U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Thrombosis
ESC Working Group

Anticoagulação oral nos dias de hoje, na doença das artérias coronárias e para além dela

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Coordenador do Centro de Investigação

CENTRO HOSPITALAR LEIRIA

Serviço de Cardiologia
Centro Hospitalar de Leiria

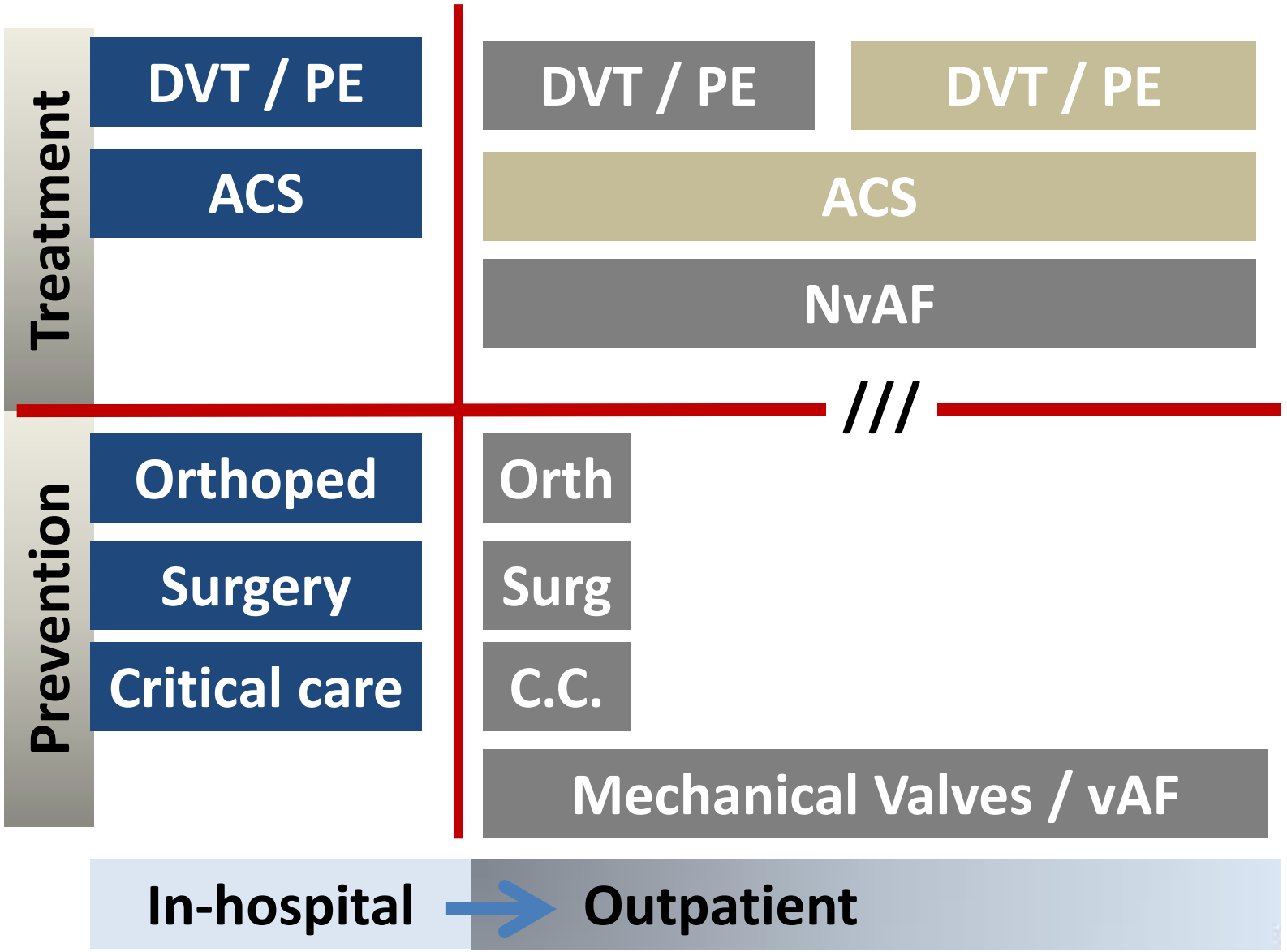
Conflitos de interesse relacionados com a presente comunicação

João Morais

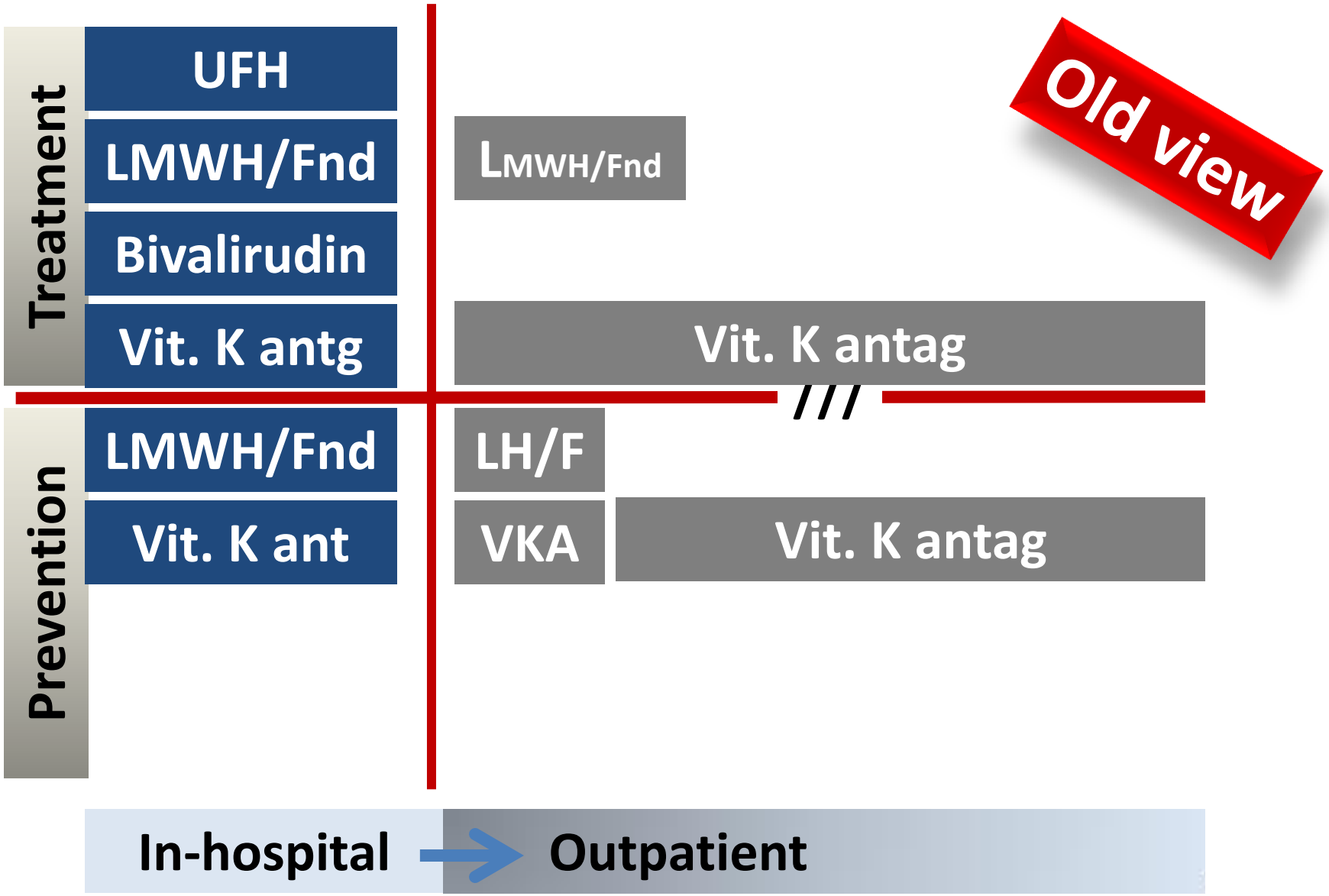
Atividades de consultadoria nacionais e internacionais, palestras em simposia promovidos pela IF

Bayer Healthcare; BMS; Boehringer Ingelheim; Daiichi Sankyo; Pfizer

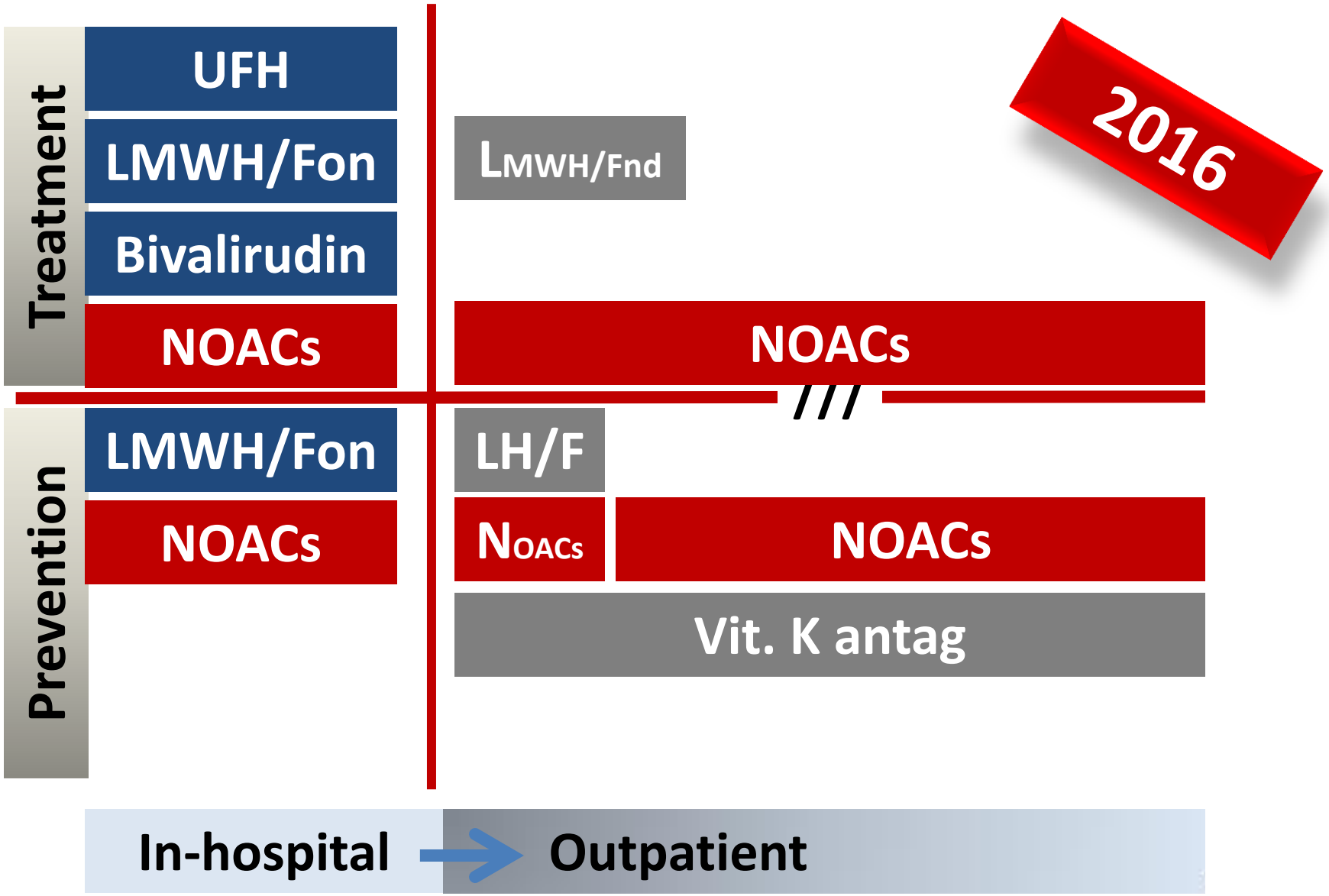
Anticoagulation in the clinical setting



Anticoagulation in the clinical setting



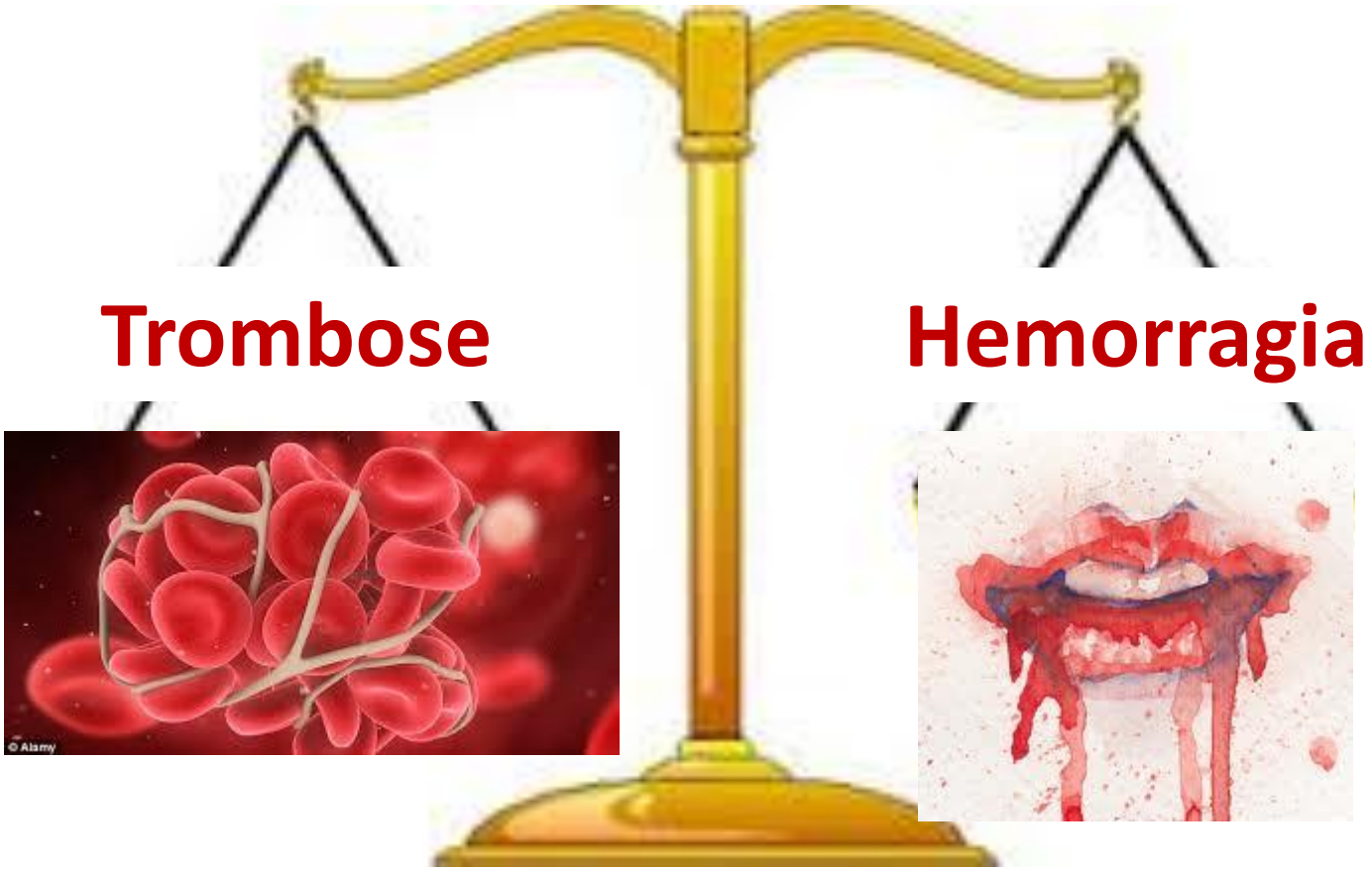
Anticoagulation in the clinical setting



Dark side of the Moon

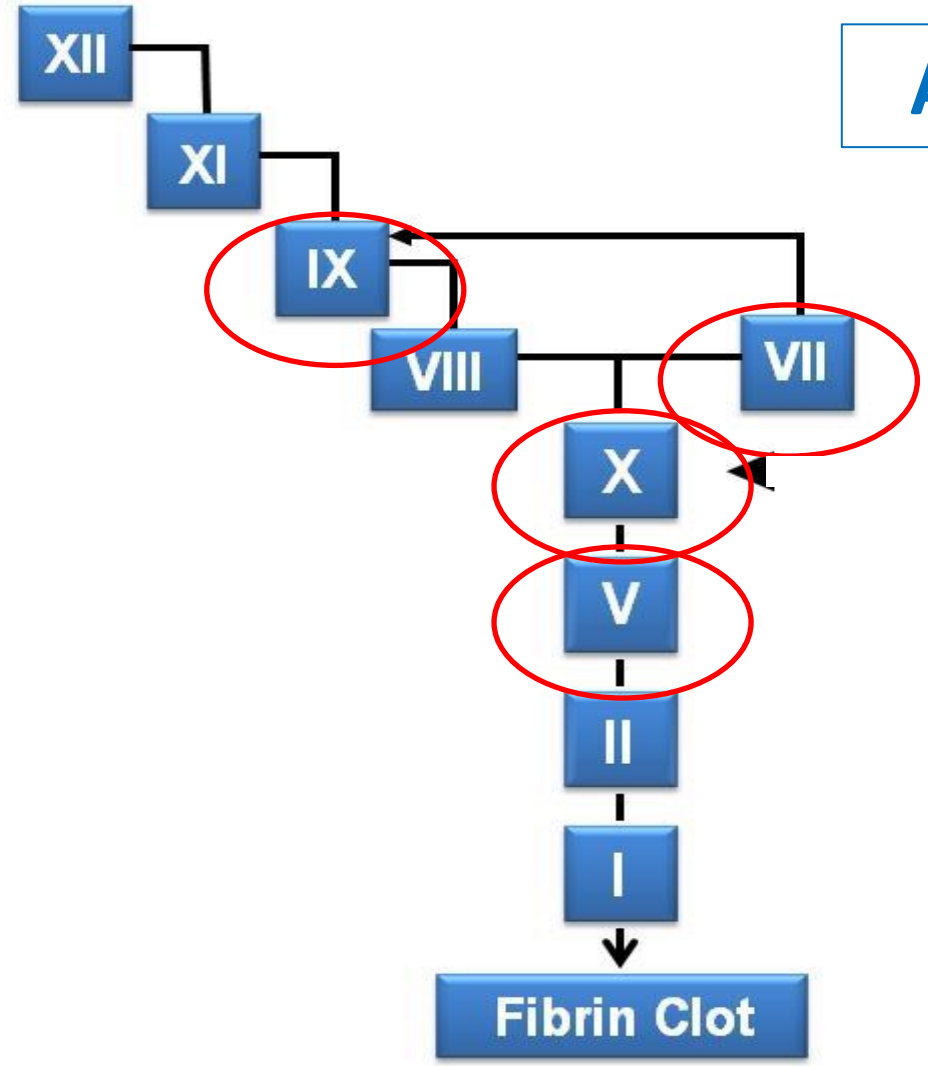
Bleeding

O balanço entre a eficácia e o risco



Conceito “net clinical benefit”

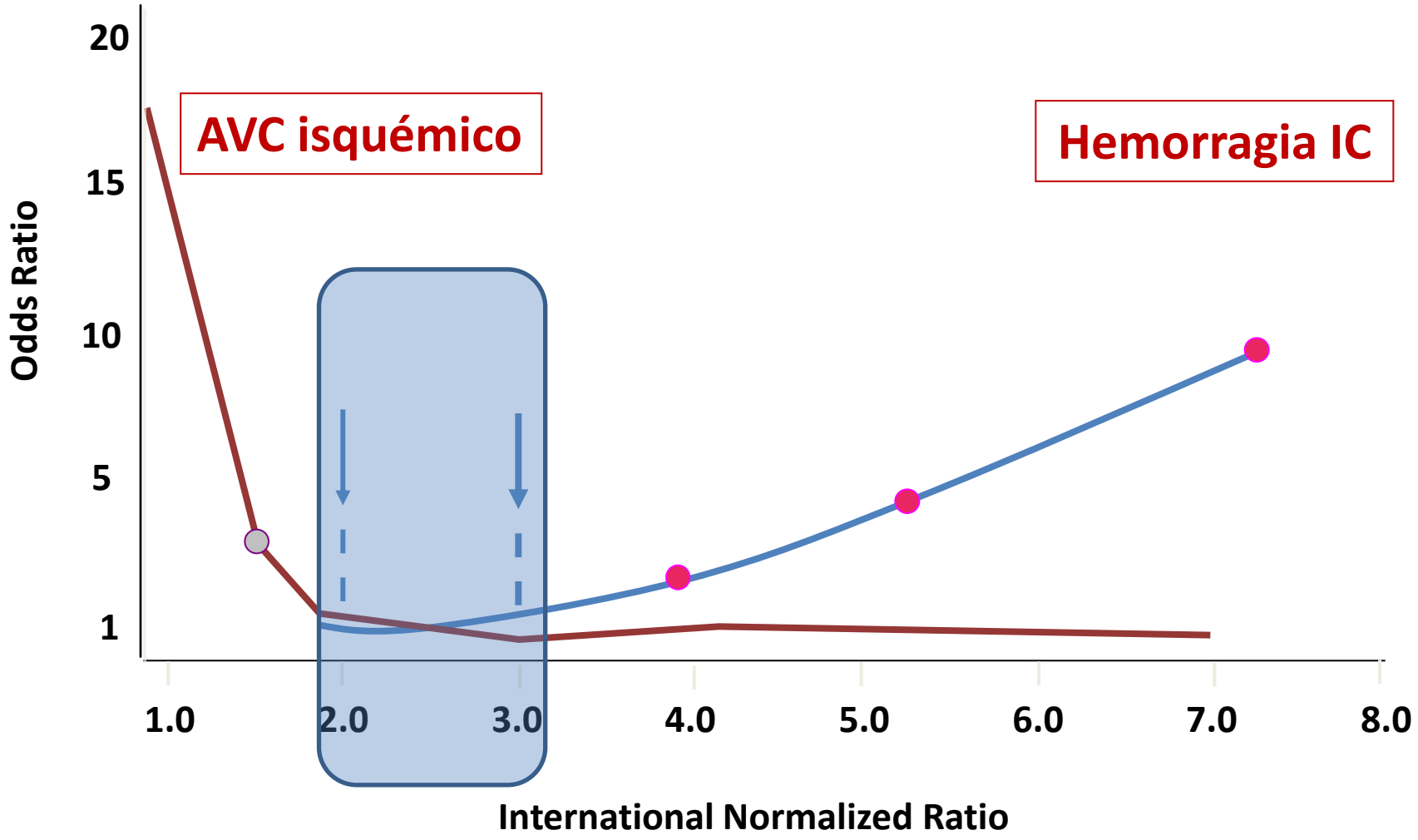
Os alvos para a hipocoagulação



Anti-Vitamina K

Varfarina
Acenocumarol

Anti-VK e risco de hemorragia

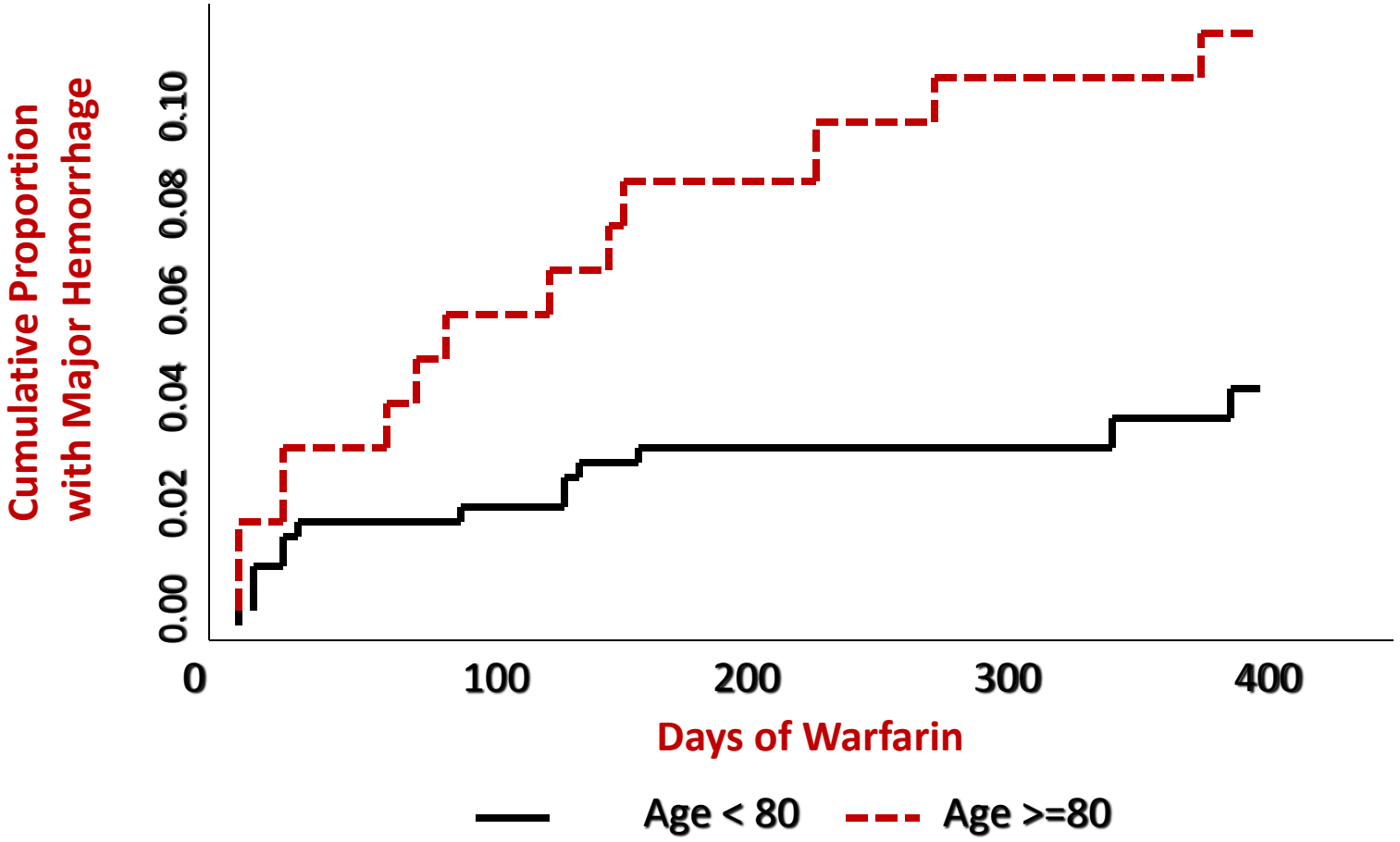


Fang MC, et al. Ann Intern Med 2004; 141:745.
Hylek EM, et al. N Engl J Med 1996; 335:540.

Anti-VK e risco de hemorragia

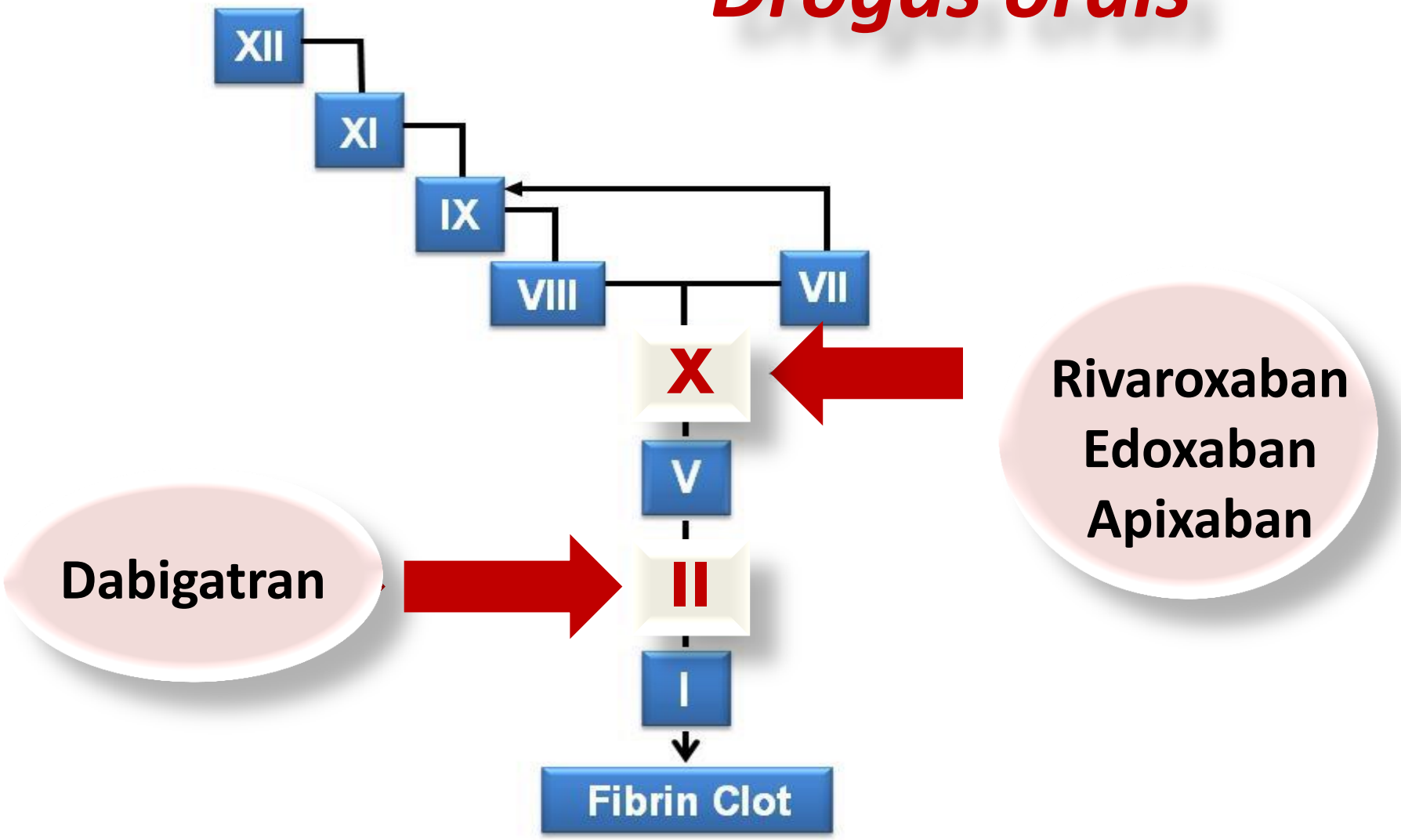
Bleeding Type	Head Bleed	Major Non-Head Bleed
1st Month Warfarin	0.92% (annualized)	1.2% (annualized)
Subsequent Warfarin	0.46% per year	0.61% per year

Cumulative Incidence of Major Bleeding in the First Year Among Patients Newly Starting Warfarin by Age



Os alvos para a hipocoagulação

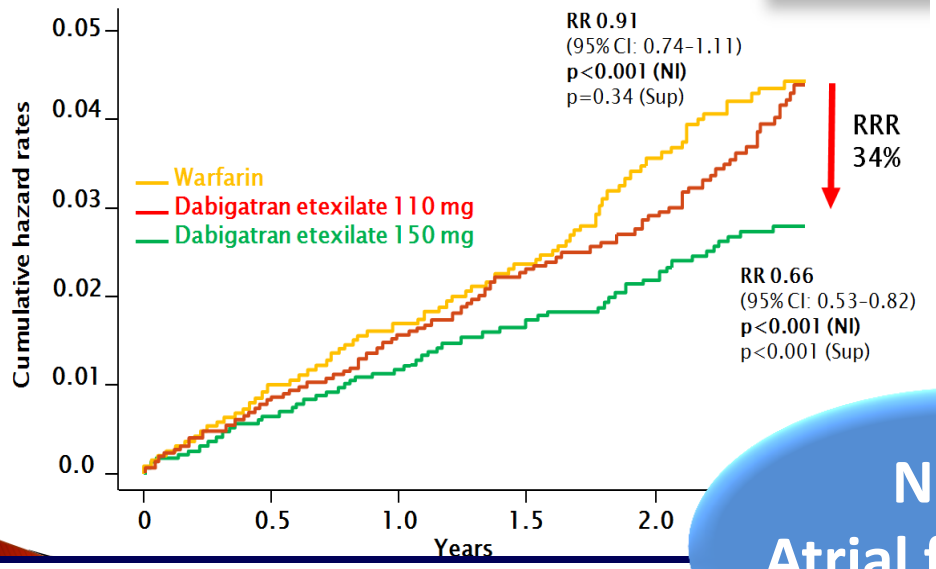
Drogas orais



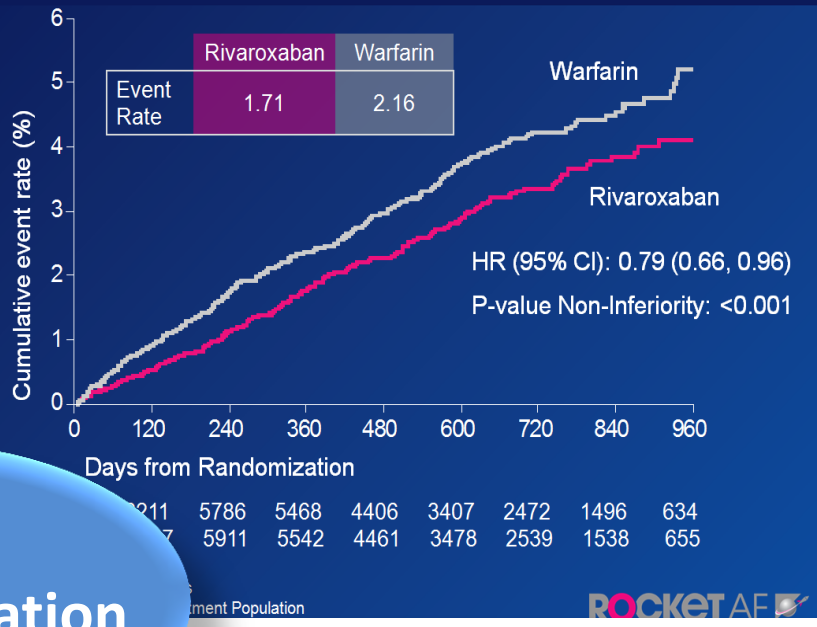
Non Vitamin K **O**ral **A**nti**C**oagulant**s**

NOACs
Atrial fibrillation
phase III trials

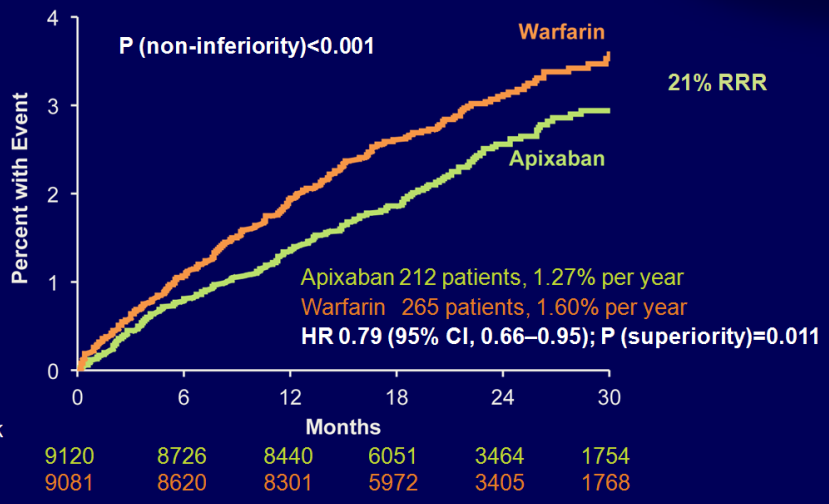
RE-LY – 1y endpoint Stroke



Primary Efficacy Outcome
Stroke and non-CNS Embolism



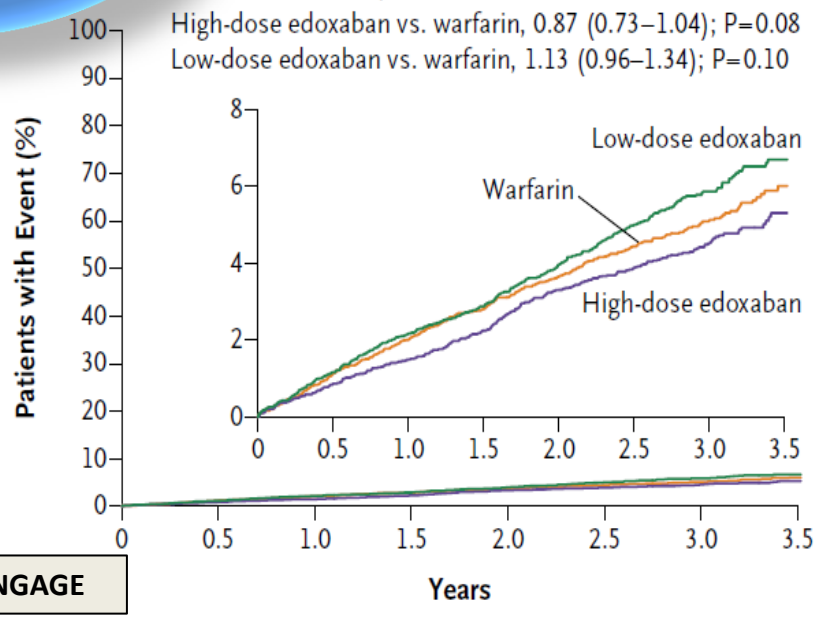
Primary Outcome
Stroke (ischemic or hemorrhagic) or systemic embolism



Duke Clinical Research Institute

UCR UPPSALA CLINICAL RESEARCH CENTER

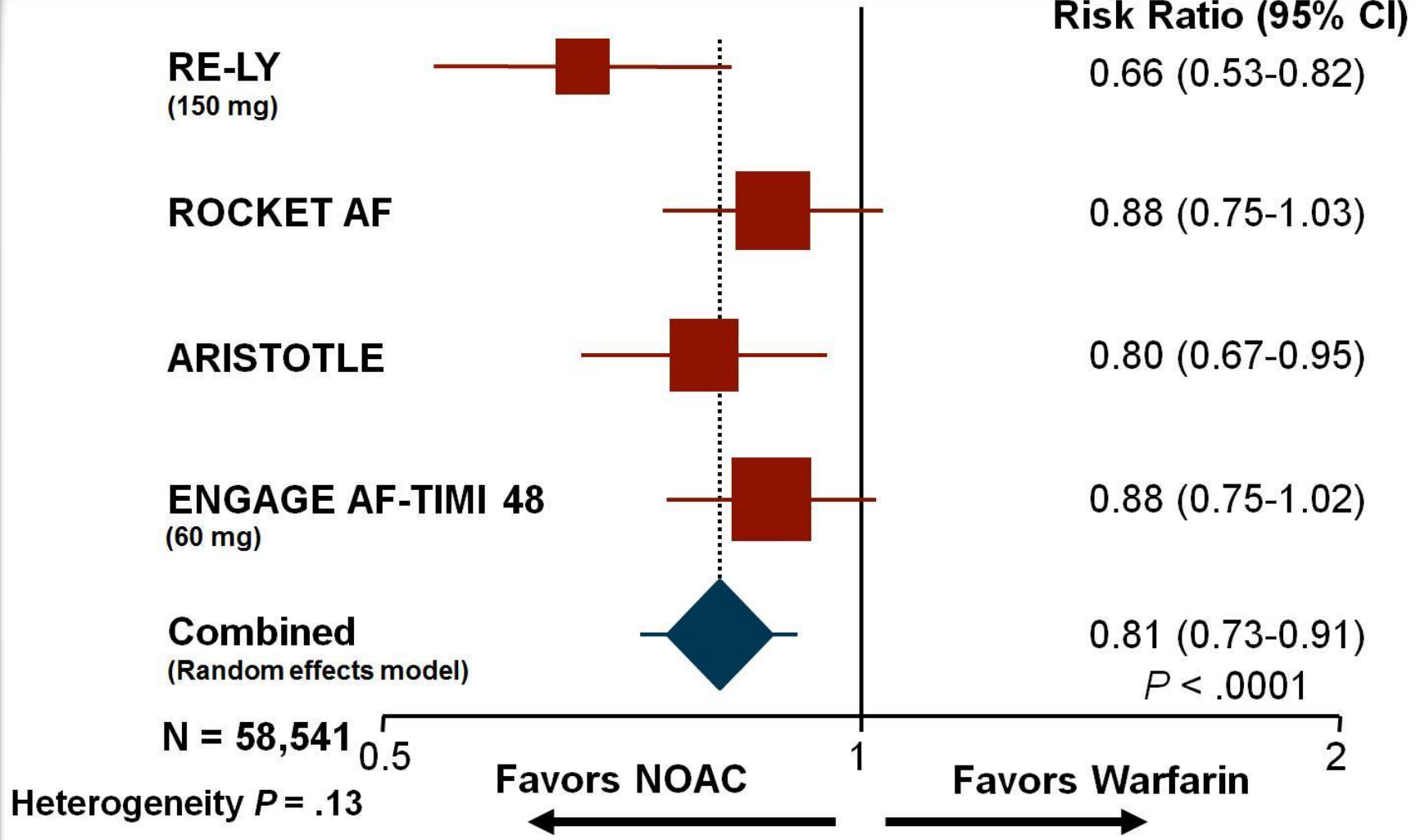
bolic Event



ENGAGE

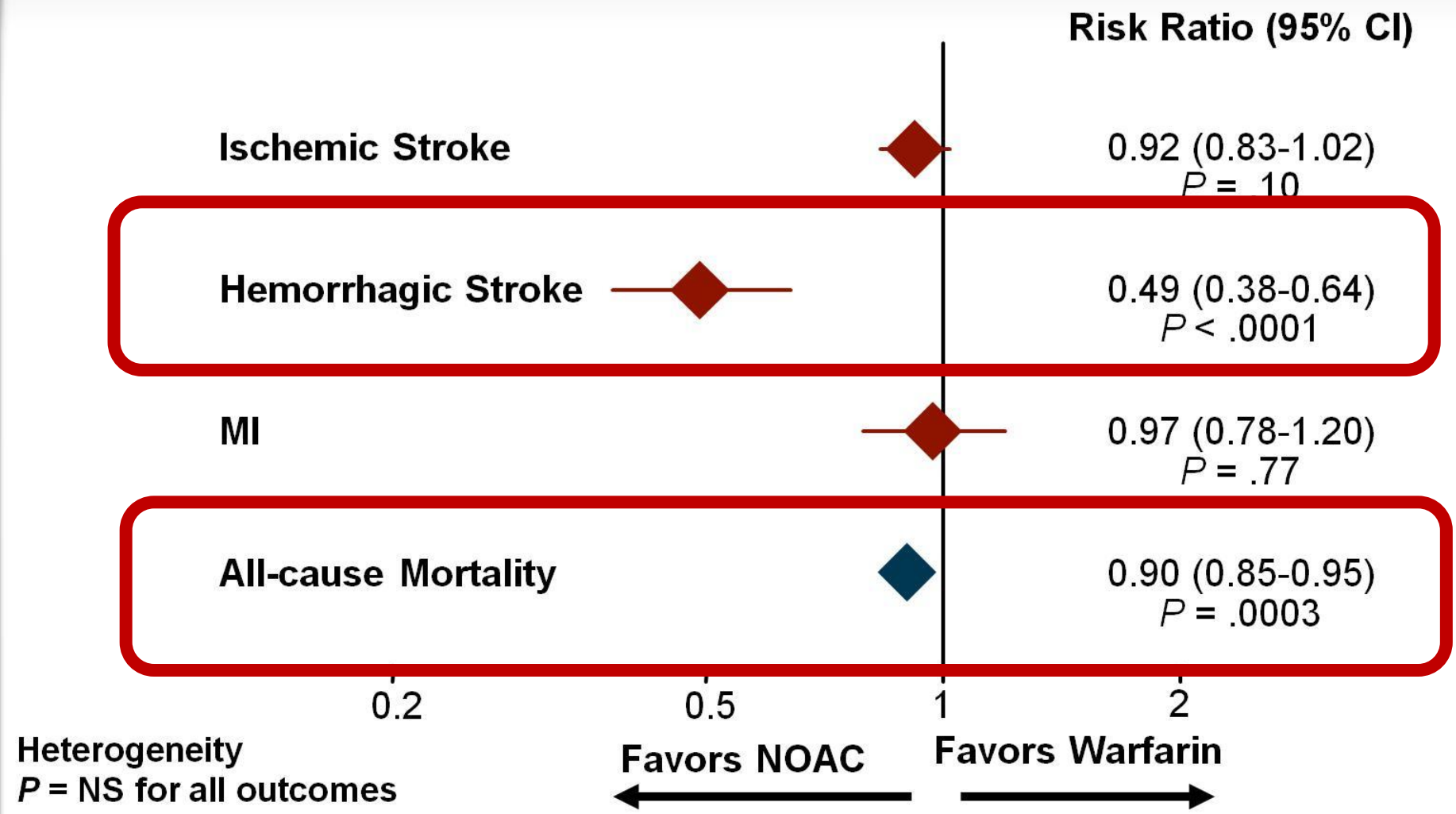
All NOACs

Stroke or Systemic Embolic Event



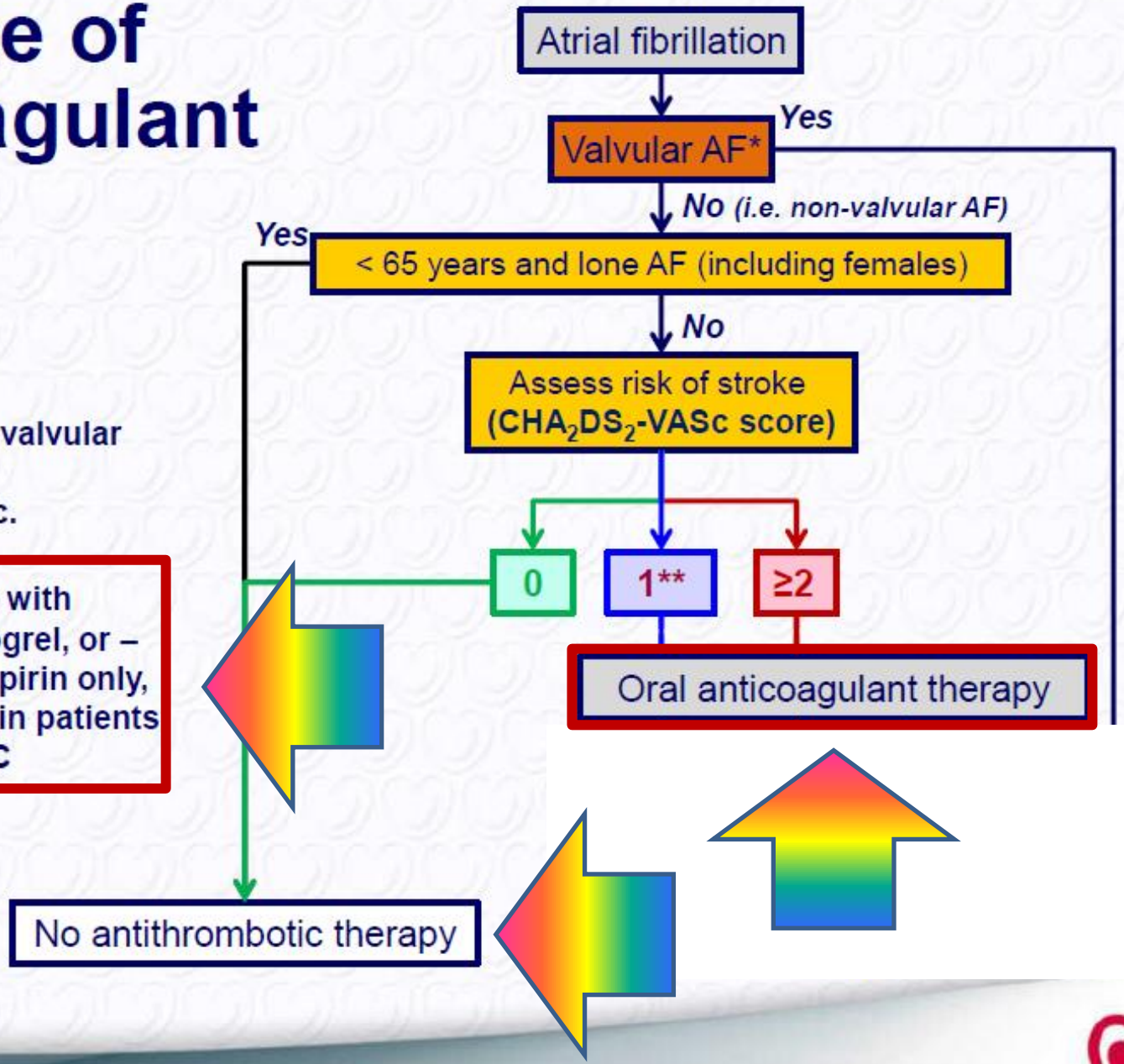
Reproduced from Ruff CT, et al. *Lancet*. 2014;383:955-962. ©2014, with permission from Elsevier.[15]

Secondary Efficacy Outcomes



Reproduced from Ruff CT, et al. *Lancet*. 2014;383:955-962. ©2014, with permission from Elsevier.[15]

Choice of Anti-coagulant



- Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, may be considered in patients who refuse any OAC

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs253

European Guidelines

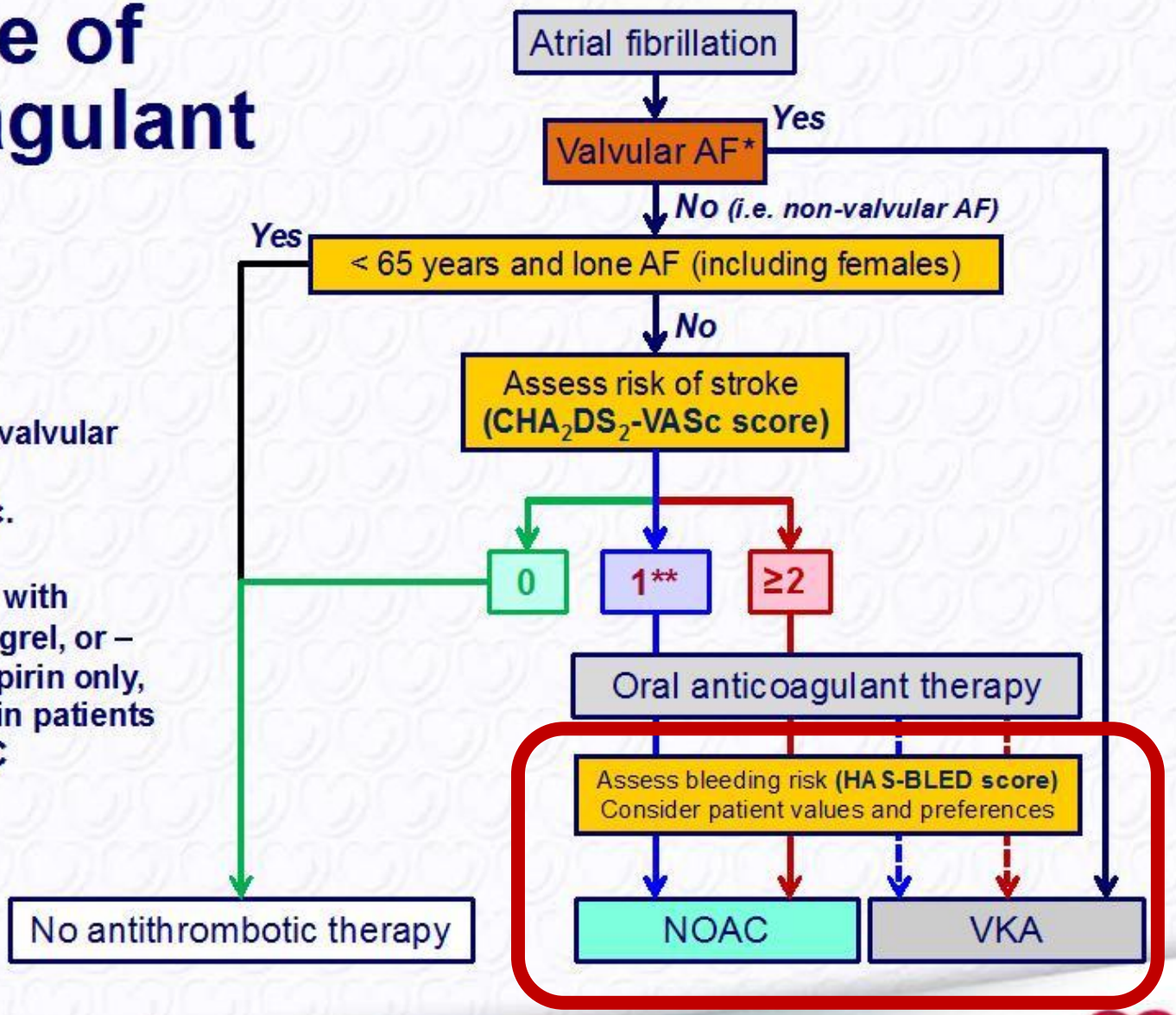
Where OAC is recommended, one of the NOACs, either:
- a direct thrombin inhibitor (dabigatran); or
- an oral factor Xa inhibitor (eg, rivaroxaban, apixaban)

… **should be considered rather than adjusted-dose VKA** (INR 2-3) for most patients with non-valvular AF, based on their net clinical benefit.

Camm AJ, et al. *Europace*. 2012;14:1385-1413.[30]

European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

Choice of Anti-coagulant



- Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, may be considered in patients who refuse any OAC

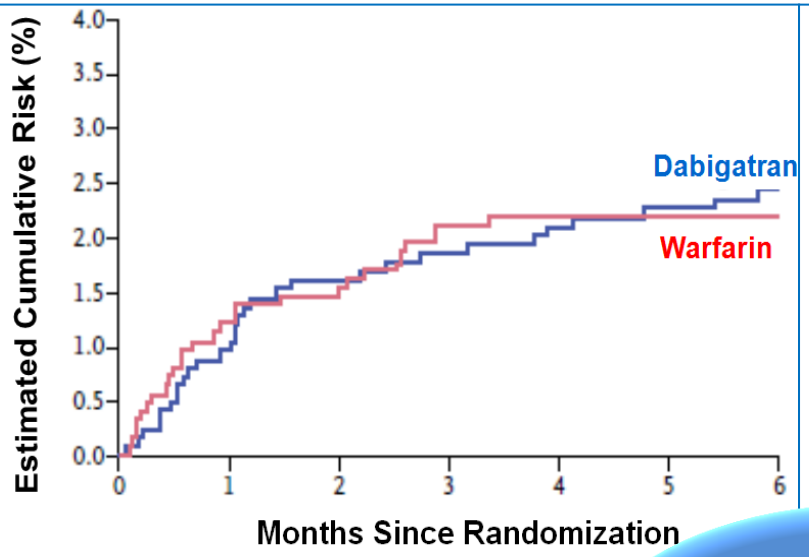
www.escardio.org/guidelines

European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

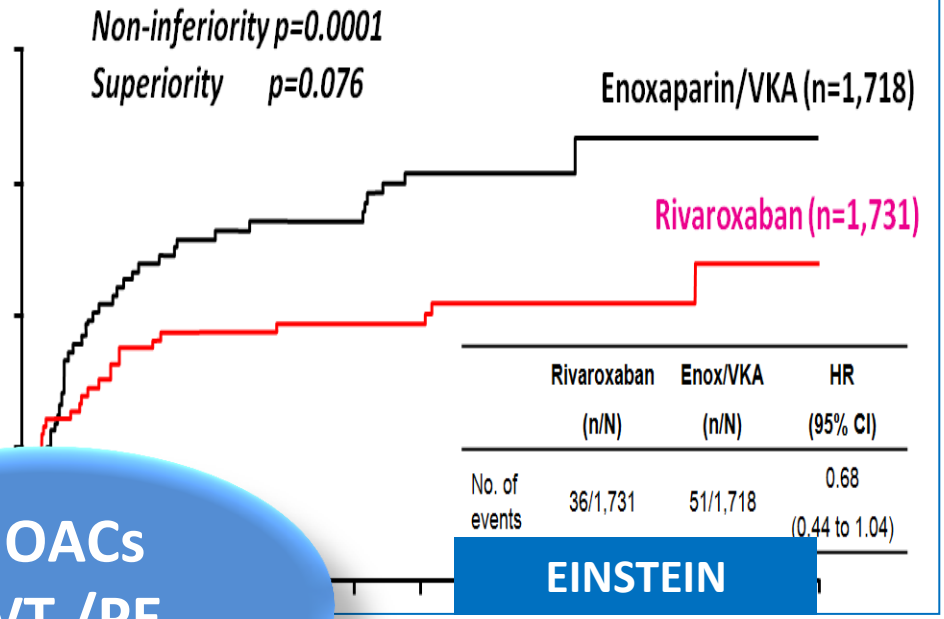
EUROPEAN SOCIETY OF CARDIOLOGY®

Hipocoagulação oral na TVP/EP

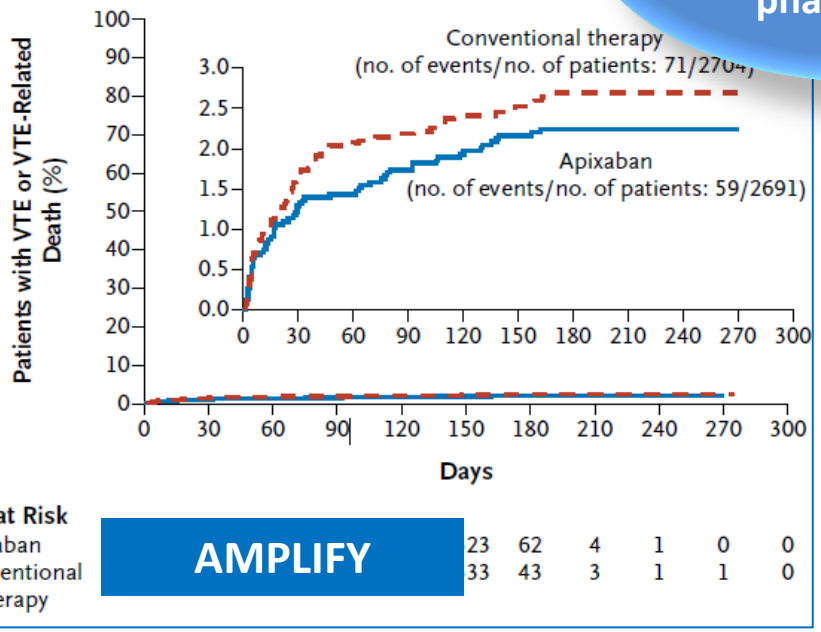
NOACs
DVT /PE
phase III trials



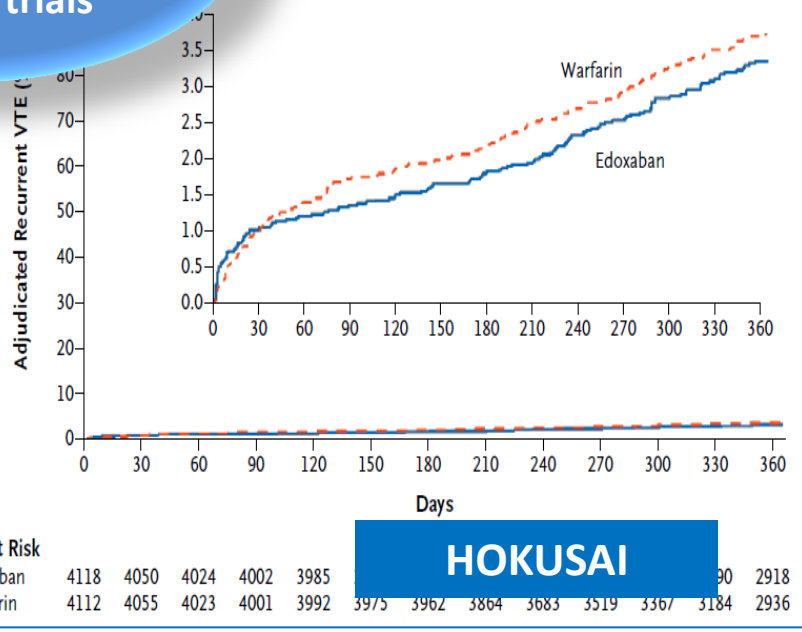
RECOVER



EINSTEIN



AMPLIFY



HOKUSAI

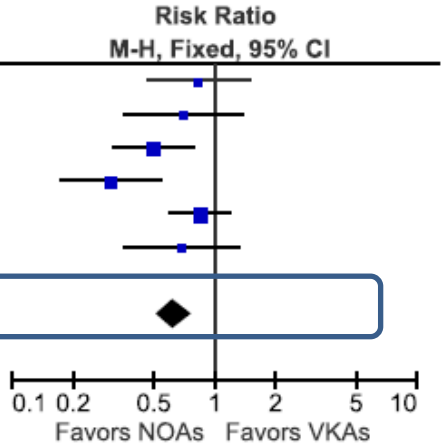
Major bleeding

a

Study or Subgroup	NOAs Events	NOAs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-COVER	20	1274	24	1265	10.3%	0.83 [0.46, 1.49]	2009
EINSTEIN-DVT	14	1718	20	1711	8.6%	0.70 [0.35, 1.38]	2010
EINSTEIN-PE	26	2412	52	2405	22.4%	0.50 [0.31, 0.80]	2012
AMPLIFY	15	2676	49	2689	21.0%	0.31 [0.17, 0.55]	2013
Hokusai-VTE	56	4118	66	4122	28.3%	0.85 [0.60, 1.21]	2013
RE-COVER II	15	1280	22	1288	9.4%	0.69 [0.36, 1.32]	2014
Total (95% CI)		**13478**		**13480**	**100.0%**	**0.63 [0.51, 0.77]**	
Total events	146		233				

Heterogeneity: Chi² = 10.65, df = 5 (P = 0.06); I² = 53%

Test for overall effect: Z = 4.46 (P < 0.00001)



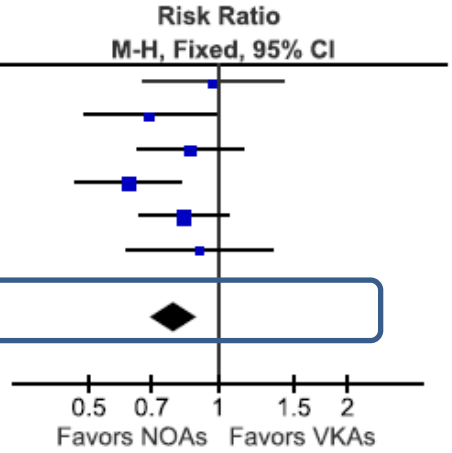
Net clinical benefit

e

Study or Subgroup	NOAs Events	NOAs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-COVER	50	1274	51	1265	9.6%	0.97 [0.66, 1.43]	2009
EINSTEIN-DVT	51	1731	73	1718	13.7%	0.69 [0.49, 0.99]	2010
EINSTEIN-PE	83	2419	96	2413	18.0%	0.86 [0.65, 1.15]	2012
AMPLIFY	74	2676	120	2689	22.4%	0.62 [0.47, 0.82]	2013
Hokusai-VTE	120	4118	144	4122	27.0%	0.83 [0.66, 1.06]	2013
RE-COVER II	45	1279	50	1289	9.3%	0.91 [0.61, 1.35]	2014
Total (95% CI)		**13497**		**13496**	**100.0%**	**0.79 [0.70, 0.90]**	
Total events	423		534				

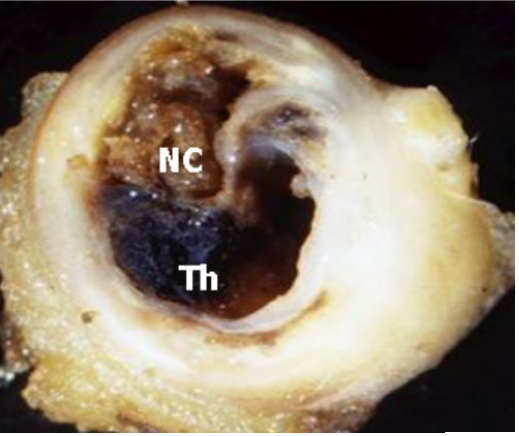
Heterogeneity: Chi² = 5.49, df = 5 (P = 0.36); I² = 9%

Test for overall effect: Z = 3.65 (P = 0.0003)



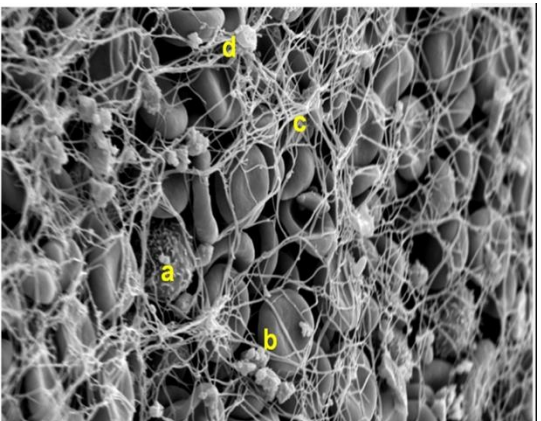
European Journal of Vascular and Endovascular Surgery (2014), http://dx.doi.org/10.1016/j.ejvs.2014.05.001

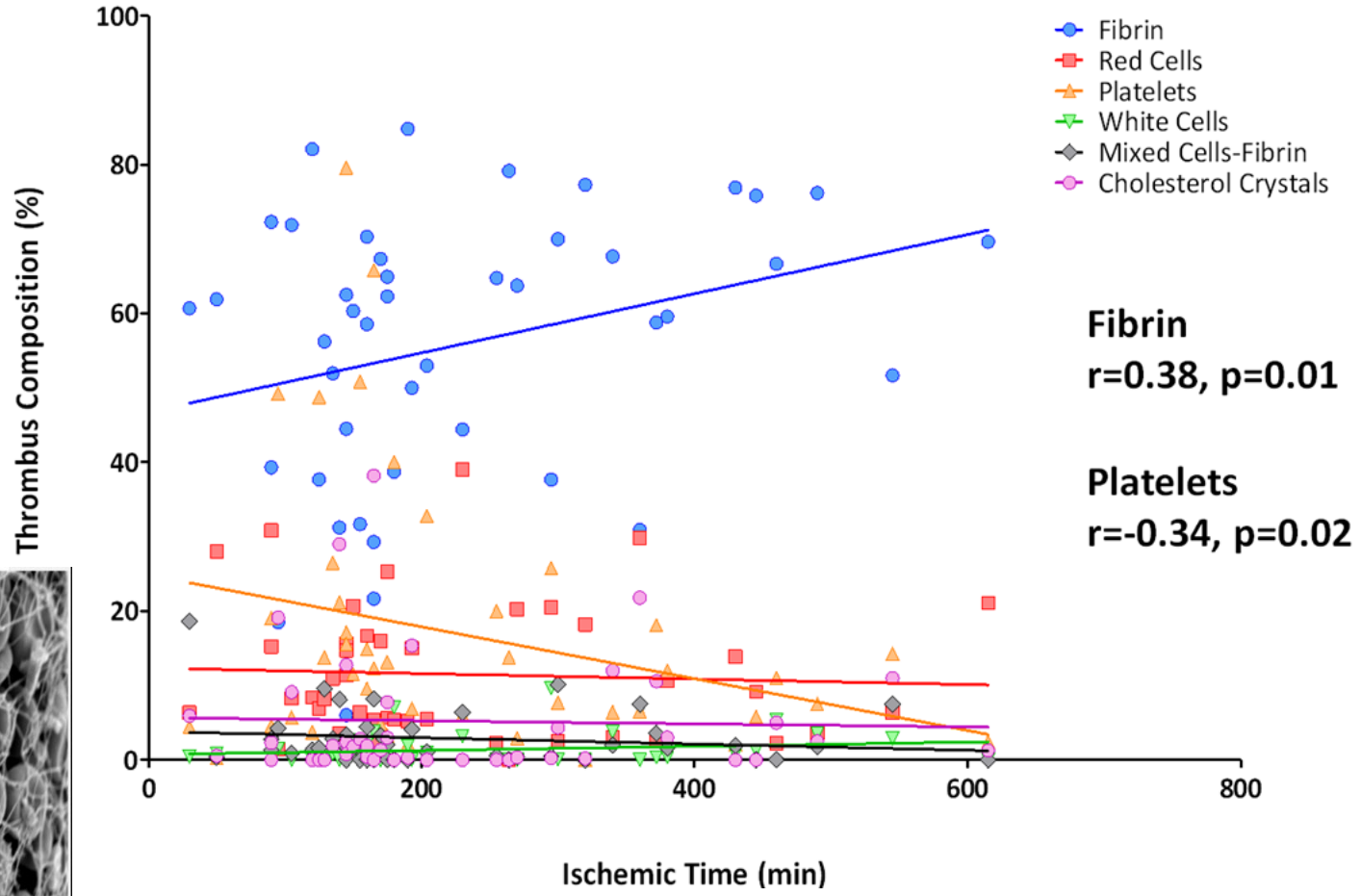
Hipocoagulação oral após SCA



Thrombus composition (STEMI)

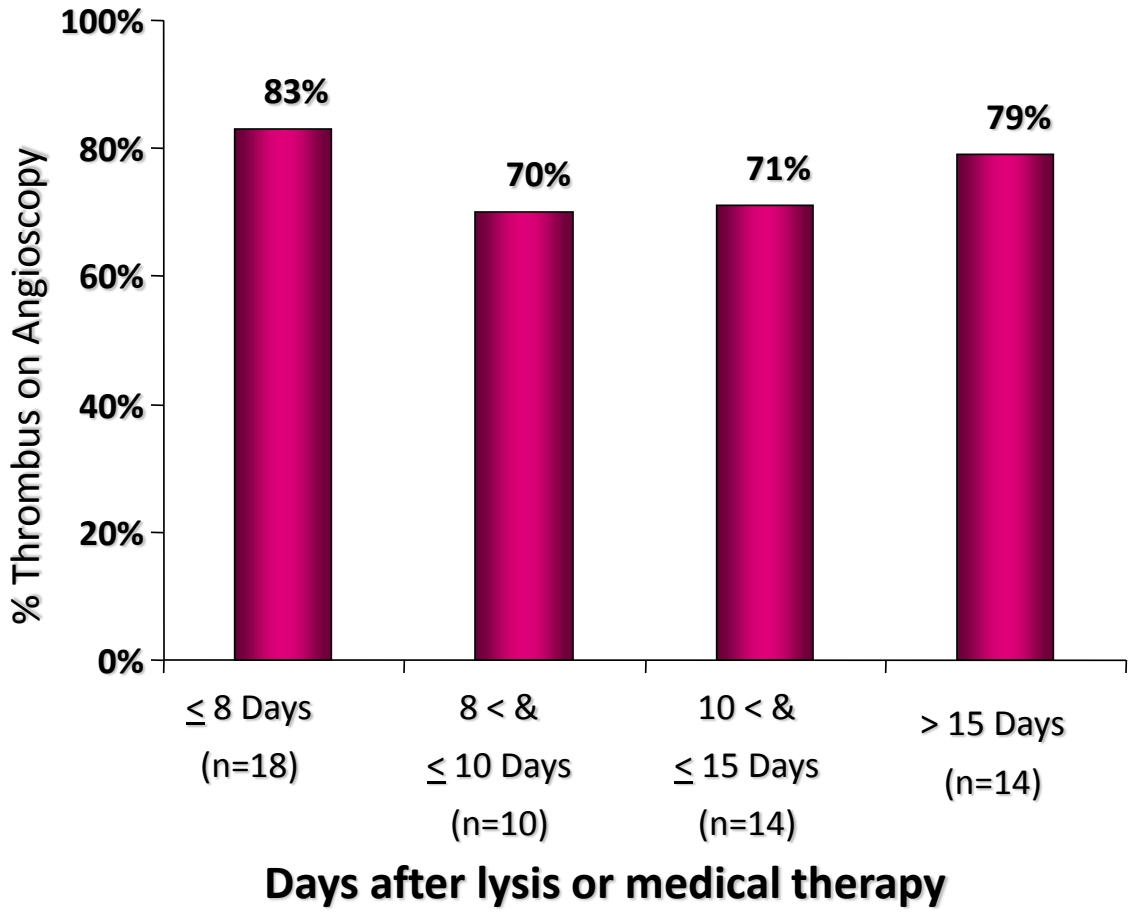
Influence of time





Silvaine J, et al. JACC 2011;57:1359

Thrombotic burden in ACS



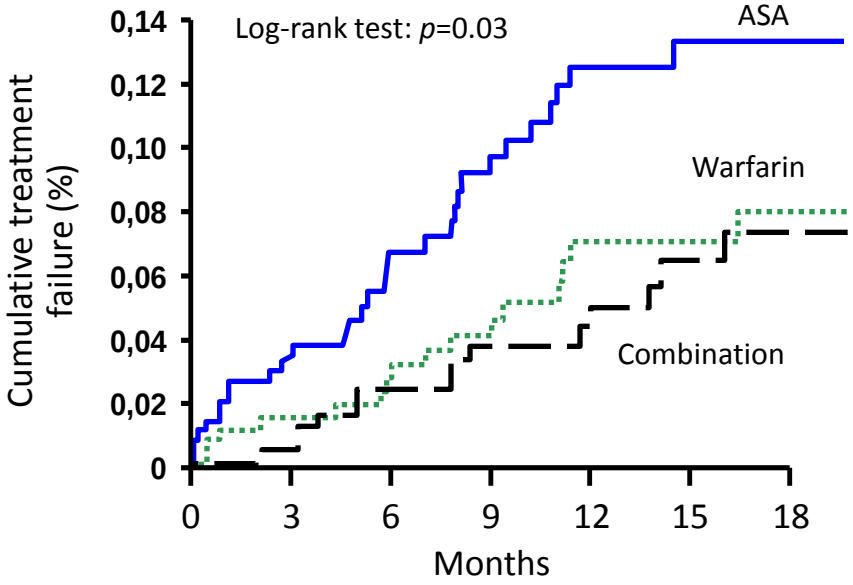
- **Angioscopic findings suggestive of plaque instability are extremely frequent (75% to 80% of the study population) as is the presence of clot even in the absence of clinical symptoms.**
- **Only 16% of clot seen on angio**

Van Belle et al. *Circulation.* 1998;97:26-33.

ASPECT-2 trial

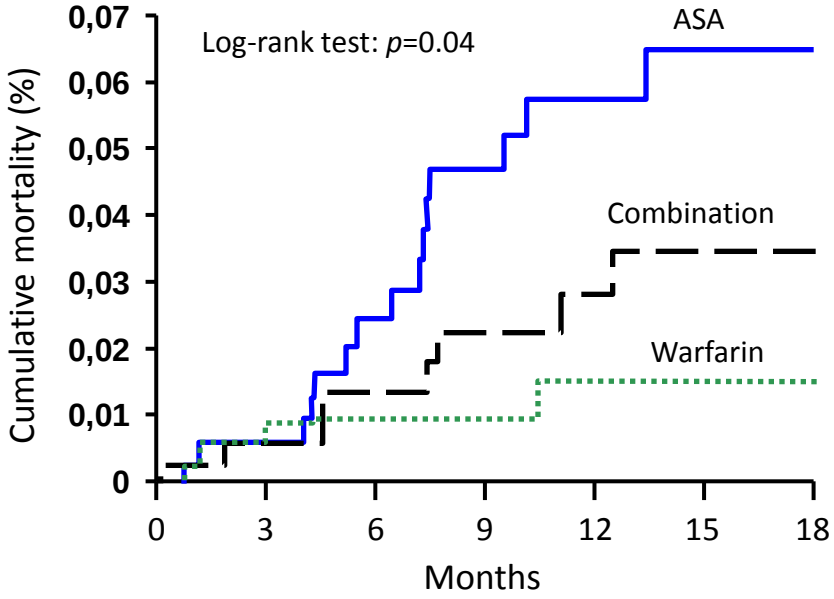
secondary prevention of ischaemic events following MI

Primary endpoint (death, MI, stroke)



Patients at risk							
Combination	325	279	233	188	159	105	54
ASA	336	282	233	186	159	100	56
Warfarin	332	293	243	197	161	102	60

Mortality

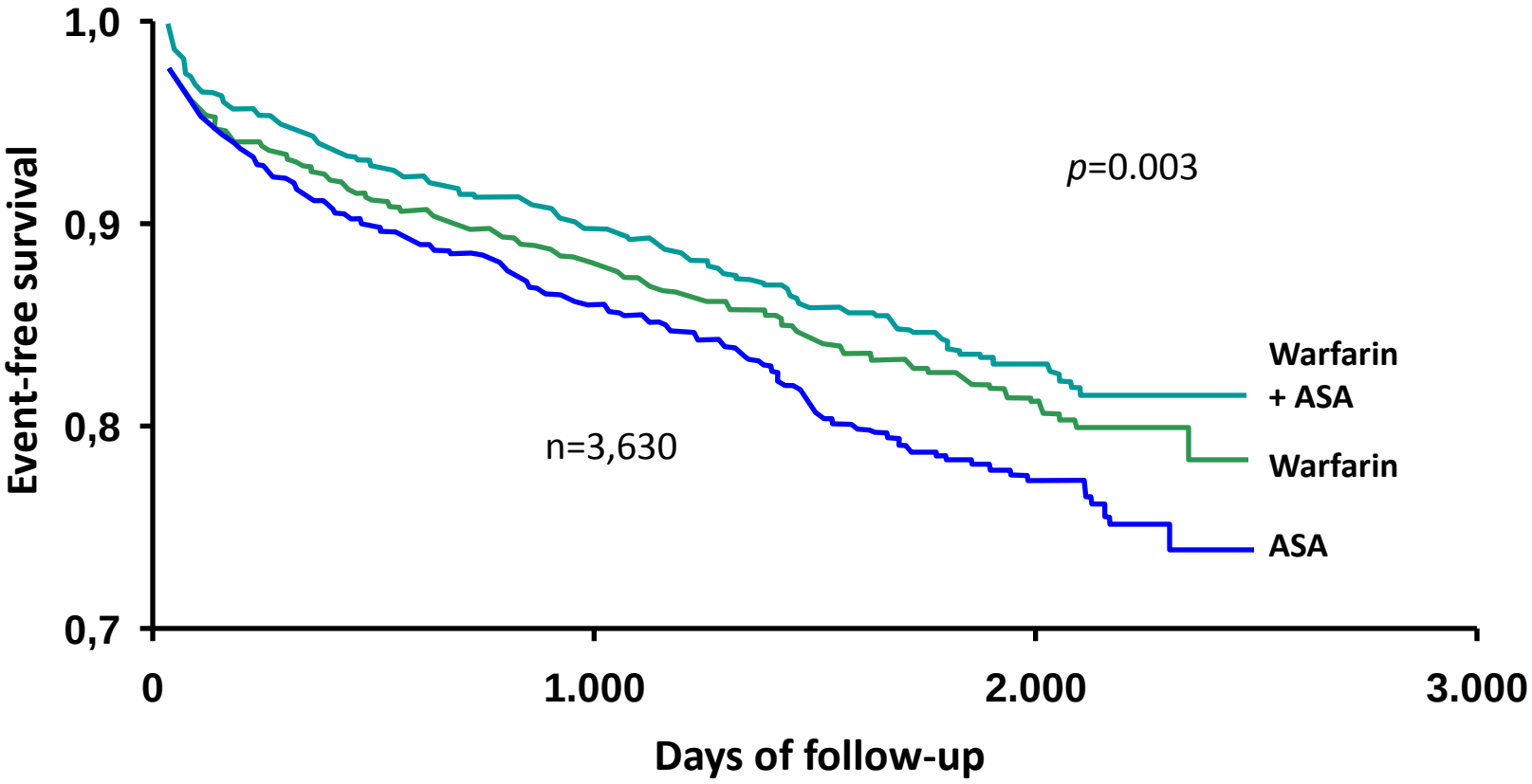


Patients at risk							
Combination	332	287	299	196	165	108	61
ASA	336	291	242	197	165	104	55
Warfarin	325	281	237	190	166	103	58

van Es RF, *et al*. *Lancet* 2002;360:109–113

WARIS-2 study

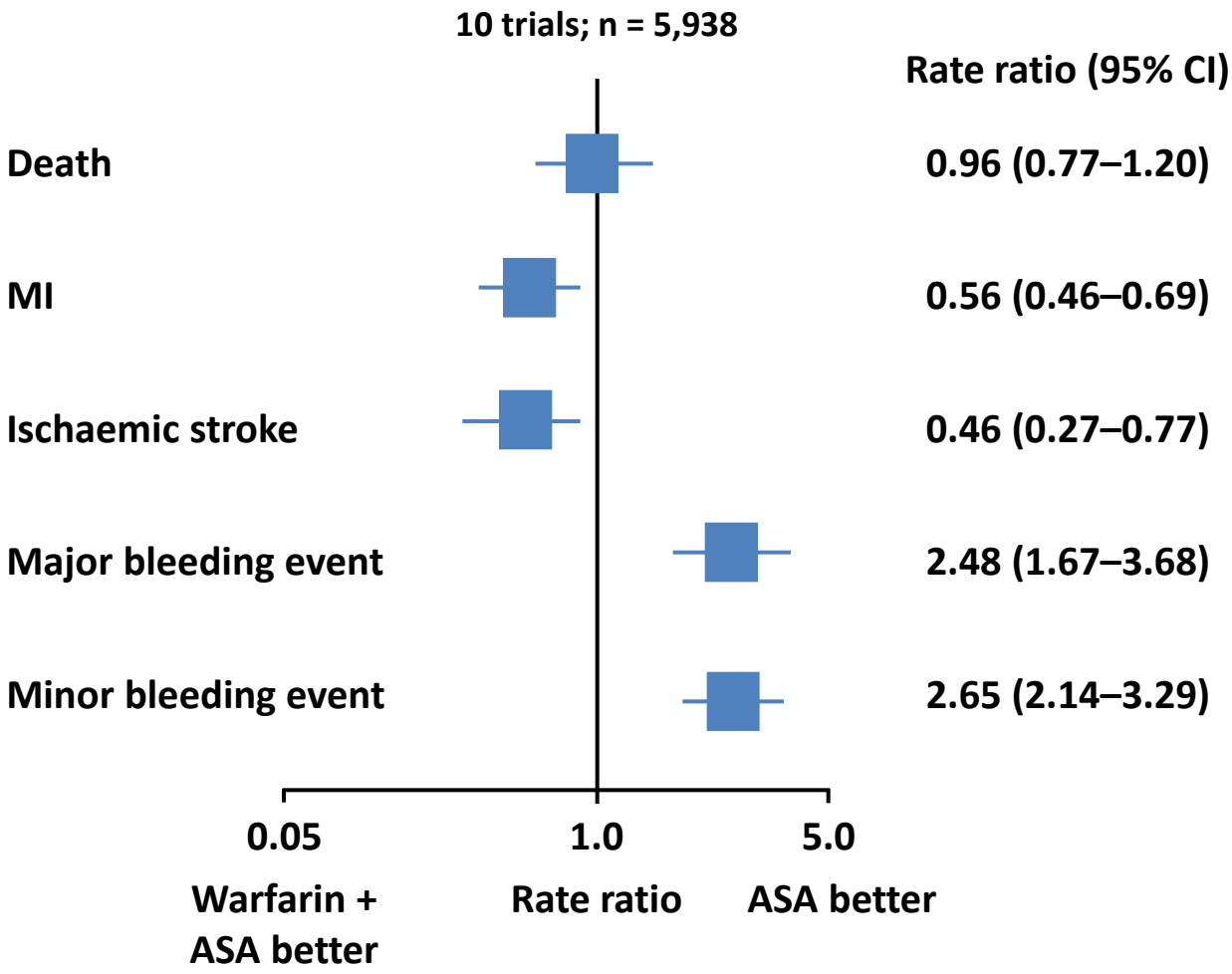
secondary prevention following MI



Event-free survival curves for the composite endpoint of death, nonfatal reinfarction, and thromboembolic stroke. The *p*-value refers to the overall difference among the curves (Tarone-Ware method)

Hurlen M, *et al. N Engl J Med* 2002;347:969–974

Secondary prevention with warfarin and ASA vs ASA alone after ACS



Rothberg MB, *et al*. *Ann Intern Med* 2005;143:241–250

NOACs em doentes com SCA

Droga	Fase II	Fase III	Resultado
Dabigatrano	RE-DEEM[1]	Não iniciada	---
Apixabano	APPRAISE[2]	APPRAISE-2[3]	Interrompido
Darexabano	RUBY-1[4]	Não iniciada	---
Rivaroxabano	ATLAS ACS TIMI 46[5]	ATLAS ACS 2 TIMI 51[6]	Positivo

1. Oldgren *et al,* 2011; 2. Alexander *et al,* 2009; 3. Alexander *et al,* 2011;
4. Steg *et al,* 2011; 5. Mega *et al,* 2009; 6. Mega *et al,* 2012

Rivaroxaban phase II trial

Patients with recent ACS
Stabilized 1–7 days post-index event

Aspirin 75–100 mg

MD decision to treat with clopidogrel

NO

YES

N = 3491

STRATUM 1
ASA alone
N=761

STRATUM 2
ASA + clop.
N=2730

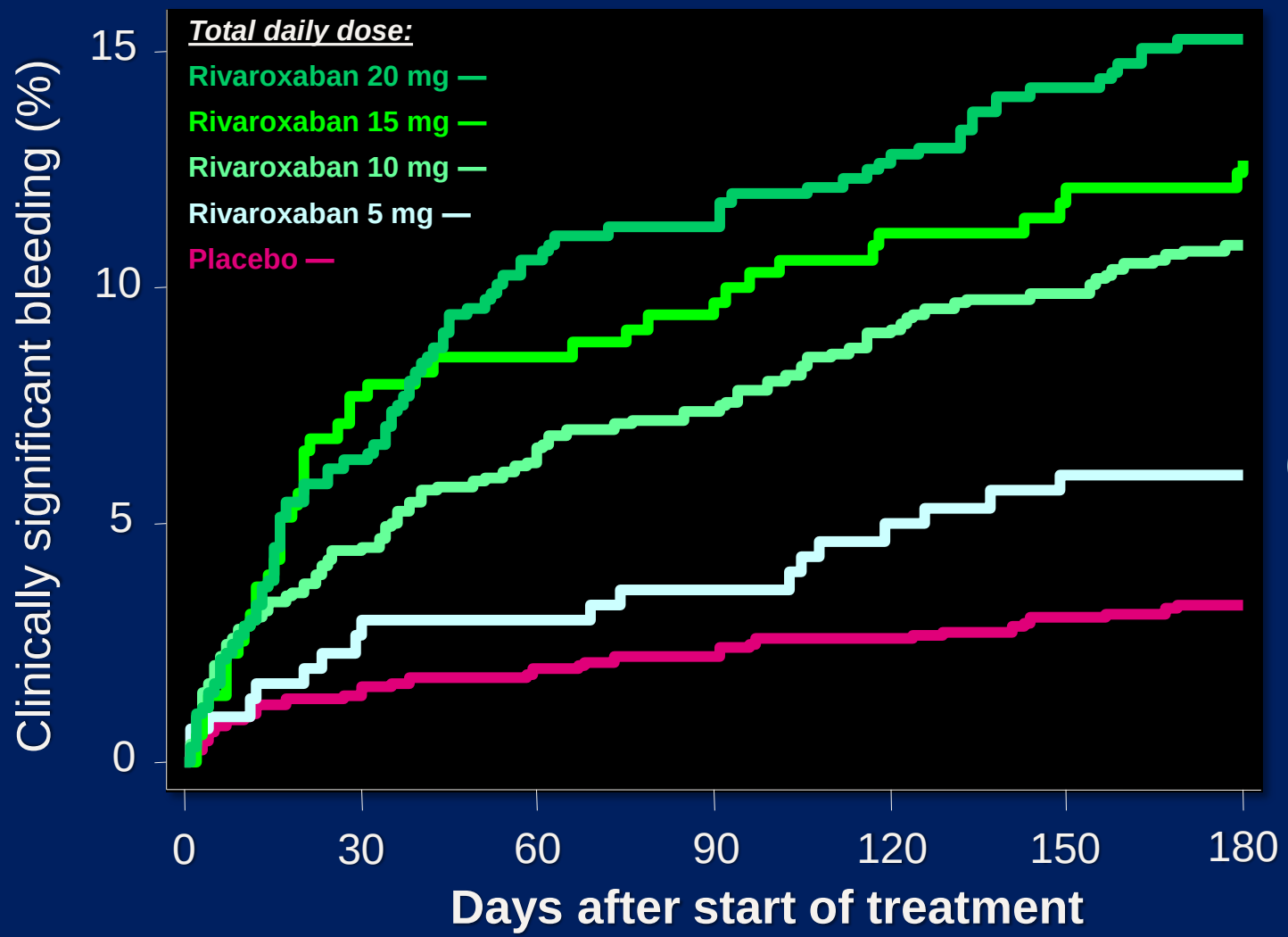
PLACEBO	RIVA OD	RIVA BID	PLACEBO	RIVA OD	RIVA BID
N=253	N=254	N=254	N=907	N=912	N=911
5 mg (77)	5 mg (77)	2.5 mg (77)	5 mg (74)	5 mg (78)	2.5 mg (76)
10 mg (98)	10 mg (99)	5 mg (97)	10 mg (428)	10 mg (430)	5 mg (430)
20 mg (78)	20 mg (78)	10 mg (80)	15 mg (178)	15 mg (178)	7.5 mg (178)
			20 mg (227)	20 mg (226)	10 mg (227)

Treat for 6 months

Gibson CM, *AHA* 2008; Mega *et al,* 2009

PRIMARY SAFETY ENDPOINT: CLINICALLY SIGNIFICANT BLEEDING

(= TIMI major, TIMI minor, bleed req. med. attn.)



		HR
Rivaroxaban 20 mg	15.3%	5.1 (3.4, 7.4)
Rivaroxaban 15 mg	12.7%	3.6 (2.3, 5.6)
Rivaroxaban 10 mg	10.9%	3.4 (2.3, 4.9)
Rivaroxaban 5 mg	6.1%	2.2 (1.25, 3.91)
Placebo	3.3%	

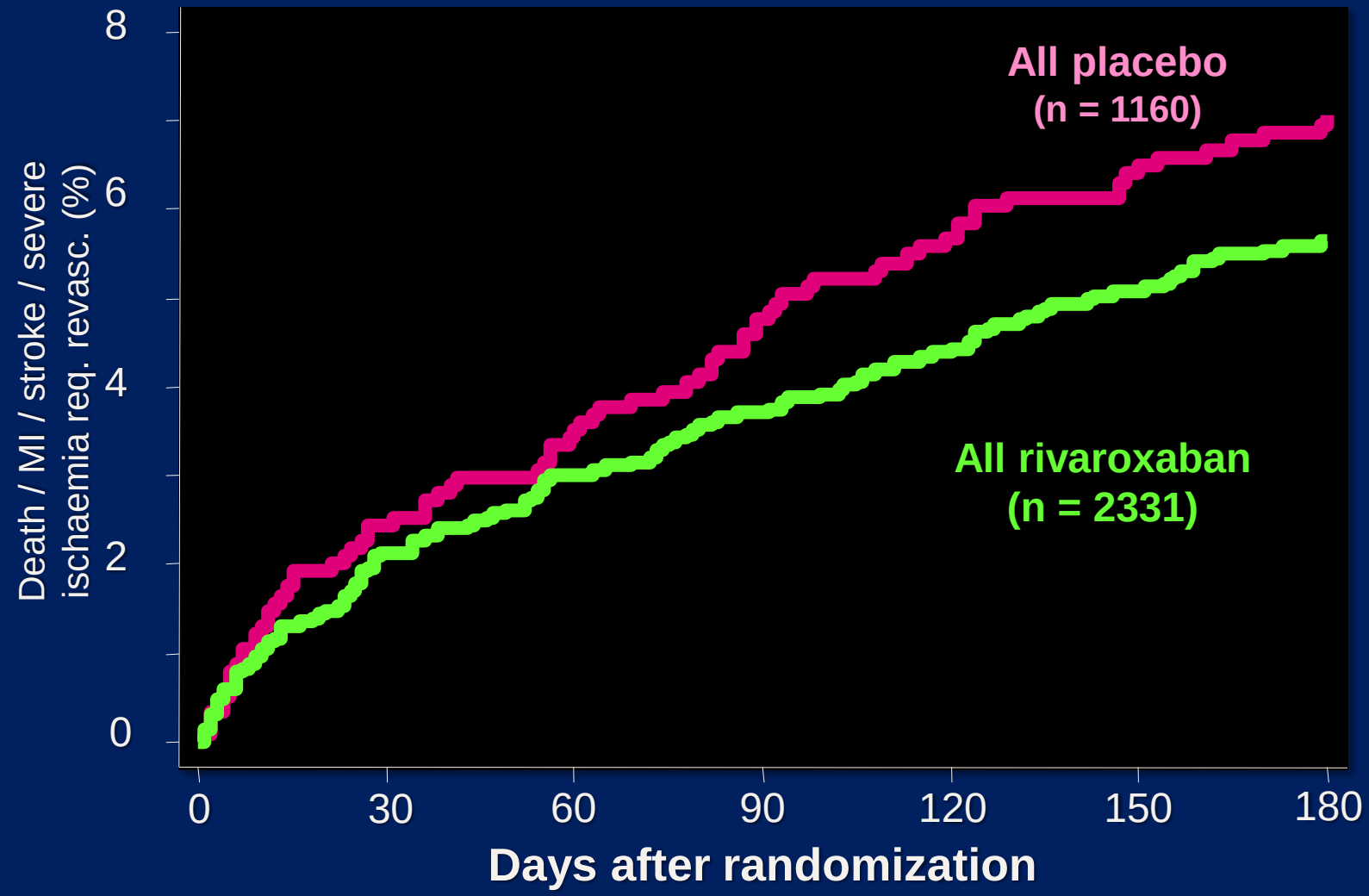
*p<0.01 for riva 5 mg vs placebo; p<0.001 for riva 10, 15, 20 mg vs placebo

Kaplan–Meier estimates for cumulative events, HR (CI), for bleeding rates during the 180 day period; CI, confidence interval; HR, hazard ratio

Gibson CM, *AHA* 2008; Mega *et al*, 2009

PRIMARY EFFICACY ENDPOINT:

Death / MI / stroke / severe ischaemia req. revascularization



Cumulative Kaplan–Meier estimates of HR and the rates of key study end points during the 180 day period; Death = all cause death. HR, hazard ratio; MI, myocardial infarction.

Gibson CM, *AHA* 2008; Mega *et al*, 2009

Recent ACS: STEMI, NSTEMI, UA

No increased bleeding risk, No warfarin, No ICH,
No prior stroke if on ASA + Thienopyridine
Stabilized 1–7 Days Post-Index Event

Stratified by thienopyridine use at MD discretion

+ ASA 75 to 100 mg/day

Placebo
N=5176
ASA + Thieno, n=4821
ASA, n=355

RIVAROXABAN
2.5 mg BID
n=5174
ASA + Thieno, n=4825
ASA, n=349

RIVAROXABAN
5.0 mg BID
N=5176
ASA + Thieno, n=4827
ASA, n=349

PRIMARY ENDPOINT:
EFFICACY: CV death, MI, stroke* (ischaemic + haemg.)
SAFETY: TIMI major bleeding not associated with CABG
Event-driven trial of 1002 events in 15,342 patients**

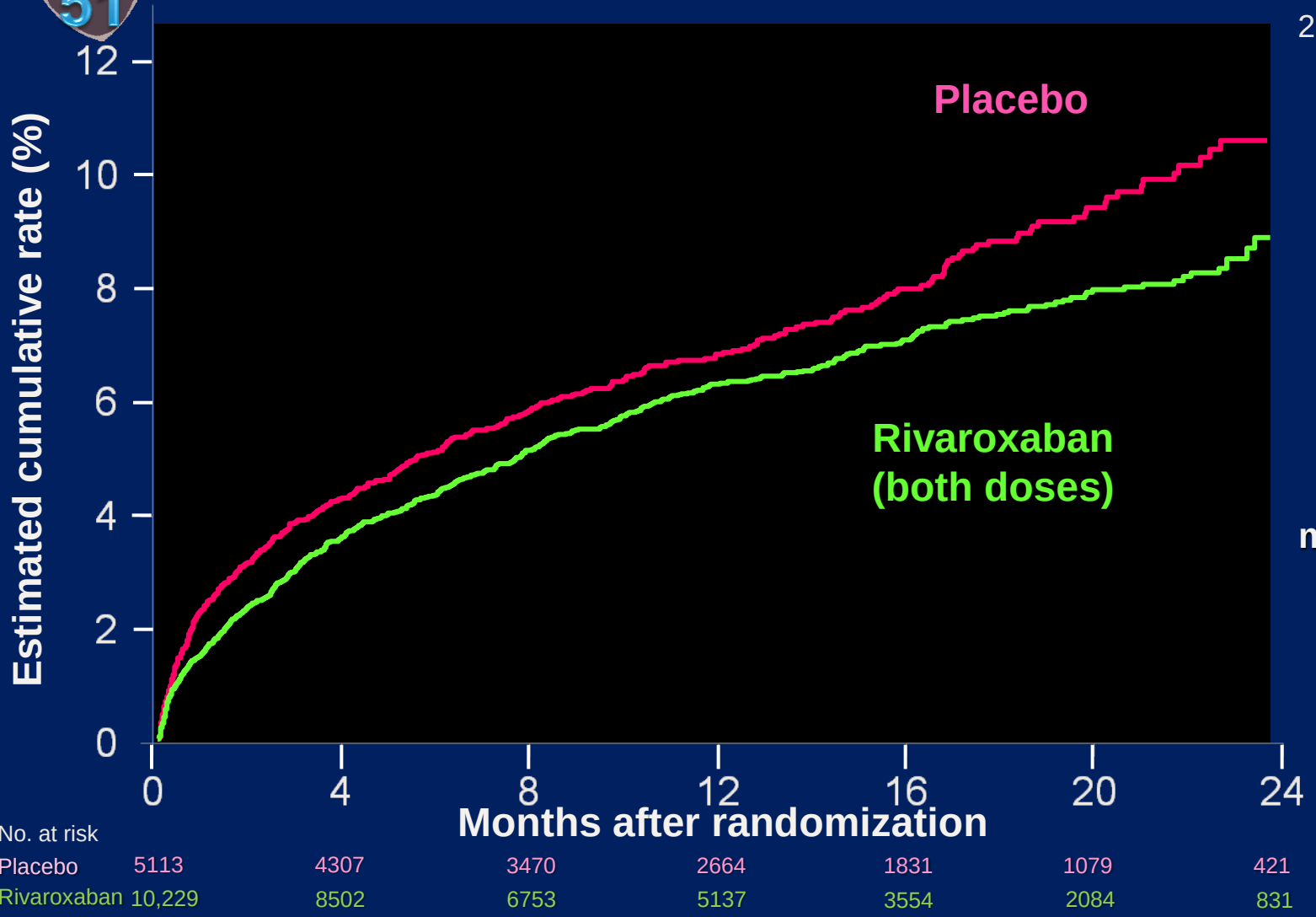
*Stroke includes ischaemic stroke, haemorrhagic stroke and uncertain stroke
**184 subjects were excluded from the efficacy analyses prior to unblinding

Gibson CM, *AHA* 2011;
Mega *et al*, 2012

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT:

CV death / MI / stroke* (ischaemic + haemg.)



2 Yr K–M estimate

10.7%

8.9%

HR 0.84
(0.74, 0.96)
ARR 1.8%

mITT: p=0.008
ITT: p=0.002

NNT=56

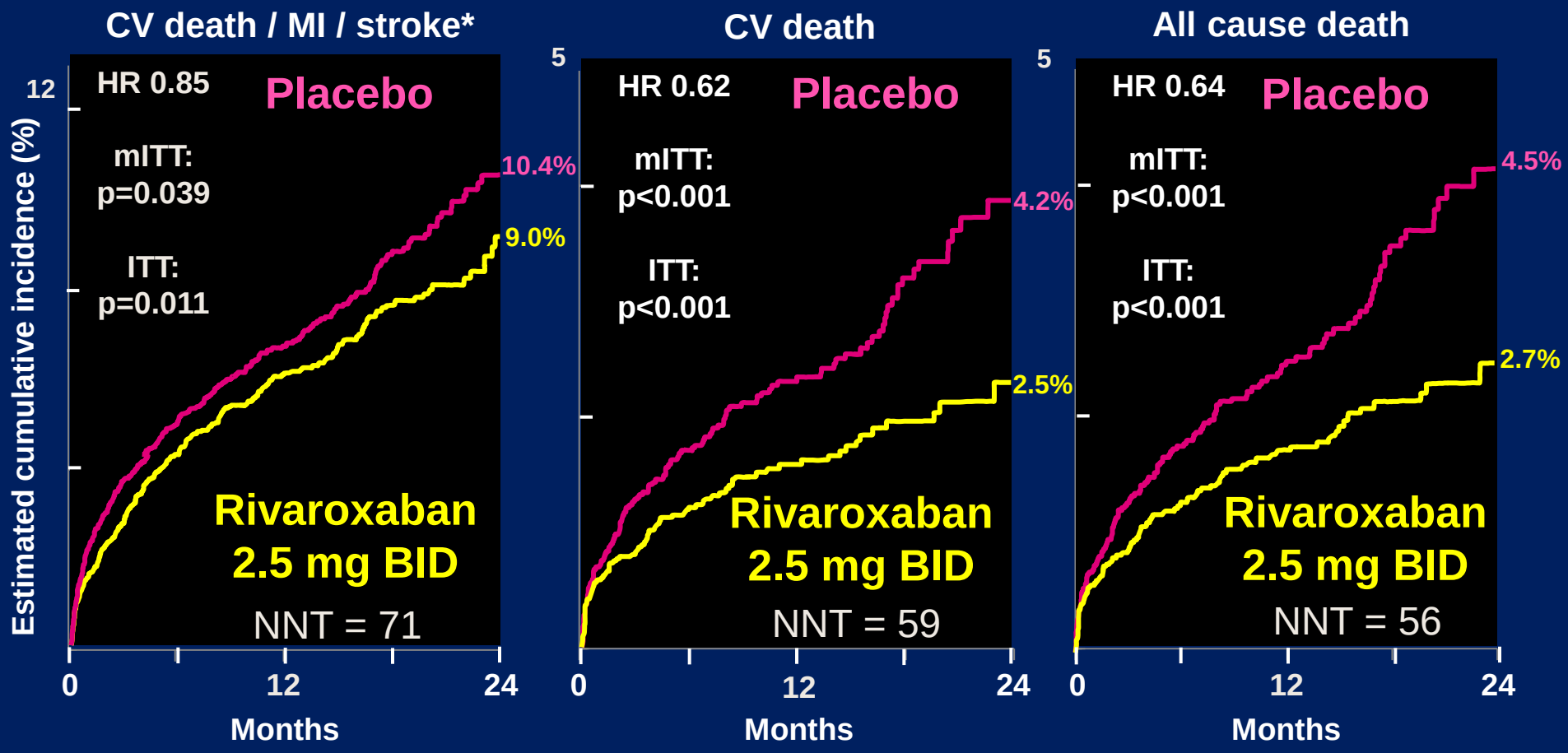
No. at risk

Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10,229	8502	6753	5137	3554	2084	831

*First occurrence of cardiovascular death, MI, stroke (ischaemic, haemorrhagic and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two-year Kaplan–Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches. Rivaroxaban = pooled rivaroxaban 2.5 mg BID and 5 mg BID.
ARR, absolute relative reduction; NNT, number needed to treat.

Gibson CM, *AHA* 2011; Mega *et al*, 2012

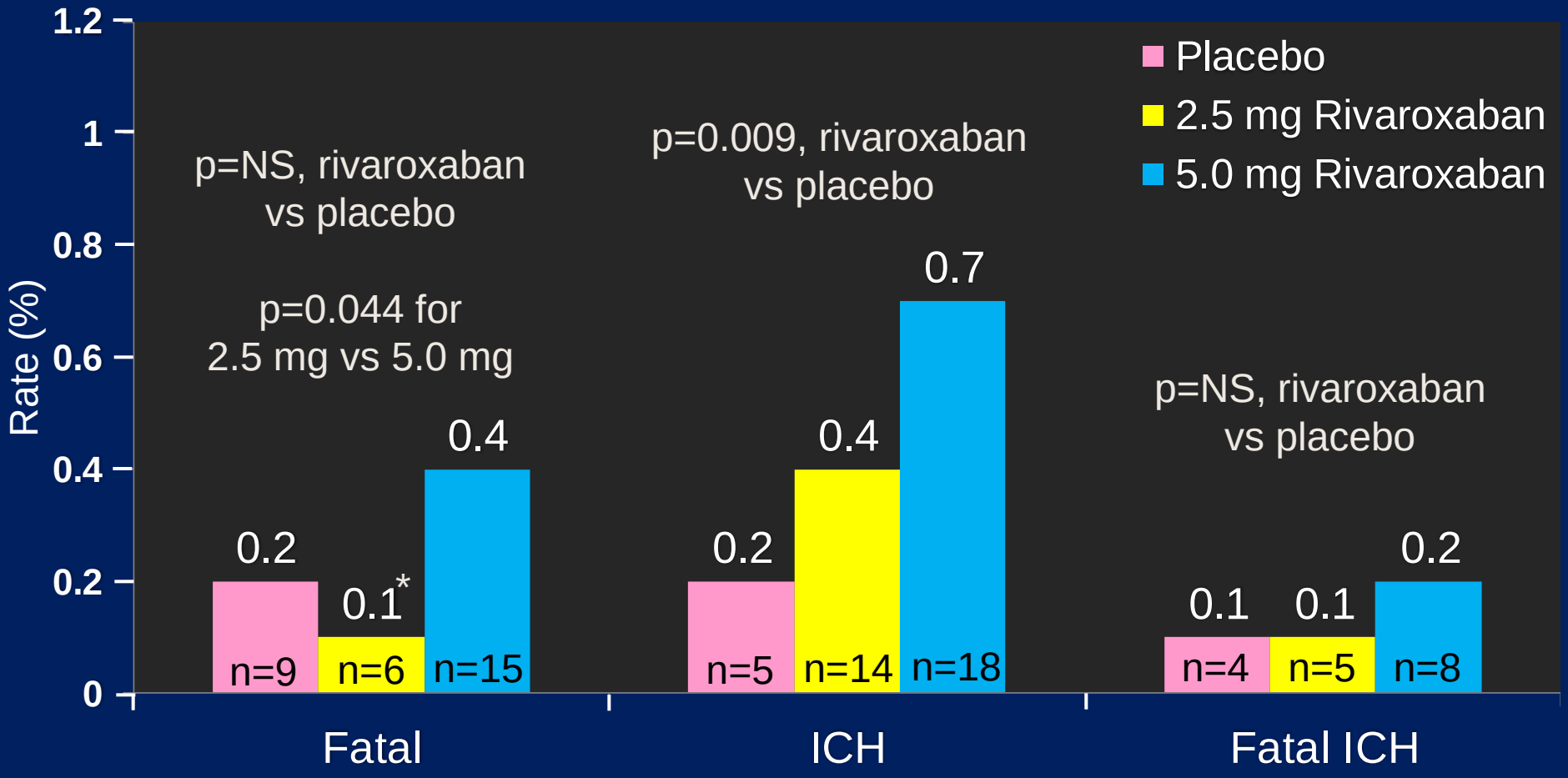
PRIMARY EFFICACY ENDPOINT*: 2.5 mg BID in patients treated with ASA + thienopyridine



*First occurrence of cardiovascular death, MI, stroke (ischaemic, haemorrhagic and uncertain) as adjudicated by the CEC. Two-year Kaplan–Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.
NNT, number needed to treat.

Gibson CM, *AHA* 2011; Mega *et al*, 2012

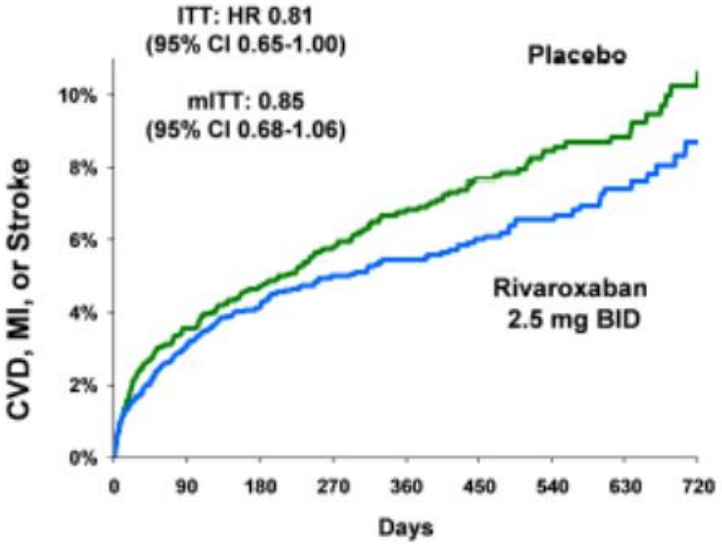
TREATMENT-EMERGENT FATAL BLEEDS AND ICH

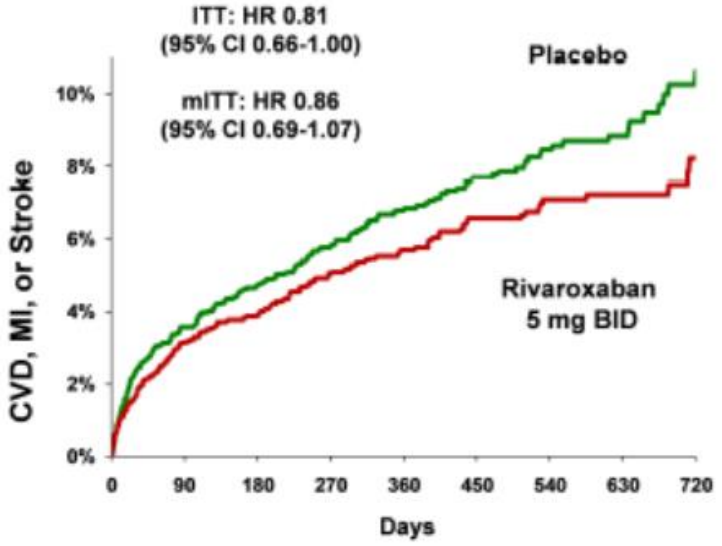


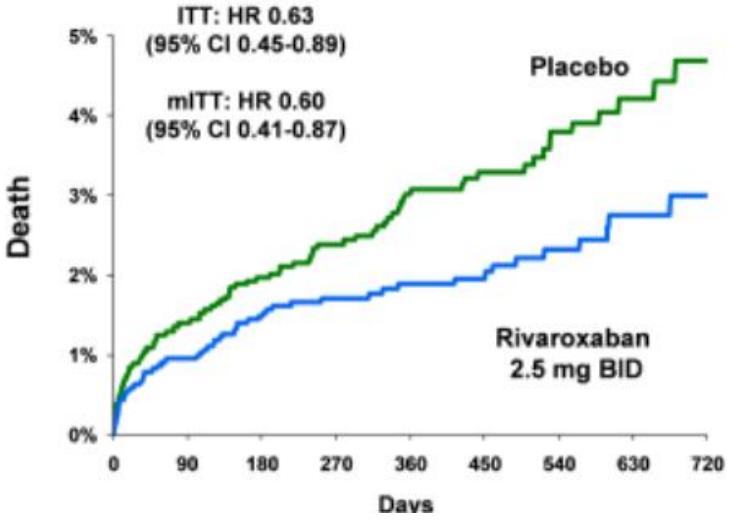
*Among patients treated with aspirin + thienopyridine, there was an increase in fatal bleeding for patients treated with 5.0 mg of rivaroxaban (15/5110) vs 2.5 mg of rivaroxaban (5/5115) (p=0.02)

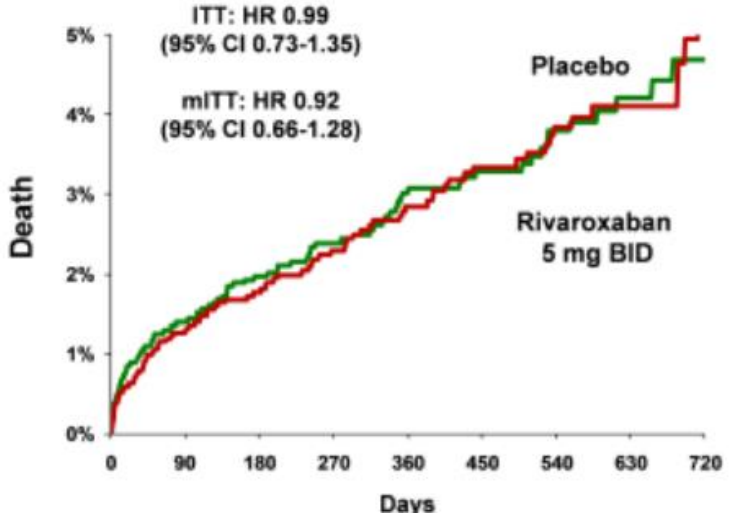
Gibson CM, *AHA* 2011; Mega *et al*, 2012

ATLAS ACS 2 - STEMI pts





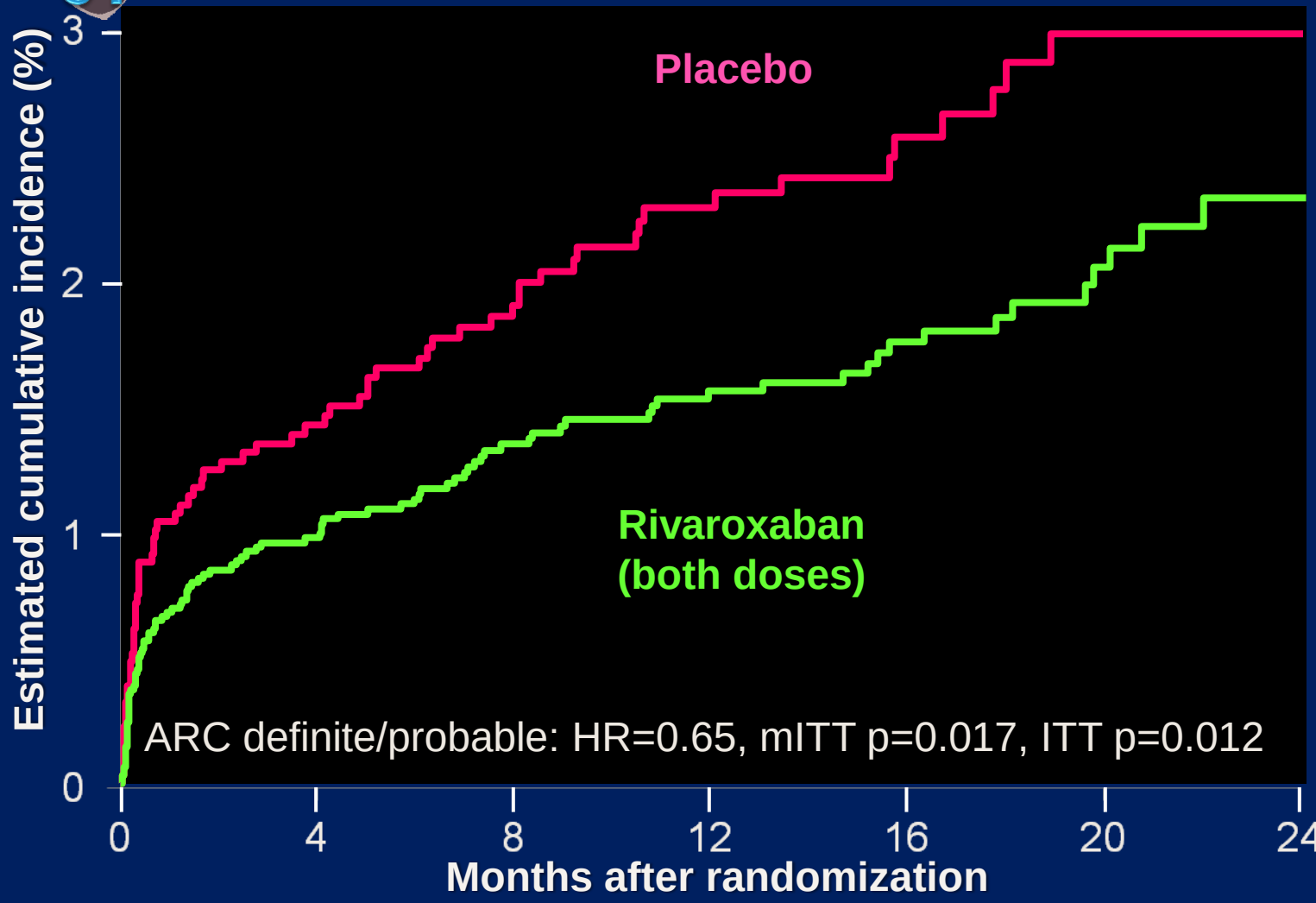




ATLAS ACS 2 TIMI 51

STENT THROMBOSIS*

ARC definite, probable, possible



2 Yr K–M estimate

2.9%

2.3%

HR 0.69
(0.51, 0.93)

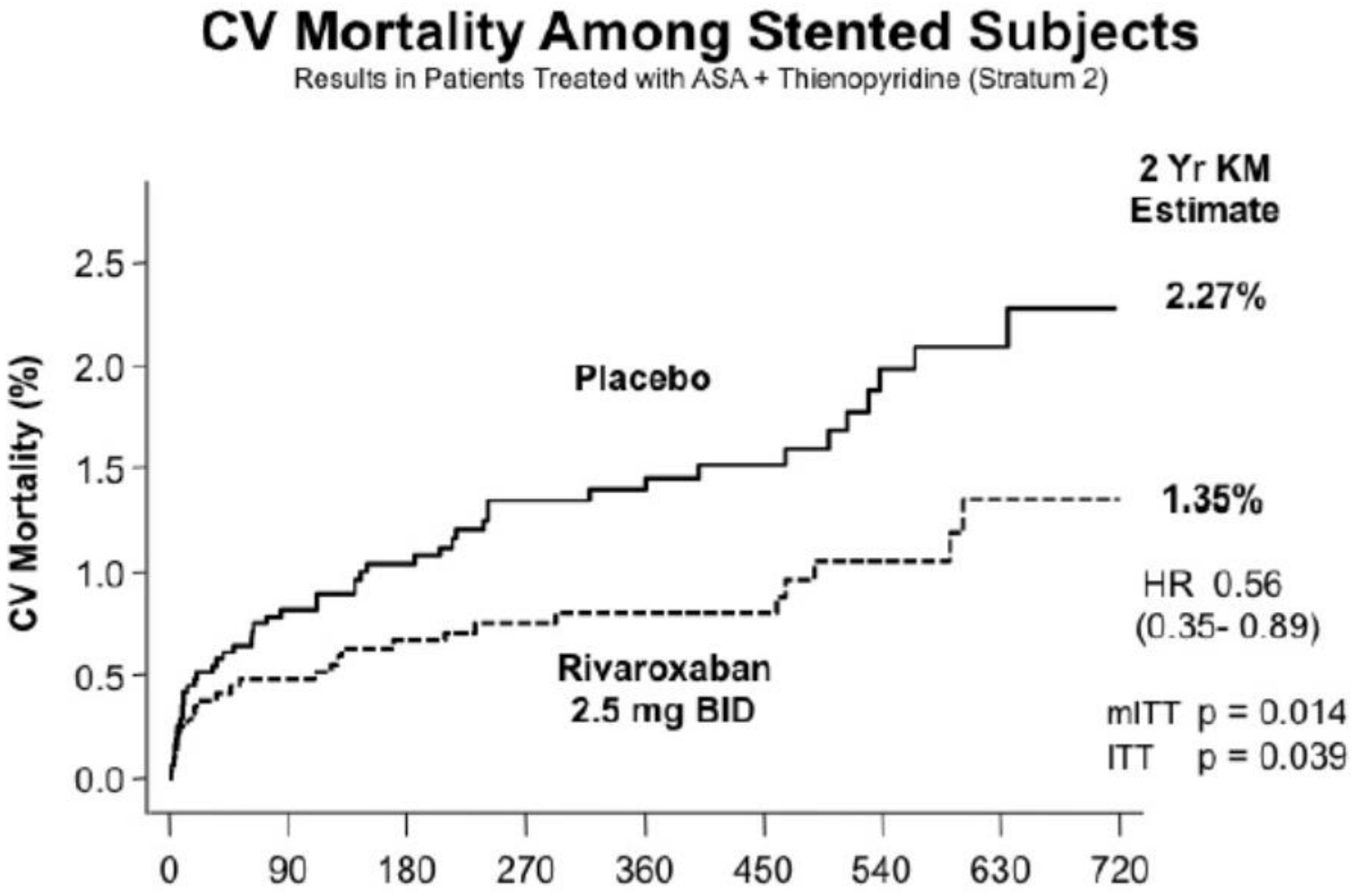
mITT: p=0.016

ITT: p=0.008

*Endpoint events are as adjudicated by the CEC across thienopyridine use strata
Two-year Kaplan–Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; Rivaroxaban = pooled rivaroxaban 2.5 mg BID and 5 mg BID.
ARC, Academic Research Consortium

Gibson CM, *AHA* 2011; Mega *et al*, 2012

ATLAS ACS 2 - stented pts

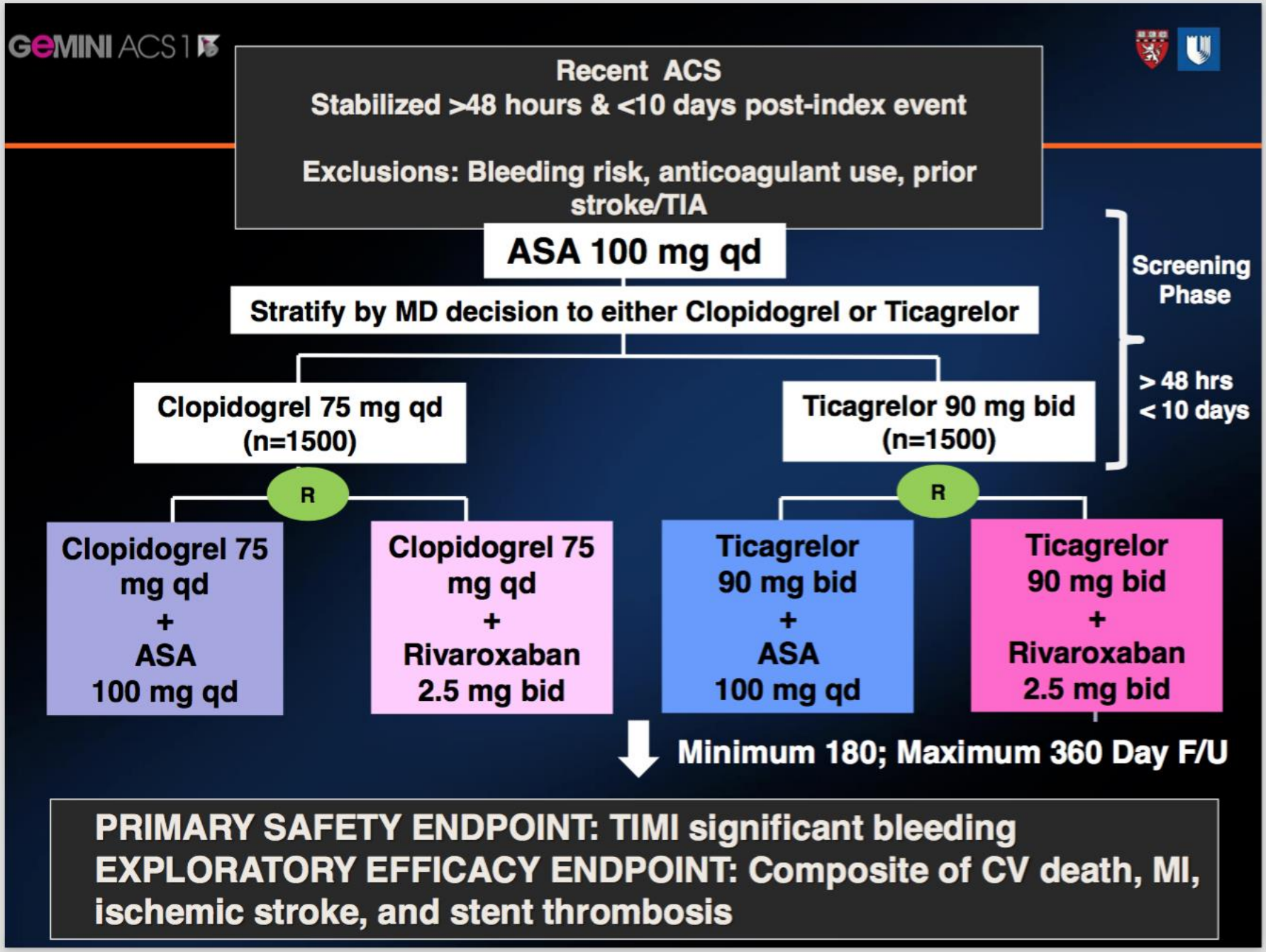


Key results in ACS trials

	TRITON TIMI–38	PLATO	TRA · CER	ATLAS-ACS 2 TIMI 51 (2.5 mg bid)
Drug	Prasugrel	Ticagrelor	Vorapaxar	Rivaroxaban
CV death, MI, stroke	HR 0.81 (95% CI 0.73, 0.90) p<0.001	0.84 (0.77, 0.92) p<0.001	0.89 (0.81, 0.98) p=0.02	0.84 (0.72, 0.97) p=0.02
Death	0.95 (0.78, 1.16) p=0.64	0.78 (0.69, 0.89) p<0.001	1.05 (0.90, 1.23) p=0.52	0.68 (0.53, 0.87) p=0.002
Stent thr.	0.48 (0.36, 0.64) p<0.001	0.75 (0.59, 0.95) p=0.02	1.12 (0.78, 1.62) p=0.54	0.65 (0.45, 0.94) p=0.02
Fatal bleeding event	4.19 (1.58, 11.11) p=0.002	0.87 (0.48, 1.59) p=0.66	1.89 (0.80, 4.45) p=0.15	0.67 (0.24, 1.89) p=0.45
ICH	1.12 (0.58, 2.15) p=0.74	1.87 (0.98, 3.58) p=0.06	3.39 (1.78, 6.45) p<0.001	2.83 (1.02, 7.86) p=0.04
Publication	NEJM 2007[1]	NEJM 2009[2]	NEJM 2012[3]	NEJM 2012[4]
	On top of clopi	On top of clopi	On top of dual APT	On top of dual APT

[NB: direct data comparisons between studies should be avoided because of differences in study populations and trial design]

1. Wiviott *et al*, 2007; Wallentin *et al*, 2009; 3. Tricoci *et al*, 2012; 4. Mega *et al*, 2012


GEMINI ACS 1
Recent ACS
Stabilized >48 hours & <10 days post-index event
Exclusions: Bleeding risk, anticoagulant use, prior stroke/TIA
ASA 100 mg qd
Stratify by MD decision to either Clopidogrel or Ticagrelor
Screening Phase
> 48 hrs
< 10 days
Clopidogrel 75 mg qd (n=1500)
Ticagrelor 90 mg bid (n=1500)
R
R
Clopidogrel 75 mg qd + ASA 100 mg qd
Clopidogrel 75 mg qd + Rivaroxaban 2.5 mg bid
Ticagrelor 90 mg bid + ASA 100 mg qd
Ticagrelor 90 mg bid + Rivaroxaban 2.5 mg bid
Minimum 180; Maximum 360 Day F/U
PRIMARY SAFETY ENDPOINT: TIMI significant bleeding
EXPLORATORY EFFICACY ENDPOINT: Composite of CV death, MI, ischemic stroke, and stent thrombosis

Antitrombóticos na prevenção secundária após SCA

Mensagens-chave

- A dupla anti-agregação plaquetar (aspirina mais um inibidor $P2Y_{12}$) é a base da prevenção secundária após SCA
- Apesar do benefício da DAPT, em todos os estudos clínicos persiste um significativo risco residual
- O racional para o uso da hipocoagulação oral após SCA está bem estabelecido
- O rivaroxabano (inibidor do factor Xa) demonstrou um claro benefício em associação à terapêutica convencional após SCA, com um risco hemorrágico aceitável

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ESC Working Group

Obrigado

João Morais

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