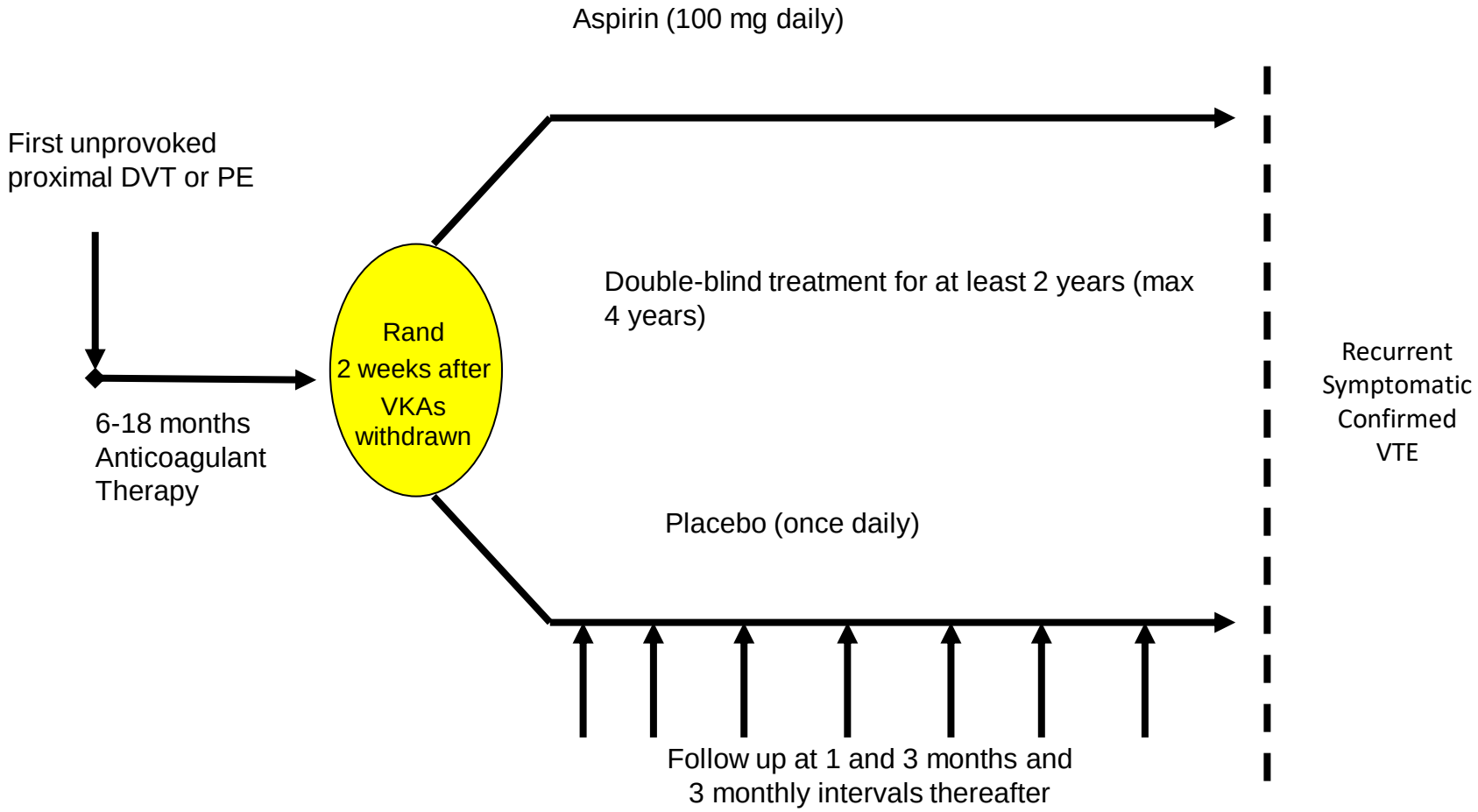
(2) a 3 to 10-fold increase in the risk of having a first VTE.

Examples:

- Surgery with general anesthesia for less than 30 min.
- Admission to hospital for less than 3 days with an acute illness.
- Estrogen therapy.
- Pregnancy or puerperium.
- Confined to bed out of hospital for at least 3 days with an acute illness.
- Leg injury associated with reduced mobility for at least 3 days.

Kearon C et al JTH 2016; 14:1480-83

WARFASA Trial Design



Becattini C et al; NEJM 2012; 366:1959-1967

WARFASA
Baseline Characteristics

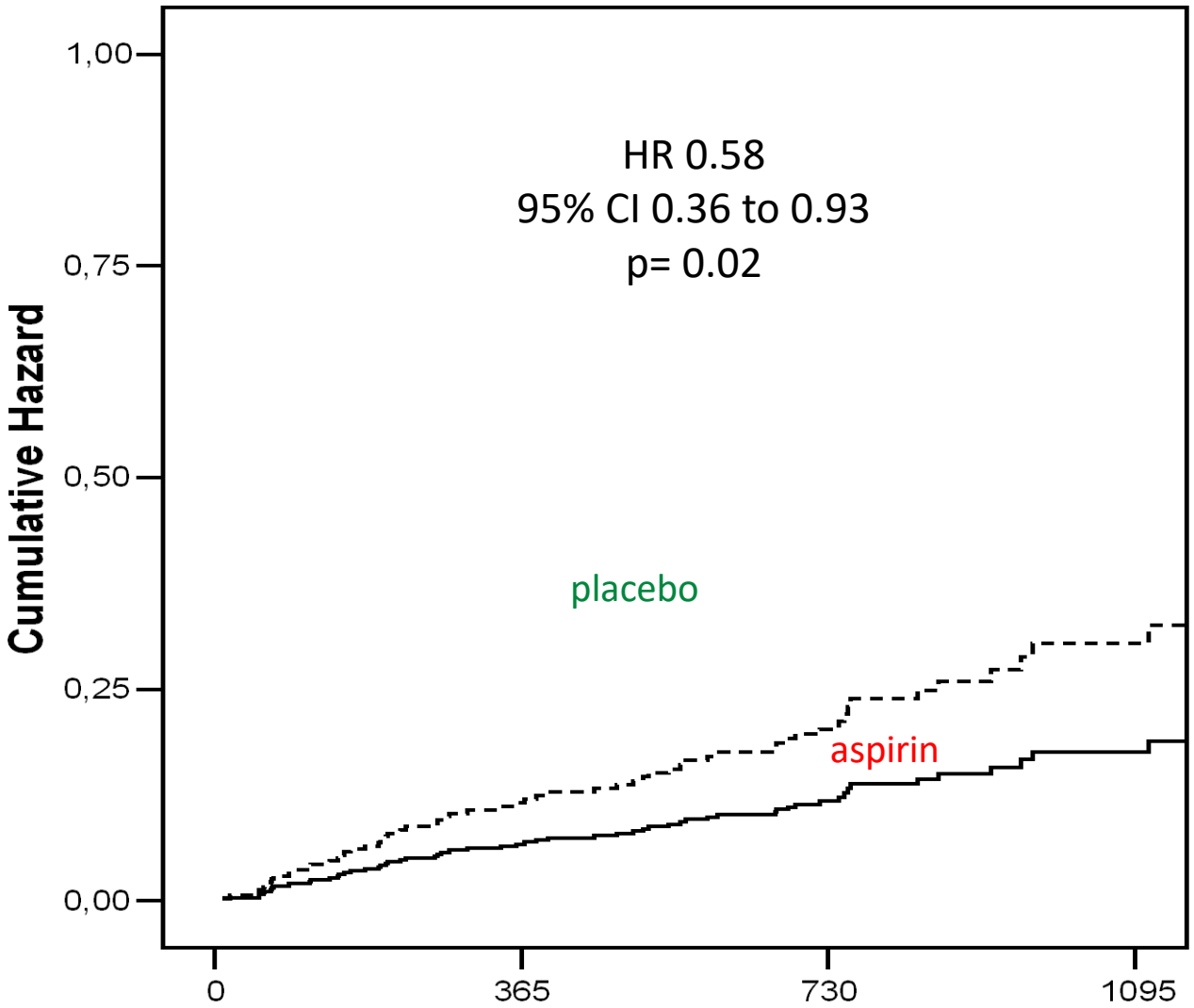
Characteristic	Placebo	Aspirin
	n=197	n=295
Age in years - mean (SD)	62.1±15.1	61.9±15.3
Body-mass index (kg/m^2)	27.5±3.8	27.1±4.0
Index event		
Deep-vein thrombosis only	130	122
Pulmonary embolism only	67	83
Months of initial AC before rand. (%)		
6	62	76
12	112	111
18	23	18

Becattini C et al; NEJM 2012; 366:1959-1967

Indicazioni all'ASA dopo la TAO

WARFASA

Primary Outcome - Recurrent VTE



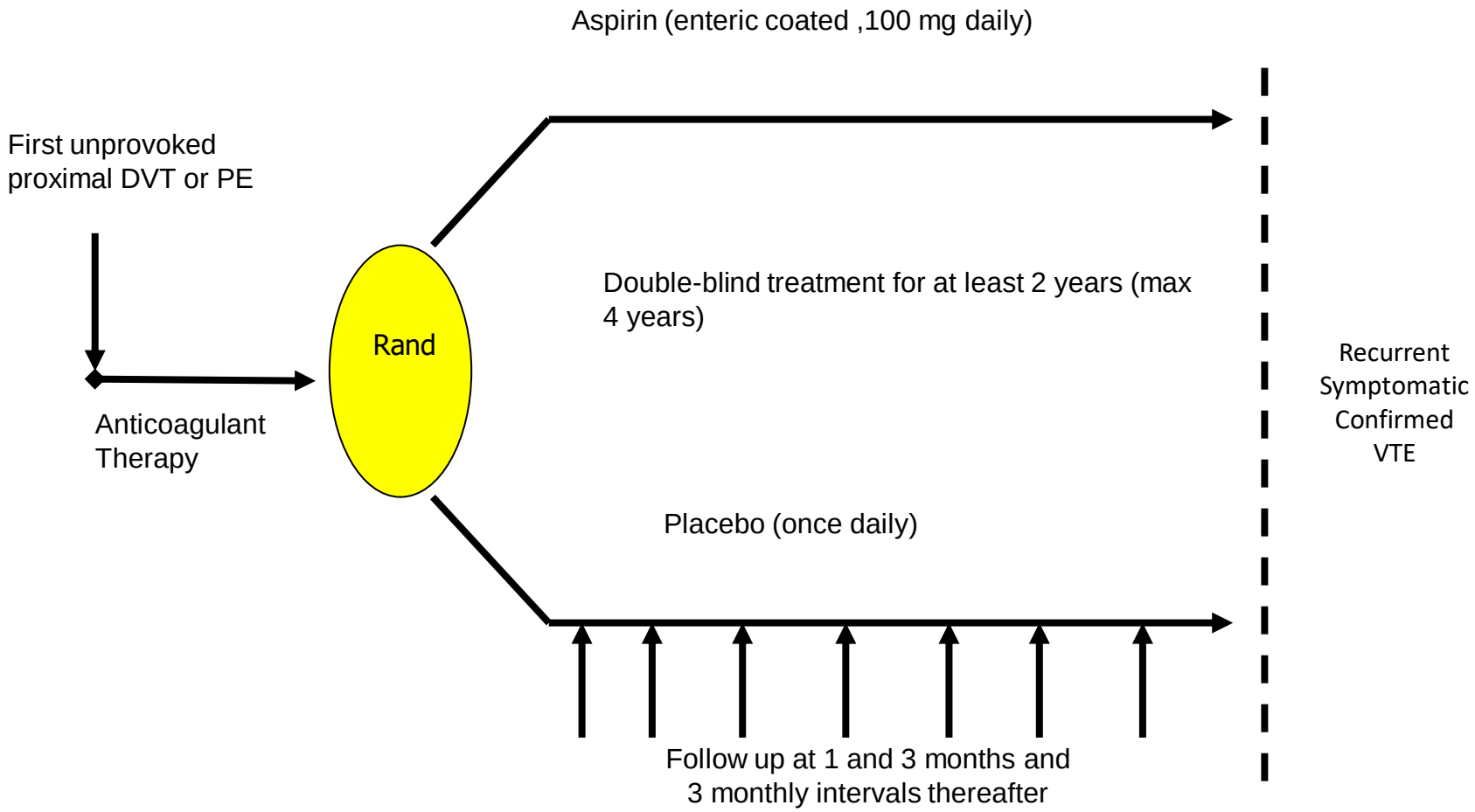
Becattini C et al; NEJM 2012; 366:1959-1967

Indicazioni all'ASA dopo la TAO

WARFASA
Secondary outcomes and Bleeding

Event	Aspirin (N = 205)	Placebo (N = 197)	Hazard Ratio (95% CI)	P Value
	number of events			
Recurrent VTE				
Total episodes	28	43	0.58 (0.36–0.93)	0.02
Pulmonary embolism	11	14	0.70 (0.32–1.54)	0.37
Fatal pulmonary embolism	1	1		
Deep-vein thrombosis	16	28	0.51 (0.27–0.94)	0.03
Episodes during treatment	23	39	0.55 (0.33–0.92)	0.02
Bleeding				
Major bleeding or clinically relevant nonmajor bleeding	4	4	0.98 (0.24–3.96)	0.97
Major bleeding	1	1		
Clinically relevant nonmajor bleeding	3	3		
Death	6	5	1.04 (0.32–3.42)	0.95
Recurrent VTE or death	33	47	0.62 (0.40–0.97)	0.04
Arterial event	8†	5‡	1.43 (0.47–4.37)	0.53
Recurrent VTE or arterial event	36	48	0.67 (0.43–1.03)	0.06

ASPIRE Trial Design



Brighton TA, et al. N Engl J Med. 2012;367:1979-87

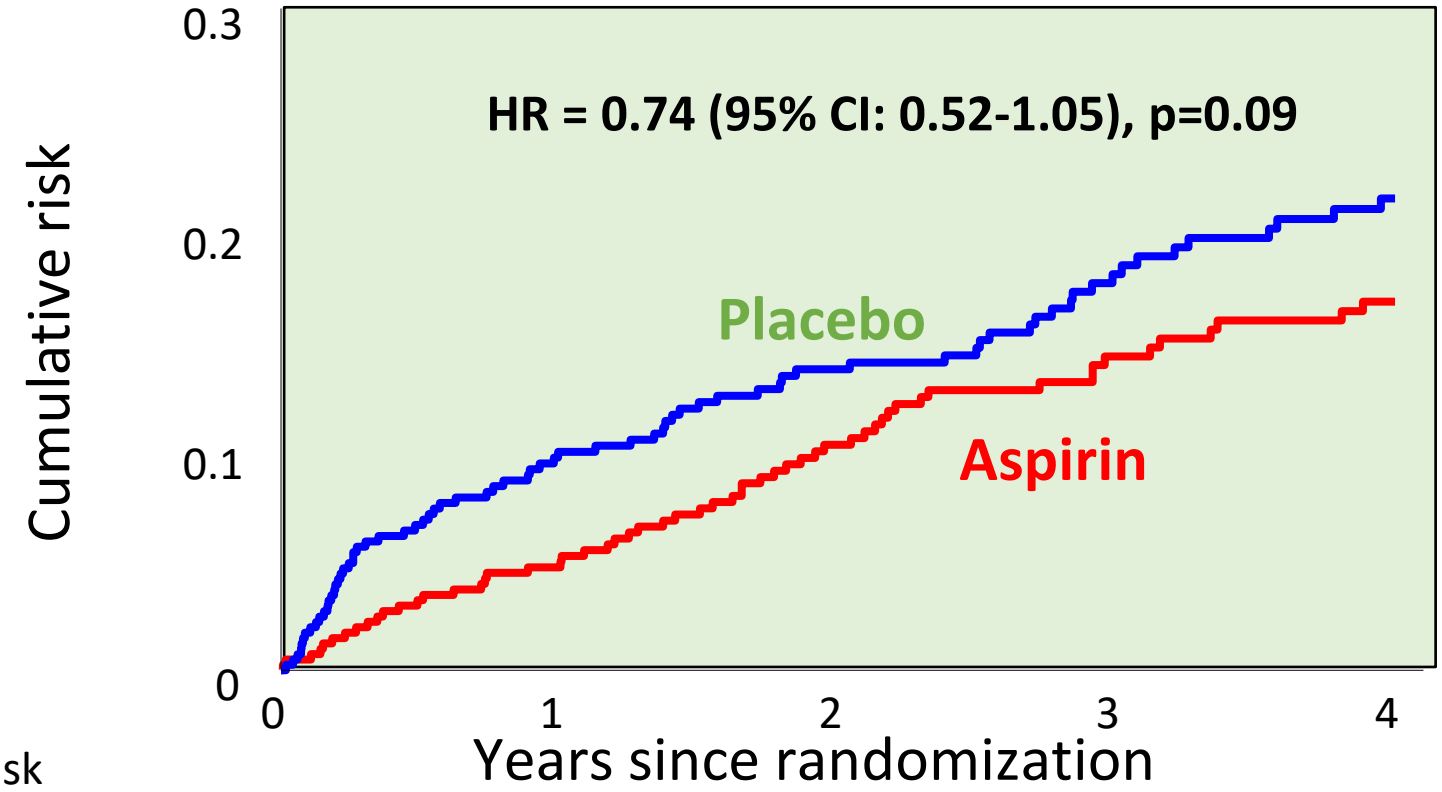
ASPIRE
Baseline Characteristics

Characteristic	Placebo	Aspirin
	n=411	n=411
Age in years - mean (SD)	54 (15.8)	55 (16.0)
Male (%)	54	55
Body-mass index (kg/m^2) (%)		
<30	66	61
≥30	34	39
Index event (%)*		
Deep-vein thrombosis only	56	57
Pulmonary embolism only	29	27
Both	14	14
Months of initial AC before rand. (%)		
<3	1	1
3–6	24	28
6–12	65	63
>12	10	8

* 6 patients (1%) in each group did not meet eligibility criteria but were included in an intention-to-treat analysis.

ASPIRE

Primary Outcome - Recurrent VTE



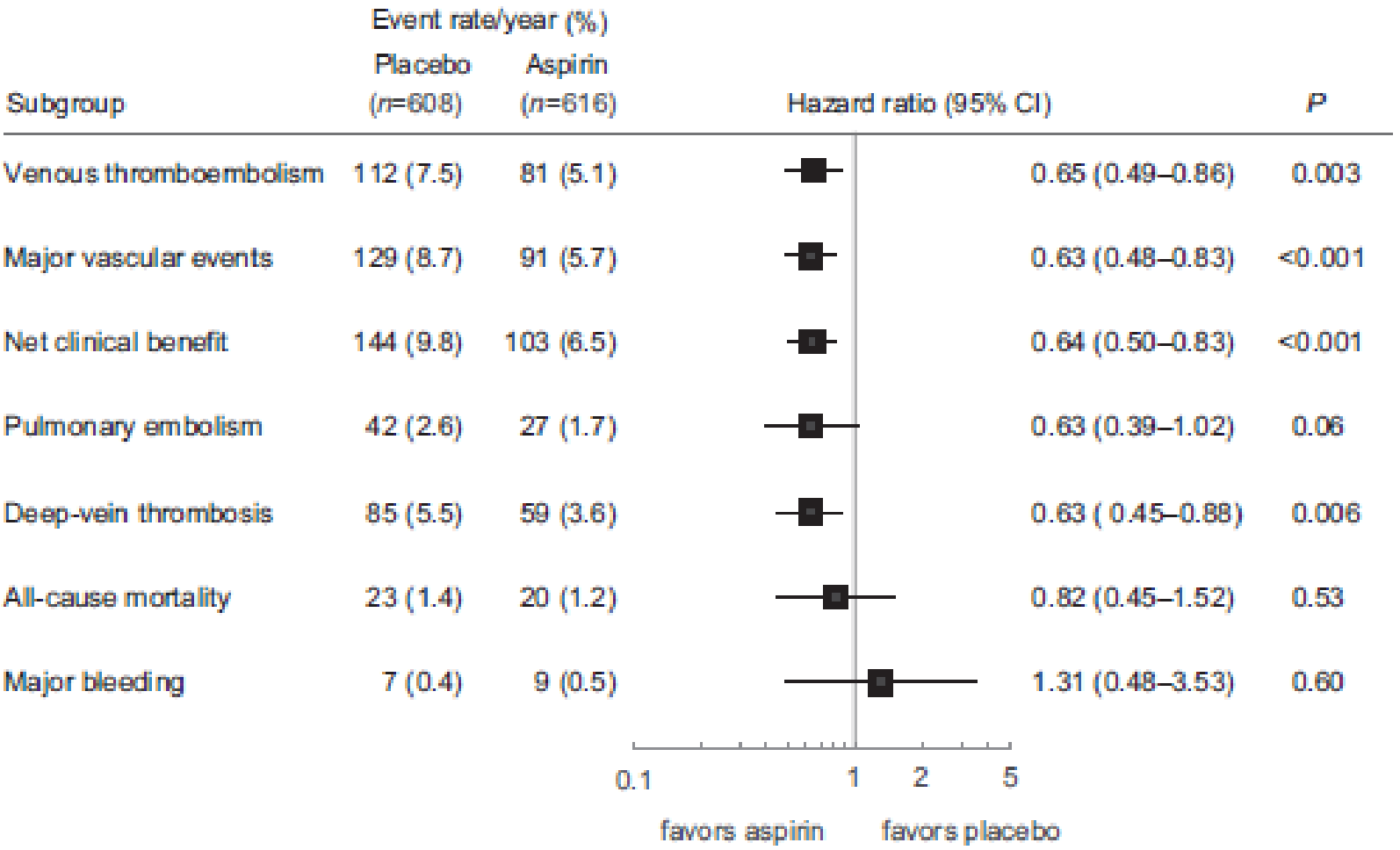
No. at risk					
Placebo	411	341	282	205	135
Aspirin	411	369	299	217	151

Brighton TA, et al. N Engl J Med. 2012;367:1979-87

ASPIRE Secondary Outcomes

Outcome	Placebo (n=411)		Aspirin (N=411)		Hazard Ratio (95% CI)	P value
	N	% p.a.	N	% p.a.		
Myocardial infarction	6		2			
Stroke	5		4			
Cardiovascular death	8		4			
Major Vascular event	88	8.0	62	5.2	0.66 (0.48–0.92)	0.01
Major bleeding	6		8			
Other clinically relevant bleeding	2		6			
Clinically relevant bleeding	8	0.6	14	1.1	1.73 (0.72–4.11)	0.22
Death from any cause	18		16			
Net Clinical Benefit	99	9.0	71	6.0	0.67 (0.49–0.91)	0.01

INSPIRE: meta-analysis ASPIRE & WARFASA



Simes J, et al.Circulation 2014;130:1062-71

Indicazioni all'ASA dopo la TAO

	Active	Control	Design	Tx Duration	Patients	Recurrent VTE (%)		Major-bleeding %	
						A	C	A	C
EINSTEIN Ext	Rivaroxaban	Placebo	Superiority	6–12 months	1196	1.3	7.1	0.7	0
AMPLIFY Ext	Apixaban	Placebo	Superiority	12 months	2486	1.7	8.8	0.1	0.5
RESONATE	Dabigatran	Placebo	Superiority	6 months	1343	0.4	5.6	0.3	0
ASPIRE	Aspirin	Placebo	Superiority	48 months	822	4.8	6.5	0.1	0.5
WARFASA	Aspirin	Placebo	Superiority	≥ 24 months	402	6.6	11.2	1.0	1.1

Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis

	DVT	PE	Non-fatal PE	Fatal PE	Mortality	CRNMB
Apixaban 2.5 mg	**0.11 (0.05 to 0.26)**	NA	0.53 (0.12 to 1.25)	0.28 (0.06 to 1.35)	0.49 (0.20 to 1.21)	1.30 (0.72 to 2.33)
Apixaban 5 mg	**0.15 (0.07 to 0.32)**	NA	**0.27 (0.09 to 0.82)**	0.44 (0.11 to 1.69)	**0.29 (0.10 to 0.87)**	**1.82 (1.05 to 3.15)**
Aspirin	0.77 (0.55 to 1.08)	0.77 (0.37 to 1.59)	0.65 (0.41 to 1.03)	0.98 (0.14 to 6.92)	0.95 (0.53 to 1.70)	1.70 (0.55 to 5.22)
Dabigatran	**0.08 (0.02 to 0.30)**	NA	**0.15 (0.03 to 0.69)**	0.35 (0.01 to 23.91)	0.26 (0.04 to 1.66)	NA
Idraparinux	0.29 (0.08 to 1.02)	**0.26 (0.07 to 0.92)**	**0.10 (0.01 to 0.73)**	2.10 (0.19 to 22.90)	2.34 (0.72 to 7.58)	
Rivaroxaban	**0.16 (0.06 to 0.41)**	NA	**0.15 (0.03 to 0.67)**	0.99 (0.06 to 15.70)	0.49 (0.04 to 5.37)	NA
Vitamin K antagonists	**0.06 (0.01 to 0.25)**	0.18 (0.02 to 1.43)	**0.09 (0.02 to 0.43)**	0.35 (0.01 to 8.54)	0.30 (0.05 to 1.82)	**4.53 (2.03 to 10.11)**

Values represent relative risks and 95% confidence intervals. Statistically significant results are in bold.

Abbreviations: CRNMB = clinically relevant non-major bleeding; DVT = deep vein thrombosis; NA = not applicable; PE = pulmonary

NA

Sobieraj N et al Thromb Res 2015

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Aspirin for Extended Treatment of VTE

***12. 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).

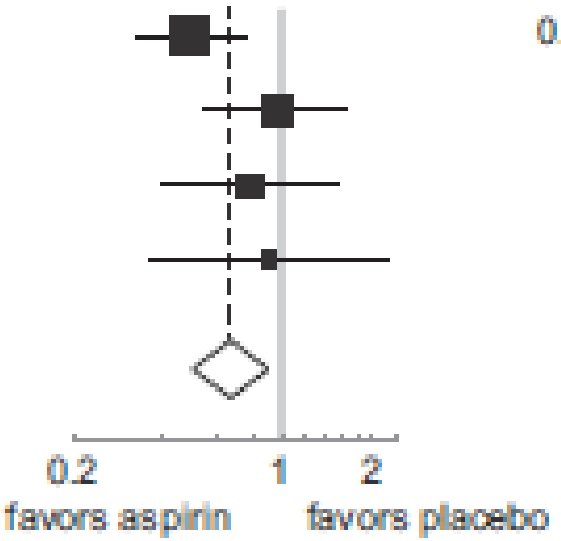
«…If a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience.
Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started. "

Kearon C et al CHEST 2016; 149:315-352

INSPIRE: meta-analysis ASPIRE & WARFASA

Effects of treatment on VTE in each year of follow-up

	Events (n/N)		Event rate (%)			*P* for
Year	Placebo	Aspirin	Placebo	Aspirin	HR (95% CI)	trend
1	60/608	31/616	11.0	5.4		0.31
2	25/489	26/531	2.7	2.6		
3	18/378	15/412	1.7	1.3		
4	9/240	9/259	1.0	0.9		
All	112/608	81/616	7.5	5.1		



Simes J, et al.Circulation 2014;130:1062-71

CONCLUSIONI

- I risultati degli studi WARFASA e ASPIRE confermano il ruolo dell'aspirina anche nel versante venoso

- Nella prevenzione secondaria prolungata del TEV ASA è meno efficace dei DOACs ma - forse - più sicuro sul versante emorragico

- Il basso costo e l'ampia disponibilità (anche in realtà meno evolute) fanno dell'ASA una risorsa interessante per questo tipo di prevenzione