Aspirin for the prevention of recurrent venous thromboembolism (VTE) after a first unprovoked event: results of the ASPIRE randomized controlled trial

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on behalf of the ASPIRE Investigators

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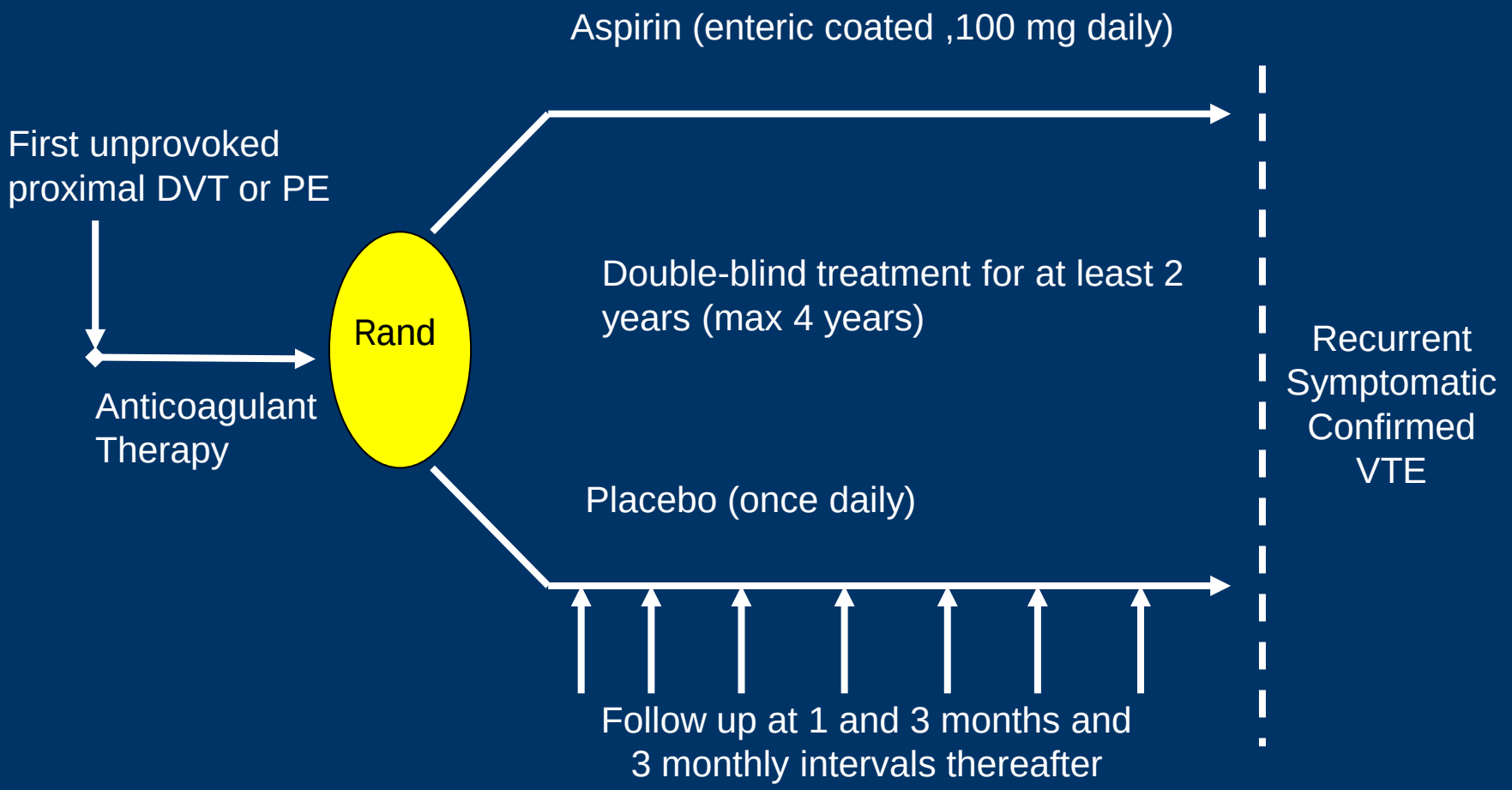
Background

- Patients with unprovoked VTE are at substantial risk of recurrent VTE after cessation of anticoagulation
- Long term anticoagulation (warfarin INR 2-3) is effective however
  - causes major (fatal) bleeding
  - inconvenient for patients (warfarin)
- Low dose aspirin prevents VTE
  - Arthroplasty – (46% RRR of PE in PEP Trial)
  - High-risk medical patients (~30% RRR)
  - Unprovoked VTE (Beccattini et al NEJM 2012)

ASPIRE Trial Design



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Eligibility

Inclusion

- Aged ≥ 18
- First unprovoked proximal DVT and/or PE
- Completion of initial anticoagulation
- Commencement of study medication recommended within 6 weeks (and as soon as possible) after cessation of initial anticoagulant therapy

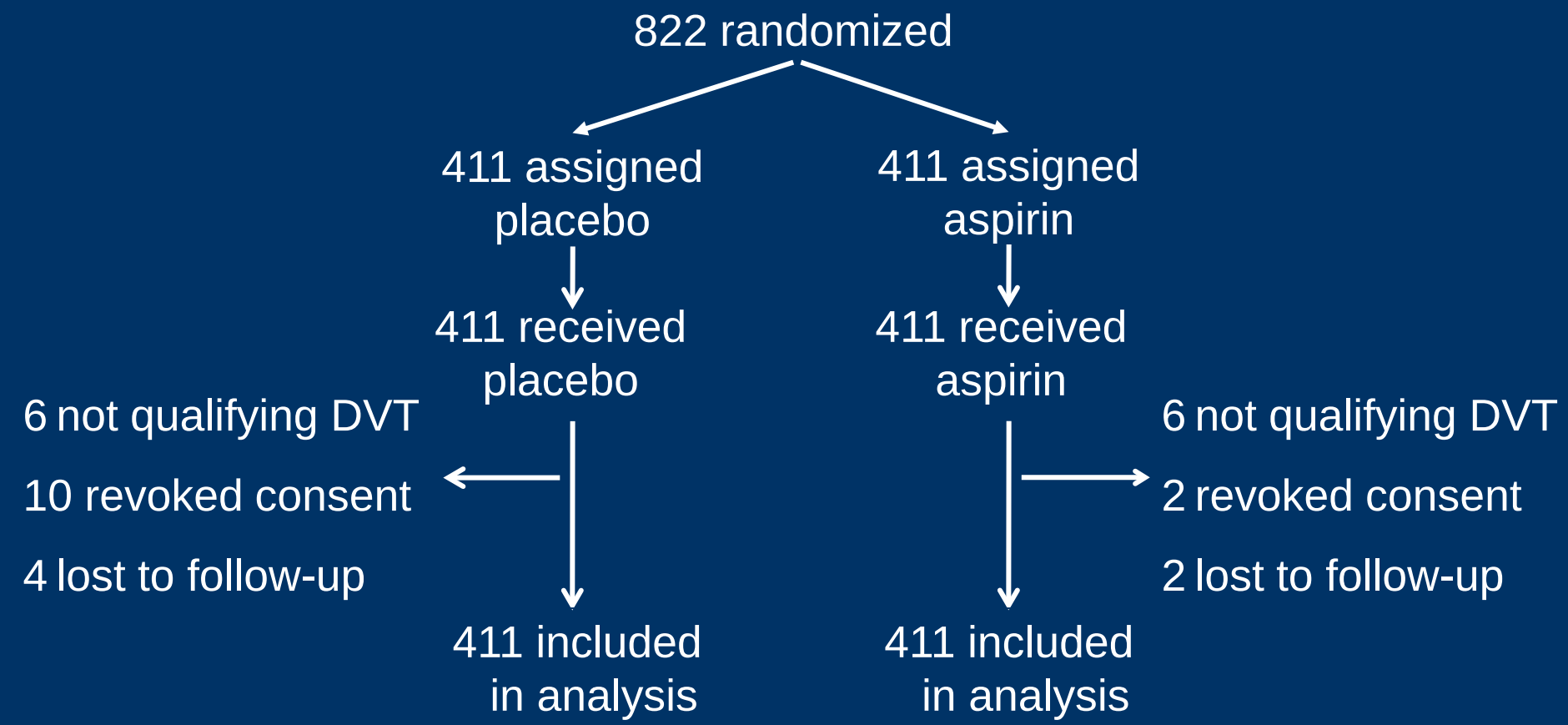
Exclusion

- Allergy, intolerance, or contraindication for aspirin
- Clear indication for aspirin, clopidogrel, or a conventional NSAID
- Indication for long-term anticoagulant therapy (e.g. prosthetic heart valve)
- Life expectancy <12 months
- Active bleeding or at high risk of bleeding
- Anticipated non-adherence to study medications
- Inability to attend follow up because of geographic inaccessibility
- Pregnant or lactating

Study Outcomes

- Primary Outcome
  - Recurrent VTE – composite of recurrent symptomatic objectively confirmed DVT, non-fatal PE or fatal PE
- Secondary Outcomes
  - Major vascular events – composite of recurrent VTE, MI, stroke, and CVS death
  - Net clinical benefit – composite of recurrent VTE, MI, stroke, major (fatal) bleeding and all cause mortality
- Bleeding - major and clinically relevant non-major
- Adjudication of all events blinded to treatment allocation and prior to primary analysis

Study Flow



First patient enrolled May 2003,
Last patient enrolled August 2011,
Follow-up completed March 2012

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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.*

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Primary Outcome

Outcome	Placebo (n=411)		Aspirin (n=411)		HR (95% CI)	P value
	N	% p.a.	N	% p.a.		
Recurrent VTE	**73**	**6.5**	**57**	**4.8**	**0.74 (0.52–1.05)**	**0.09**
DVT only	43	3.8	39	3.3	0.86 (0.56–1.33)	0.50
Distal	14		11			
Proximal	38		30			
Other site	2		3			
PE ± DVT †	30	2.7	18	1.5	0.57 (0.32–1.02)	0.06

† 1 fatal PE in each cohort

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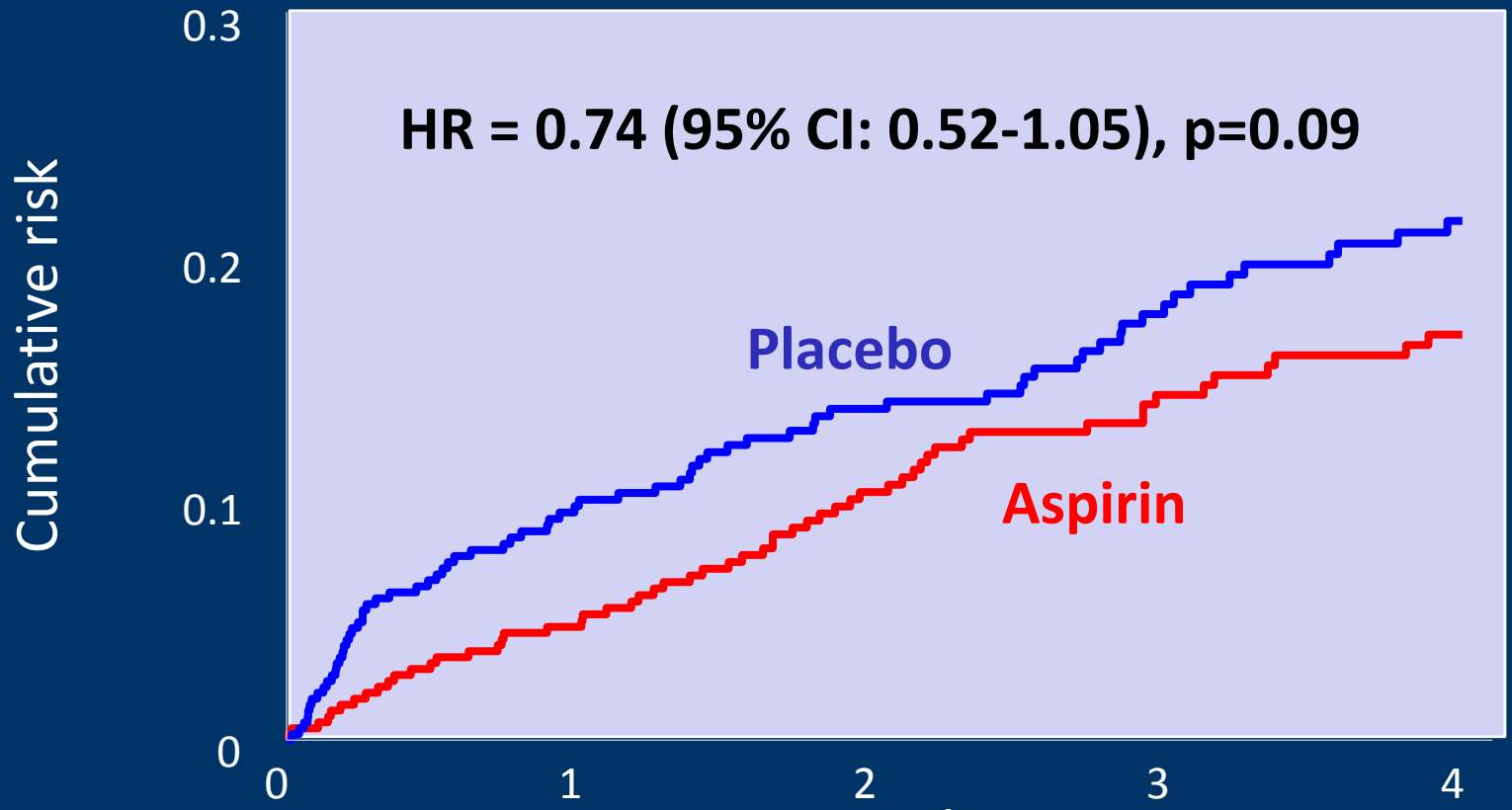
Primary Outcome - Recurrent VTE



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

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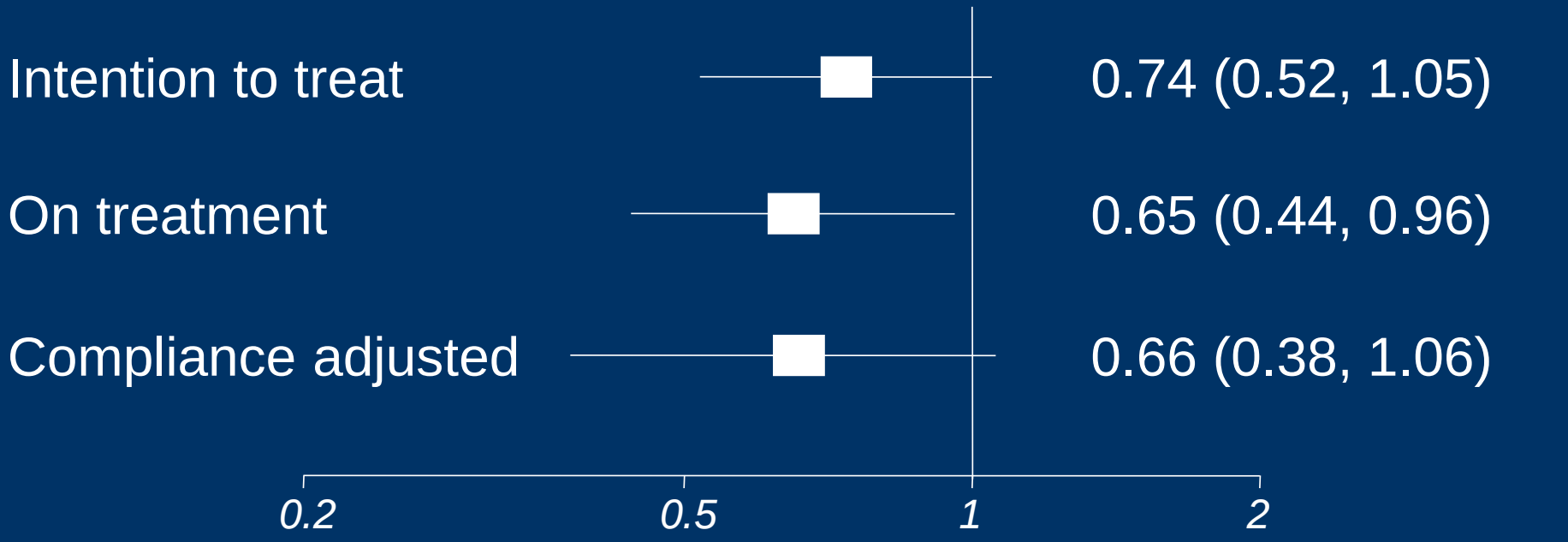
Aspire effect allowing for non-adherence to study medication



- ITT: analysis by randomised treatment
- On treatment: censoring at discontinuation of study meds
- Compliance adjusted: ITT effect adjusted for average compliance

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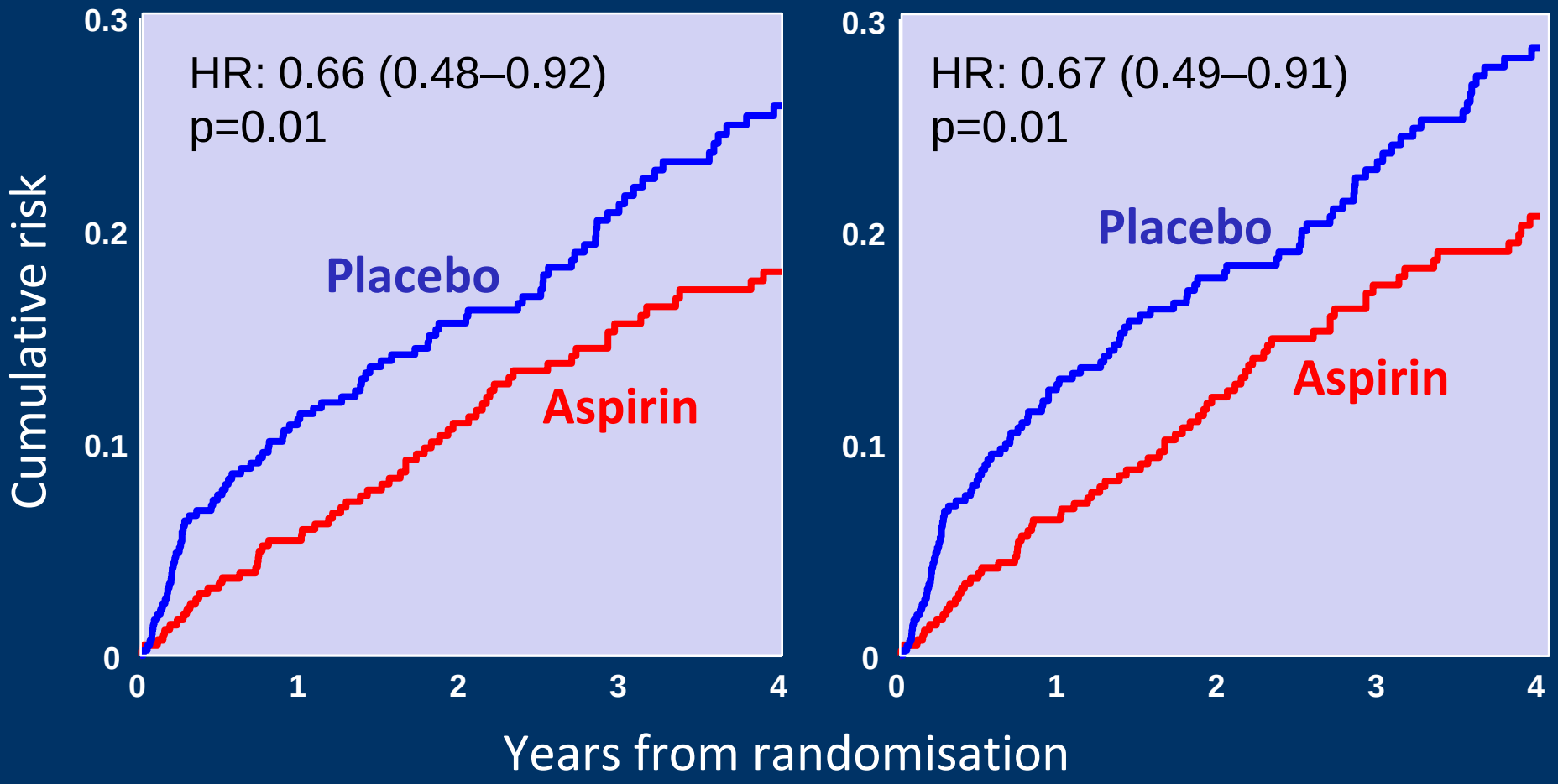
Secondary Outcomes

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

Major Vascular and Net Clinical Benefit



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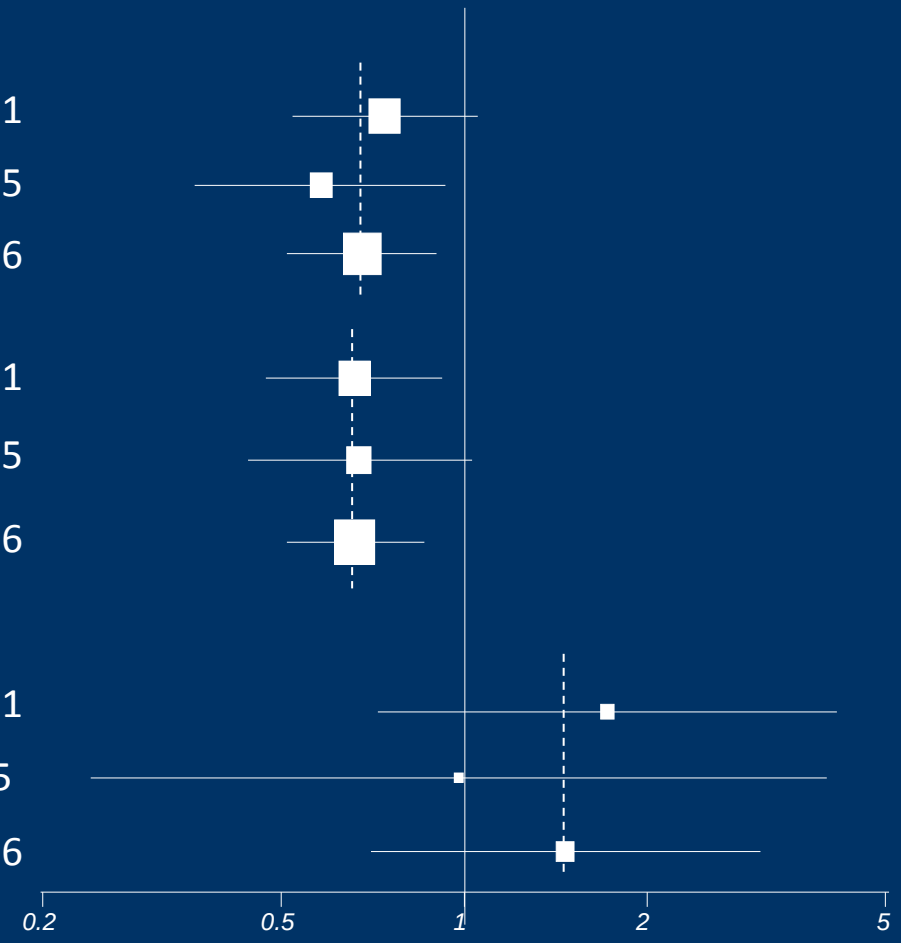
Meta-analysis ASPIRE & WARFASA

Outcome & study		Placebo events/*n*	Aspirin events/*n*	Hazard Ratio	*P*
VTE	ASPIRE	73/411	57/411	0.74	0.09
	WARFASA	43/197	28/205	0.58	0.02
	Pooled	116/608	85/616	0.68	0.007
Major vascular events	ASPIRE	88/411	62/411	0.66	0.01
	WARFASA	48/197	36/205	0.67	0.06
	Pooled	136/608	98/616	0.66	0.002
Clinically relevant bleeds	ASPIRE	8/411	14/411	1.72	0.22
	WARFASA	4/197	4/205	0.98	0.97
	Pooled	12/608	18/616	1.47	0.31



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Conclusions

- ASPIRE study, in conjunction with other data, provides consistent and convincing evidence that low-dose aspirin prevents recurrent VTE and major vascular events in patents with first unprovoked VTE
- Aspirin is an attractive option for patients who do not wish to continue anticoagulation beyond their initial therapy
  - Simple therapy
  - Widely available
  - Low cost
  - Well tolerated with low risks bleeding
  - Benefits not solely restricted to prevention of recurrent VTE

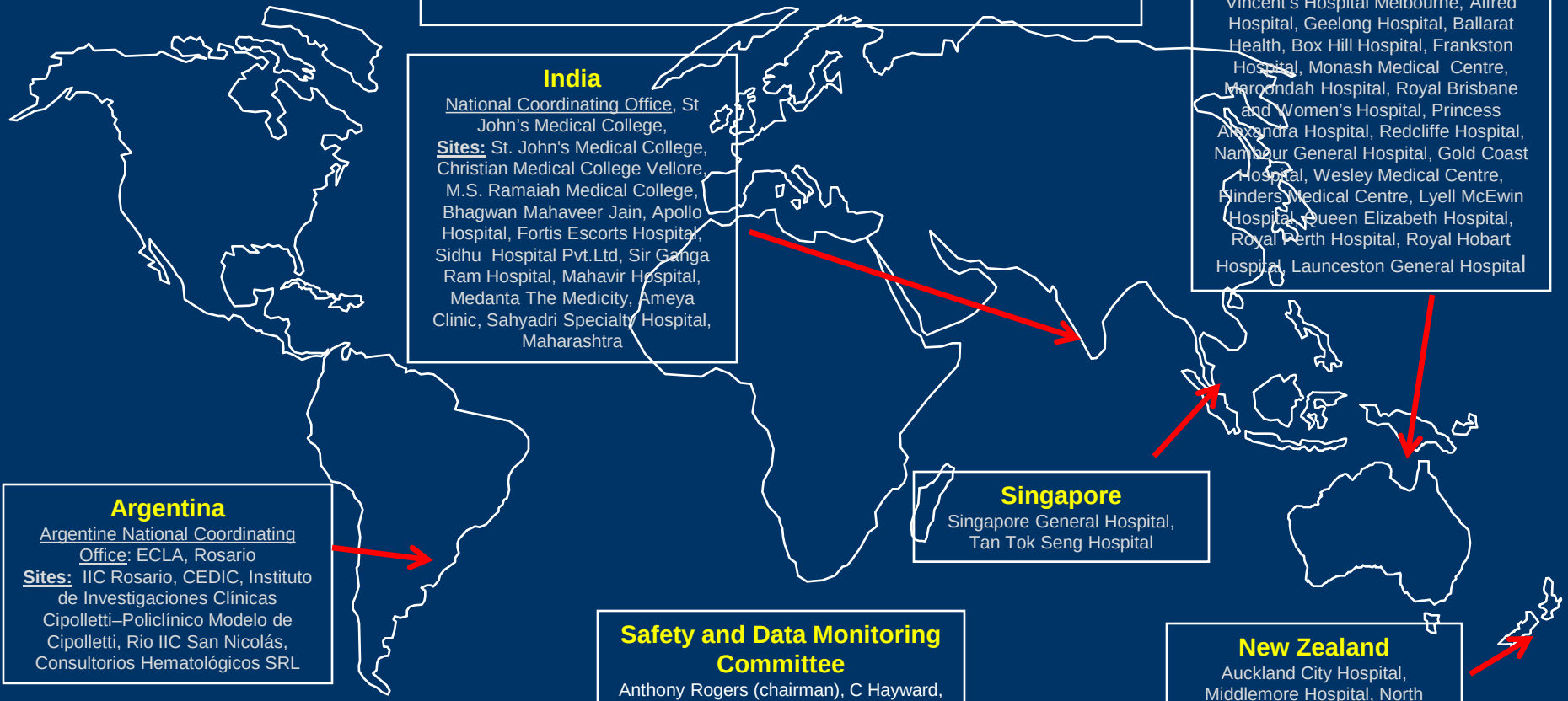
Acknowledgements

Management Committee

T Brighton (Co-PI), J Eikelboom (Co-PI), W Hague, A Kirby, R Mister, A Gallus, P Ockelford, R Baker, H Gibbs, P Coughlin, D Xavier, R Diaz, G Agnelli, J Simes (study chairman)

Support

National Health and Medical Research Council, Australia (project grant) Health Research Council, New Zealand (project grant) Australasian Society of Thrombosis and Haemostasis (grant) Bayer Pharma AG (aspirin and placebo)



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Australia

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