A PATIENT UNSUITABLE FOR WARFARIN TREATMENT

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אוניברסיטת בר-אילן
הפקולטה לרפואה

CASE PRESENTATION

- 82 Years old man, HTN, DM
- Severe osteoarthritis
- Normal LV function
- Creatinine = 1.4 mg/dl
- eGFR = 40 ml/min
- Weight = 70 kg
- Paroxysmal AF
- Receives warfarin
- Unable to monitor INR routinely
- Highly labile INR
- Hematuria – INR 4.5

CHA_2DS_2-VASc

CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 yrs	**2**
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	**2**
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 yrs	1
Sex **c**ategory (i.e. female gender)	1

Total score	Patients (n=7329)	Adjusted stroke rate (%/year)*
0	1	0.0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

*Theoretical rates without therapy; assuming that warfarin provides a 64% reduction in stroke risk, based on Hart RG et al. 2007

TE = thromboembolism

Lip G et al. Chest 2010;137:263-72; Lip G et al. Stroke 2010; 41:2731–8;
Camm J et al. Eur Heart J 2010; 31:2369–429; Hart RG et al. Ann Intern Med 2007;146:857–67

HAS-BLED

HAS-BLED risk criteria	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. age >65 yrs)	1
Drugs or alcohol (1 point each)	1 or 2

INR = international normalized ratio

HAS-BLED total score	N	Number of bleeds	Bleeds per 100 patient-yrs*
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.5
6	2	0	0.0
7	0	–	–
8	0	–	–
9	0	–	–

*P value for trend = 0.007

Pisters R et al. Chest. 2010;138:1093–100; ESC guidelines: Camm J et al. Eur Heart J 2010;31:2369–429

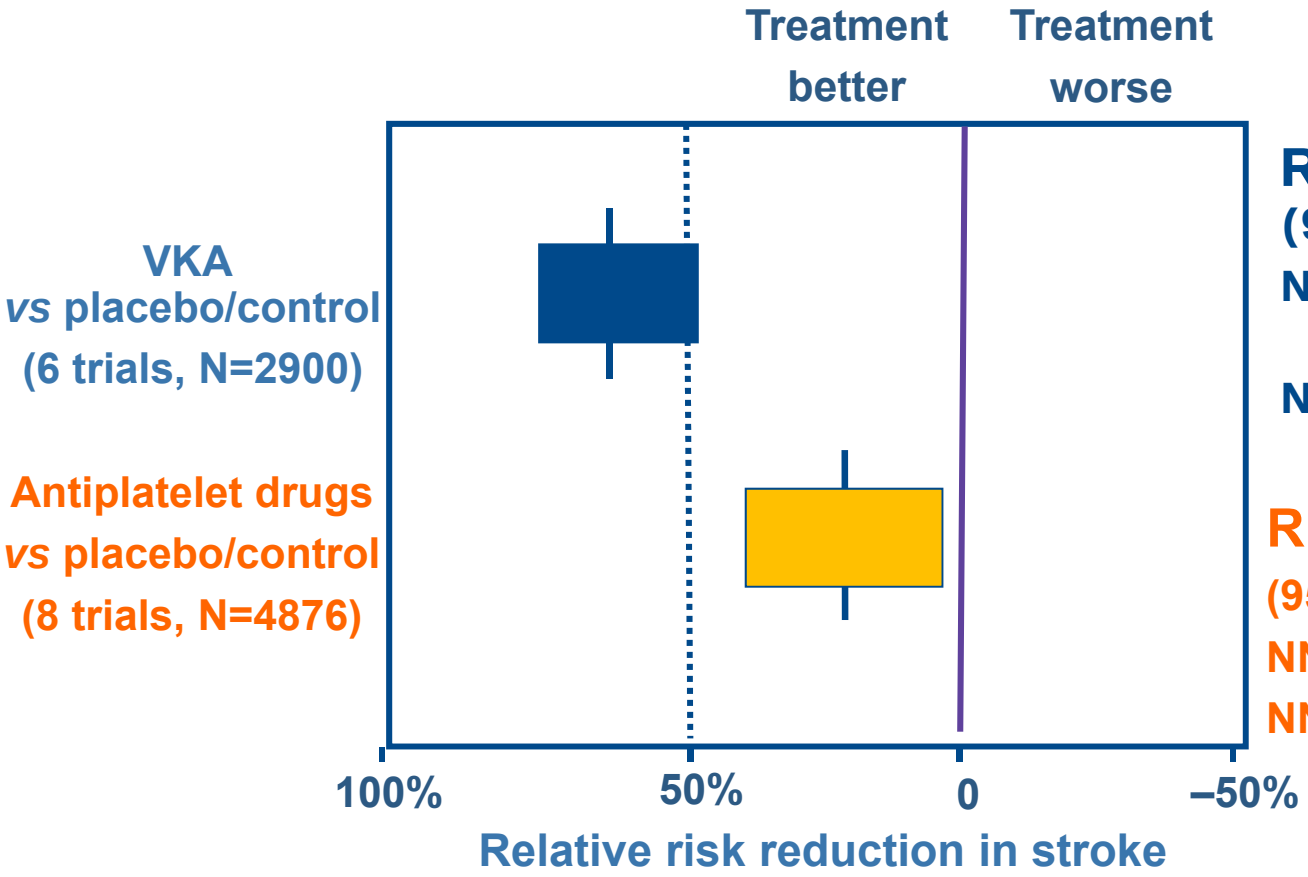
What is the next step?

- Continue warfarin
- Switch to ASA
- Switch to ASA + Clopidogrel
- Start NOAC

Which NOAC?

1. Dabigatran 110 mg bid
2. Rivaroxaban 15 mg qd
3. Apixaban 5 mg bid

In historical trials in AF patients, VKA and antiplatelet agents reduced stroke by ~60% and ~20%, respectively



RRR 64%
(95% CI: 49 to 74)
NNT: 40* (primary prevention)
NNT: 14* (secondary prevention)

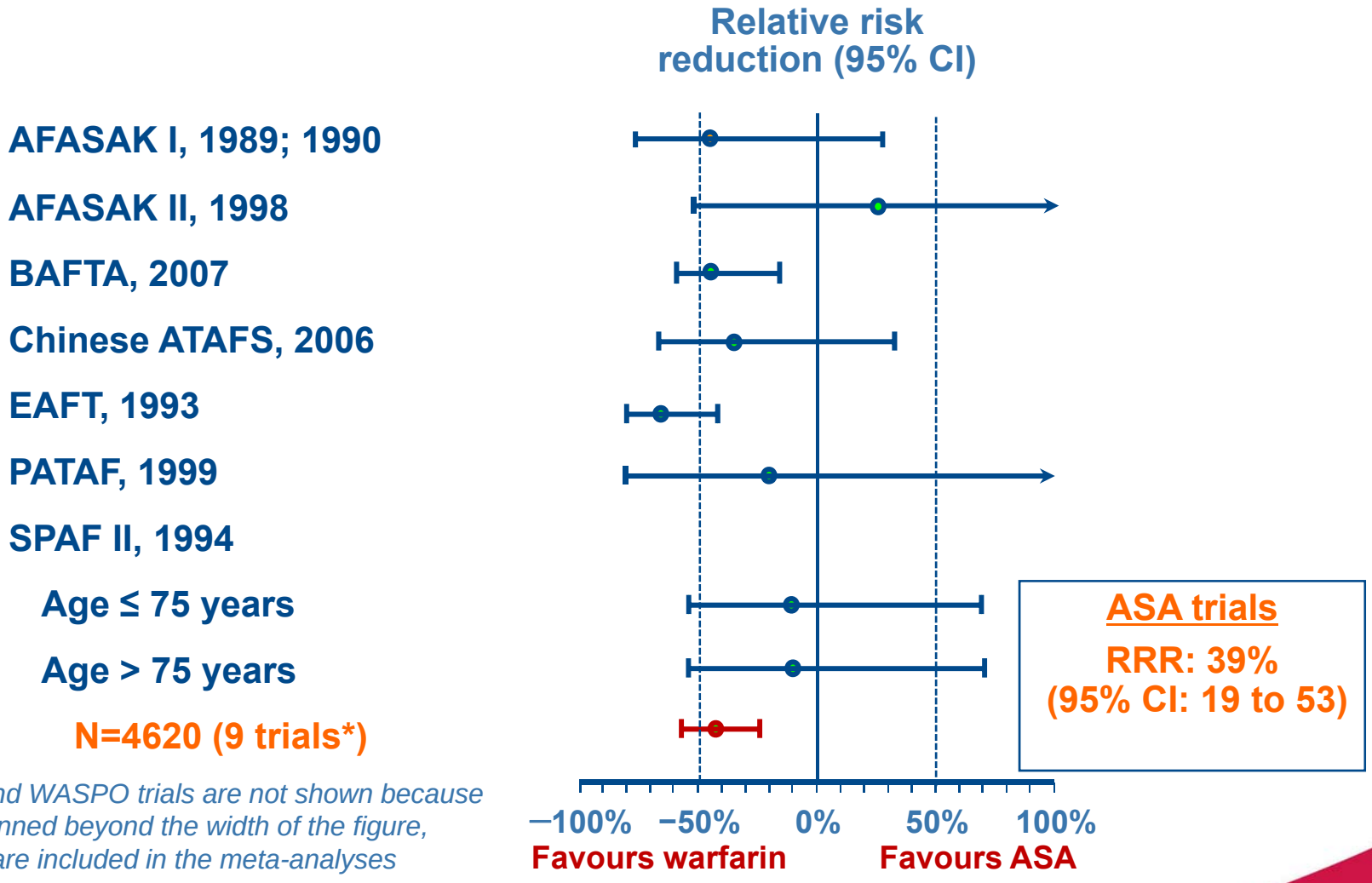
RRR 22%**
(95% CI: 6 to 35)
NNT: 111* (primary prevention)
NNT: 34* (secondary prevention)

*NNT for one year to prevent one stroke

**If data confined to ASA, the RRR is 19% (95% CI: -1 to 35, NS)

Hart et al. Ann Intern Med 2007;146:857-67.

ASA was less effective than VKA in historical trials in AF patients

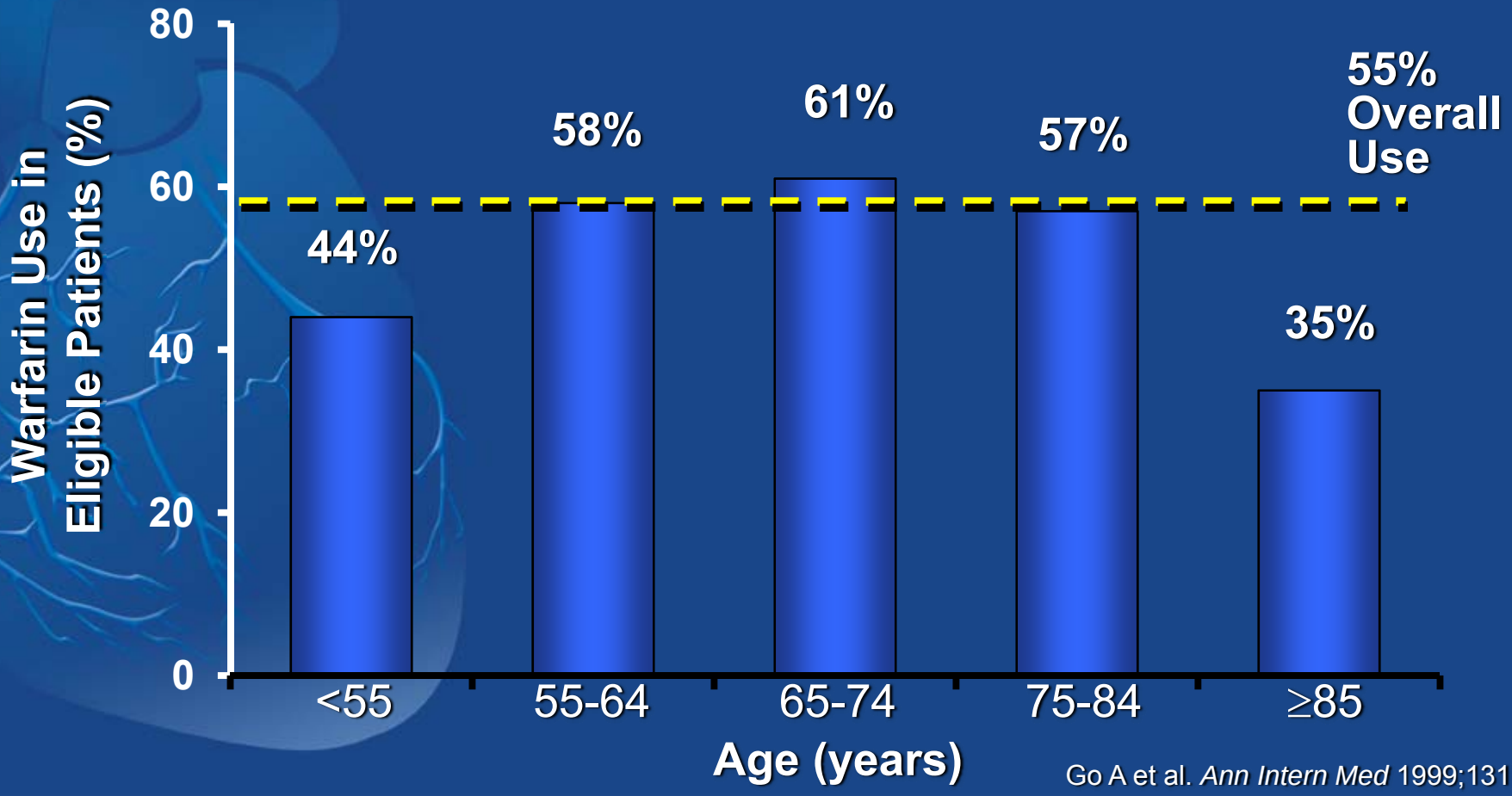


**The Vemmos and WASPO trials are not shown because the 95% CIs spanned beyond the width of the figure, but their results are included in the meta-analyses*

Adapted from Hart et al. Ann Intern Med 2007;147:590-592.

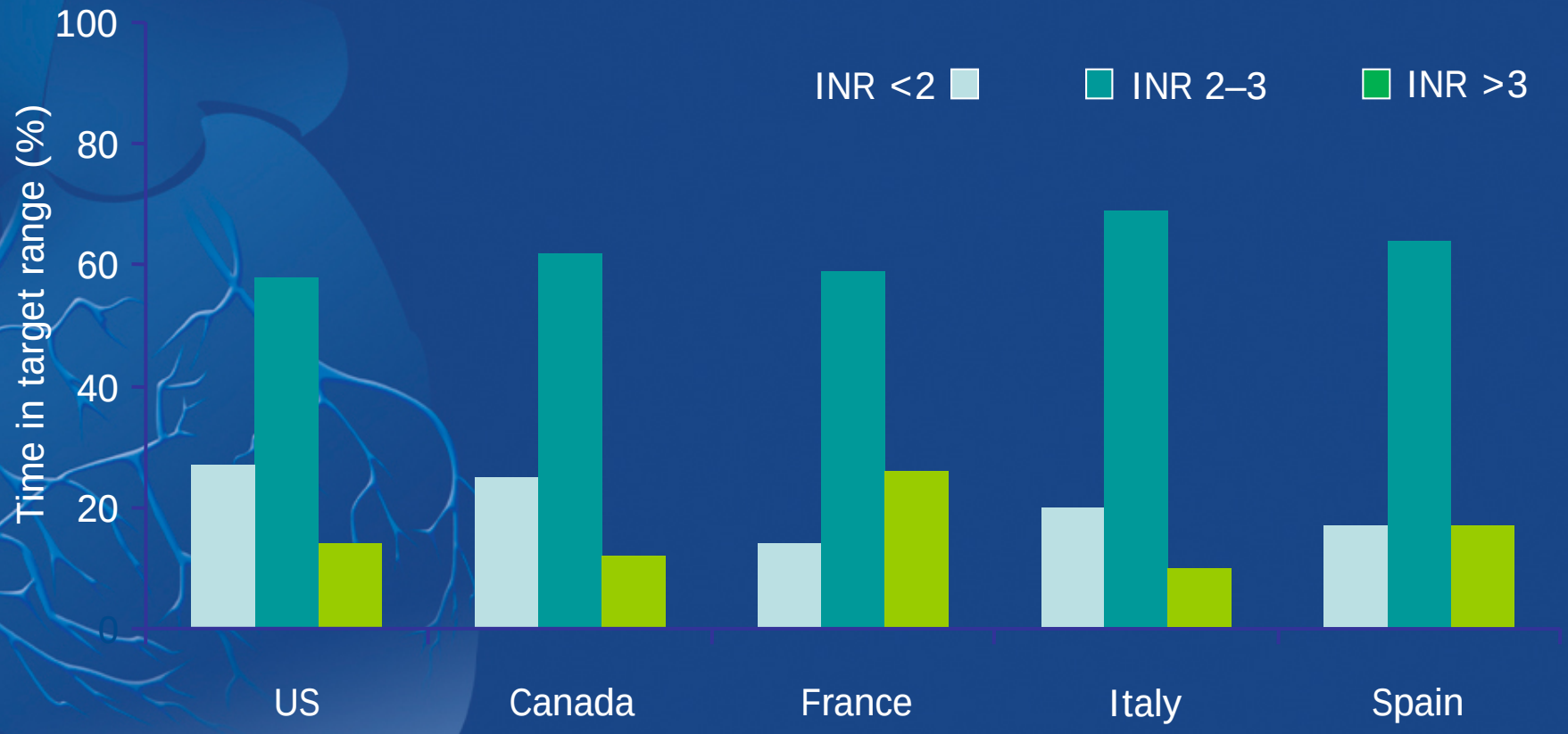
Warfarin for Atrial Fibrillation

Limitations Lead to Under-treatment



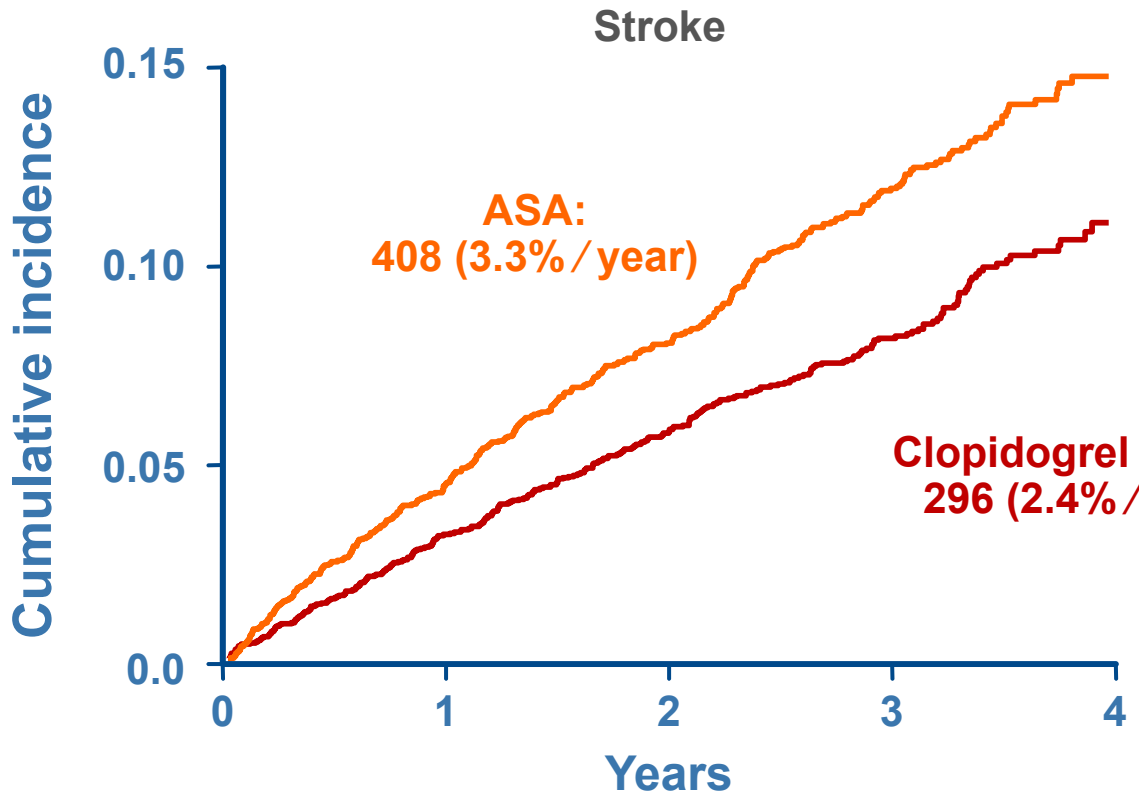
Go A et al. *Ann Intern Med* 1999;131:927.

The INR for VKAs is often outside the therapeutic range: international study of anticoagulation management



Dual antiplatelet therapy was more effective than ASA for stroke prevention

ACTIVE A trial: AF patients who had an increased risk of stroke and for whom VKA therapy was unsuitable (n=7,554)



RRR : 28%
RR 0.72
(95% CI, 0.62-0.83)
p <0.001

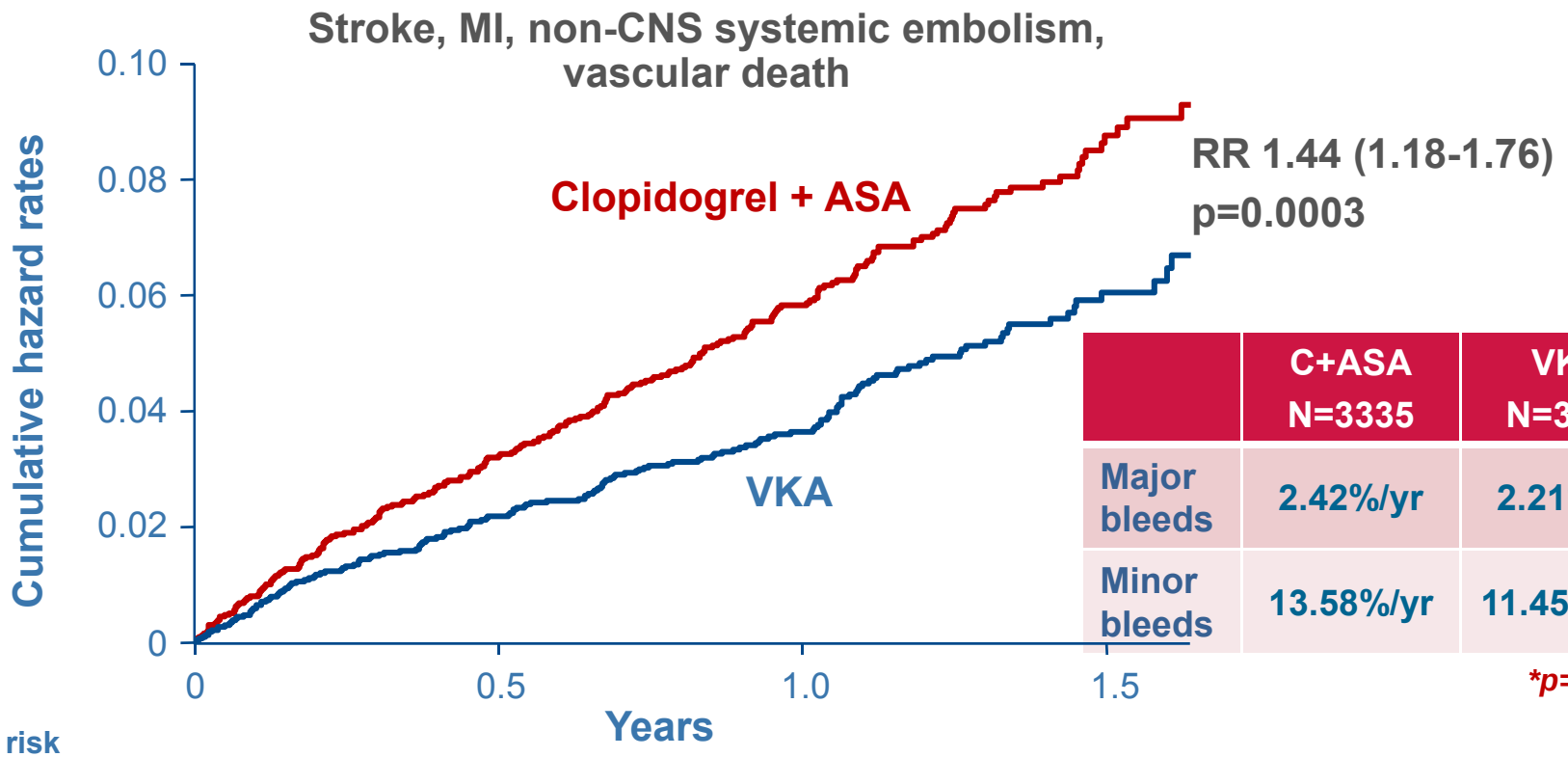
Adapted from ACTIVE Investigators. N Engl J Med 2009;360:2066-78.

ACTIVE-A - Bleeding complications

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Major	251	2.0	162	1.3	1.57	1.29-1.92	<0.001
Severe	190	1.5	122	1.0	1.57	1.25-1.98	<0.001
Fatal	42	0.3	27	0.2	1.56	0.96-2.53	0.07
Intra-cranial	54	0.4	29	0.2	1.87	1.19-1.94	0.006
Extra-cranial	200	1.6	134	1.1	1.51	1.21-1.88	<0.001

VKA was superior to clopidogrel+ASA for prevention of vascular events in AF patients at high risk of stroke

ACTIVE-W trial: in 6706 AF patients with ≥ 1 risk factor for stroke



	C+ASA N=3335	VKA N=3371
Major bleeds	2.42%/yr	2.21%/yr
Minor bleeds	13.58%/yr	11.45%/yr*

*p=0.0009

No. at risk

Clopidogrel+ASA:	3335	3152	2389	927
VKA:	3371	3221	2458	924

ACTIVE-W. Lancet 2006;367:1903-12.

In real-world studies, AF patients receiving antiplatelet therapy have higher rates of ischemic stroke than VKA-treated patients

Rate of events / 100 person yrs – Median (Range)

	No therapy	Antiplatelet therapy	VKA GP, Hosp	VKA AC Clinic
Ischemic strokes	**4.45** (0.25-5.9)	**4.45** (2.0-1.0)	**1.66** (0-4.9)	**1.72** (0.97-2.00)
Major bleeding	**1.3** (1.0-3.3)	**1.42** (1.4-1.9)	**2.0** (0.3-4.4)	**1.7** (0-7.2)

GP: General practice; Hosp: Hospital; AC Clinic: Anticoagulation clinic.

Ogilvie et al. Thromb Haemost 2011;106:34-44.

AVERROES: Apixaban in patients with atrial fibrillation who have failed or are unsuitable for VKA treatment

N=5,599

Event-driven

Patient Population

- Patients with AF and one or more risk factors for stroke
- Not receiving VKA therapy (demonstrated or expected to be unsuitable for VKA)

Apixaban 5 mg BD
(2.5 mg in selected patients)

Aspirin 81–324 mg OD

Primary Outcomes

- Confirmed ischaemic stroke, haemorrhagic stroke, or systemic embolism

Secondary Outcomes

- Confirmed ischaemic stroke, haemorrhagic stroke, systemic embolism, myocardial infarction, or vascular death

522 centres

Reasons for unsuitability of vitamin K antagonist therapy

Reason for unsuitability of therapy[a]	Apixaban (n=2808)	Aspirin (n=2791)	Previous use of VKA (n=2216)	No previous use of VKA (n=3383)
Assessment that INR could not be maintained in therapeutic range	**465 (17)**	**468 (17)**	**932 (42)**	**–**
Adverse event not related to bleeding during VKA therapy	**86 (3**	**94 (3)**	**180 (8)**	**–**
Serious bleeding event during VKA therapy	**92 (3)**	**82 (3)**	**173 (8)**	**–**
Assessment that INR could not or was unlikely to be measured at requested intervals	**1196 (43)**	**1191 (43)**	**827 (37)**	**1560 (46)**
Expected difficulty in contacting patient for urgent change in dose of VKA	**322 (11)**	**331 (12)**	**167 (8)**	**486 (14)**

Connolly SJ et al. *N Engl J Med* 2011;364:806–817

Reasons for unsuitability of vitamin K antagonist therapy (contd.)

Reason for unsuitability of therapy[a]	Apixaban (n=2808)	Aspirin (n=2791)	Previous use of VKA (n=2216)	No previous use of VKA (n=3383)
Uncertainty about patient's ability to adhere to instruction regarding VKA therapy	**437 (16)**	**405 (15)**	**262 (12)**	**580 (17)**
Concurrent medications that could alter activity of VKA	**50 (2)**	**53 (2)**	**33 (1)**	**70 (2)**
Concurrent medications whose metabolism could be affected by VKA	**35 (1)**	**46 (2)**	**19 (1)**	**62 (2)**
Assessment that patient would be unable or unlikely to adhere to restrictions on factors such as alcohol and diet	**134 (5)**	**141 (5)**	**127 (6)**	**148 (4)**

Reasons for unsuitability of vitamin K antagonist therapy (contd.)

Reason for unsuitability of therapy[a]	Apixaban (n=2808)	Aspirin (n=2791)	Previous use of VKA (n=2216)	No previous use of VKA (n=3383)
Hepatic disease	13 (<1)	9 (<1)	4 (<1)	18 (1)
Mild cognitive impairment	85 (3)	86 (3)	56 (3)	115 (3)
Heart failure or cardiomyopathy	179 (6)	188 (7)	95 (4)	272 (8)
Other factors that could be associated with increased risk of VKA use	96 (3)	123 (4)	121 (5)	98 (3)
$CHADS_2$ score of 1 and VKA therapy not recommended by physician	590 (21)	605 (22)	458 (21)	737 (22)
Other characteristics indicating risk of stroke too low to warrant treatment with VKA	55 (2)	40 (1)	32 (1)	63 (2)

Connolly SJ et al. *N Engl J Med* 2011;364:806–817

Reasons for unsuitability of vitamin K antagonist therapy (contd.)

Reason for unsuitability of therapy[a]	Apixaban (n=2808)	Aspirin (n=2791)	Previous use of VKA (n=2216)	No previous use of VKA (n=3383)
Patient's refusal to take VKA	**1053 (38)**	**1039 (37)**	**819 (37)**	**1273 (38)**
Other reasons	**184 (7)**	**189 (7)**	**249 (11)**	**124 (4)**
$CHADS_2$ score of 1 as only reason for unsuitability of VKA therapy	**313 (11)**	**336 (12)**	**216 (10)**	**433 (13)**
Patient's refusal to take VKA as only reason for unsuitability	**421 (15)**	**394 (14)**	**199 (9)**	**616 (18)**
Multiple reasons for unsuitability of VKA therapy	**1444 (51)**	**1440 (52)**	**1436 (65)**	**1448 (43)**

Connolly SJ et al. *N Engl J Med* 2011;364:806–817

Baseline characteristics

Characteristic	Apixaban	Aspirin
Randomized	**2808**	**2791**
Age (mean and SD)	**70 ± 9 yrs**	**70 ± 10 yrs**
Male	**59%**	**58%**
$CHADS_2$ score (mean and SD)	**2.0 ± 1.1**	**2.1 ± 1.1**
0–1	**36%**	**37%**
2	**37%**	**34%**
3+	**27%**	**29%**
Prior stroke/TIA	**14%**	**13%**

TIA, transient ischaemic attack

Connolly SJ et al. *N Engl J Med* 2011;364:806–817

Baseline characteristics (contd.)

Characteristic	Apixaban	Aspirin
Diabetes	19%	20%
Hypertension	86%	87%
Heart failure	40%	38%
Baseline aspirin	76%	75%
Unsuitable for VKA		
VKA used and discontinued	40%	
VKA expected unsuitable	60%	

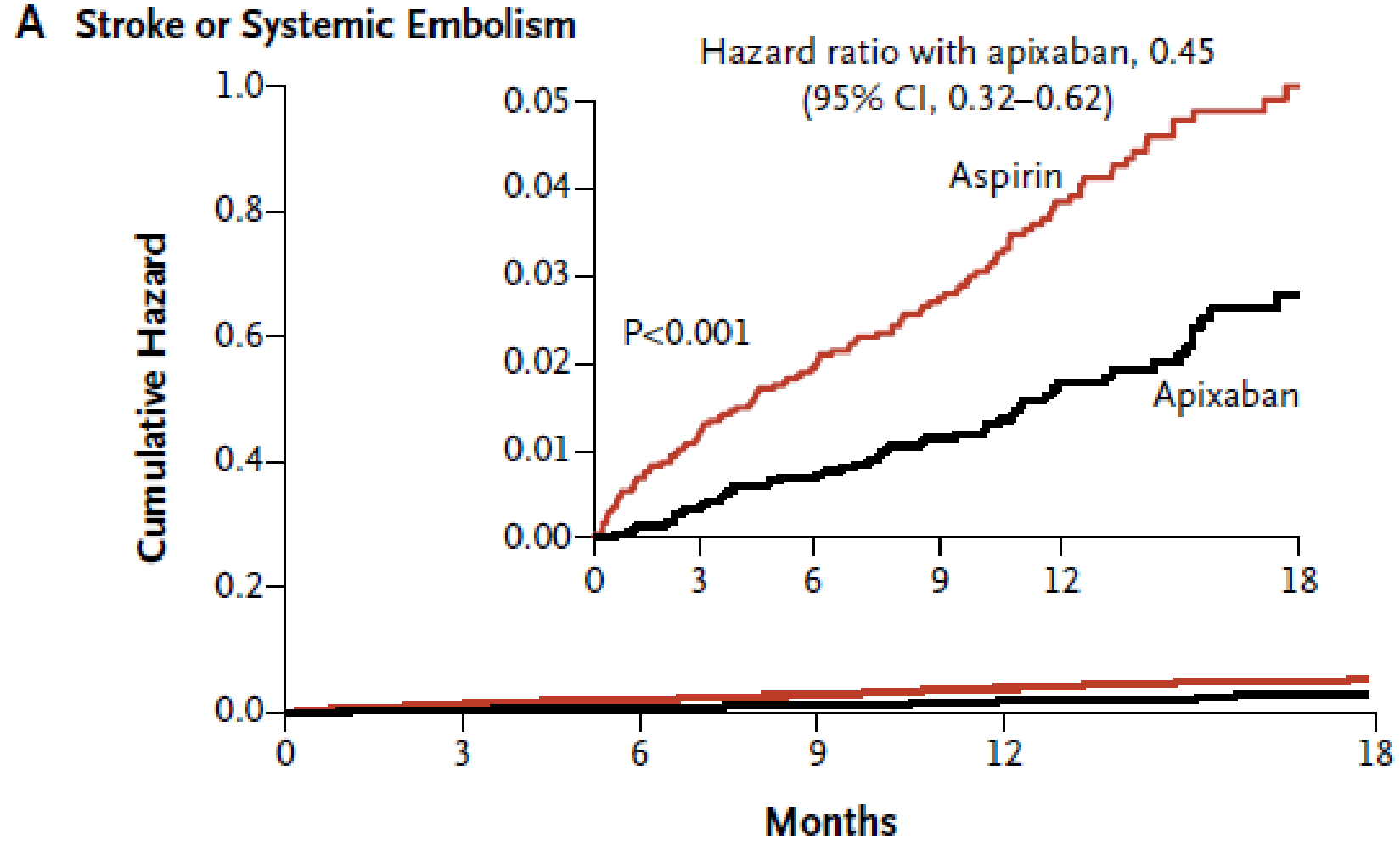
VKA, vitamin K antagonist

Connolly SJ et al. *N Engl J Med* 2011;364:806–817

Study design and execution

- DMC recommended early study termination at 1st analysis of efficacy – May 28, 2010
  - 4 SD x 2 in favour of apixaban
  - Long-term open-label apixaban follow-up*
- 94% patients received apixaban 5 mg BID
- 91% patients received aspirin ≤162 mg daily
- Median follow-up: 1.1 year

Connolly SJ et al. *N Engl J Med* 2011;364:806–817
*Clinicaltrials.gov NCT00496769



No. at Risk

Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615

Primary outcome events

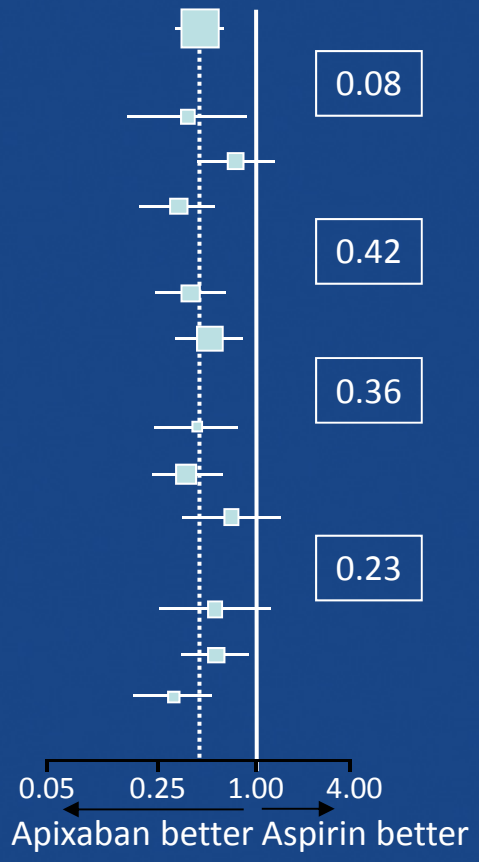
Outcome	Apixaban (n=2808) No. of patients with first event	Apixaban (n=2808) %/yr	Aspirin (n=2791) No. of patients with first event	Aspirin (n=2791) %/yr	Apixaban *vs* aspirin Hazard ratio	95% CI	p
Stroke or SE	51	1.6	113	3.7	0.45	0.32–0.62	<0.001
Stroke	49	1.6	105	3.4	0.46	0.33–0.65	<0.001
Ischemic	35	1.1	93	3.0	0.37	0.25–0.55	<0.001
Haemorrhagic	6	0.2	9	0.3	0.67	0.24–1.88	0.45
Type not determined	9	0.3	4	0.1	2.24	0.69–7.27	0.18
SE	2	0.1	13	0.4	0.15	0.03–0.68	0.01

Secondary and other efficacy outcomes

Outcome	Apixaban (n=2808)		Aspirin (n=2791)		Apixaban *vs* aspirin		
	No. of patients with first event	%/yr	No. of patients with first event	%/yr	Hazard ratio	95% CI	p
Stroke, SE, MI, or vascular death	132	4.2	197	6.4	0.66	0.53-0.83	<0.001
MI	24	0.8	28	0.9	0.86	0.50-1.48	0.59
Vascular death	84	2.7	96	3.1	0.87	0.65-1.17	0.37
CV hospitalization	367	12.6	455	15.9	0.79	0.69-0.91	<0.001
Total death	111	3.5	140	4.4	0.79	0.62-1.02	0.07

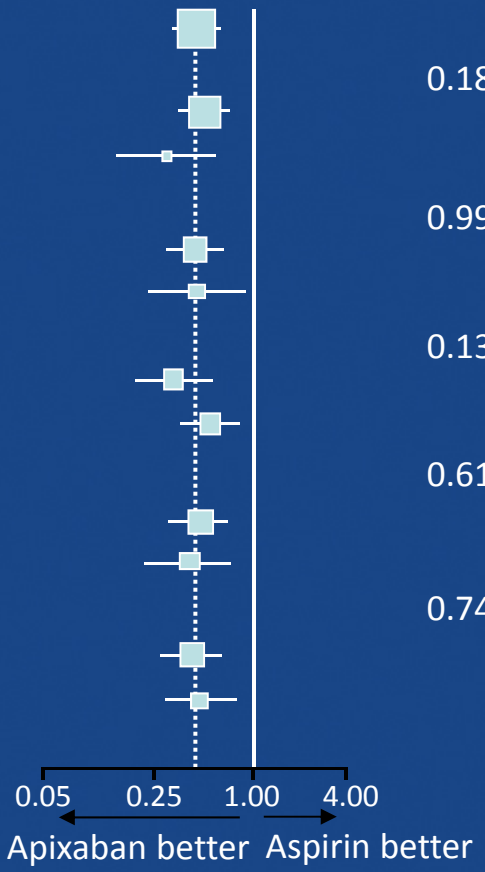
Stroke or systemic embolism (1)

Characteristic	No. of patients	Aspirin *no. of events (%/yr)*	Apixaban *no. of events (%/yr)*	Hazard ratio with Apixaban (95% CI)	P value for interaction
Overall	5599	113 (3.7)	51 (1.6)		
Age					0.08
<65 yr	1714	19 (2.0)	7 (0.7)		
65 to <75 yr	1987	28 (2.7)	24 (2.0)		
≥75 yr	1897	66 (6.1)	20 (2.0)		
Sex					0.42
Female	2321	64 (4.9)	25 (1.9)		
Male	3277	49 (2.7)	26 (1.4)		
Estimated GFR					0.36
<50 ml/min	1198	36 (5.8)	16 (2.5)		
50 to <80 ml/min	2374	59 (4.5)	22 (1.7)		
≥80 ml/min	2021	18 (1.6)	13 (1.1)		
$CHADS_2$ score					0.23
0–1	2026	18 (1.6)	10 (0.9)		
2	1999	40 (3.7)	25 (2.1)		
≥3	1570	55 (6.3)	16 (1.9)		

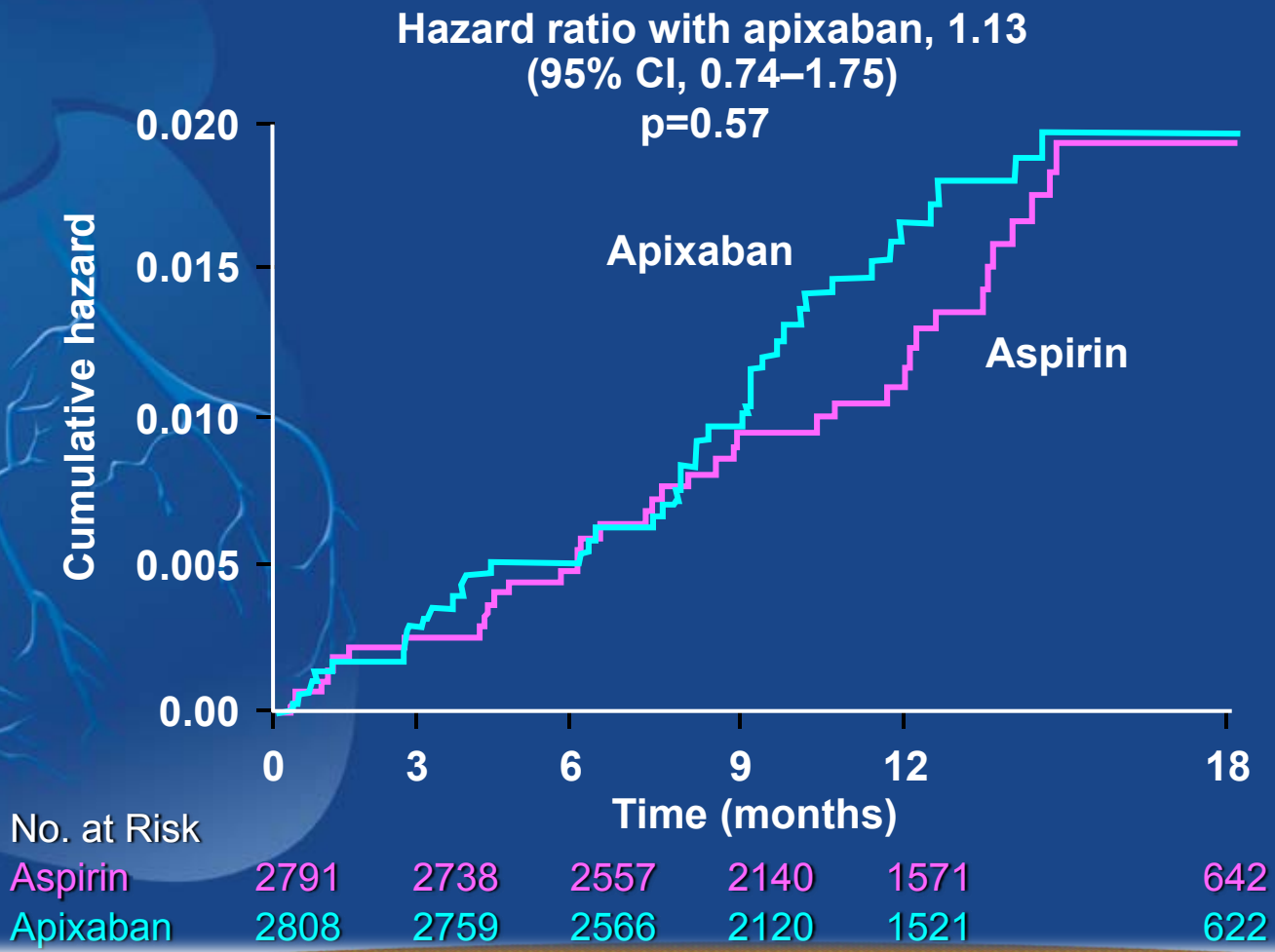


Stroke or systemic embolism (2)

Characteristic	No. of patients	Aspirin *no. of events (%/yr)*	Apixaban *no. of events (%/yr)*	P value for interaction
Overall	5599	113 (3.7)	51 (1.6)	
Prior stroke or TIA				0.18
No	4835	80 (3.0)	41 (1.5)	
Yes	764	33 (8.3)	10 (2.5)	
Study aspirin dose				0.99
<162 mg daily	3602	85 (4.3)	39 (1.9)	
≥162 mg daily	1978	27 (2.4)	12 (1.1)	
Previous VKA use				0.13
Yes	2216	52 (4.2)	17 (1.4)	
No	3383	61 (3.3)	34 (1.8)	
Patient refused VKA				0.61
No	3506	73 (3.8)	35 (1.8)	
Yes	2092	40 (3.4)	16 (1.4)	
Heart failure				0.74
No	3428	66 (3.6)	28 (1.5)	
Yes	2171	45 (3.8)	23 (1.8)	



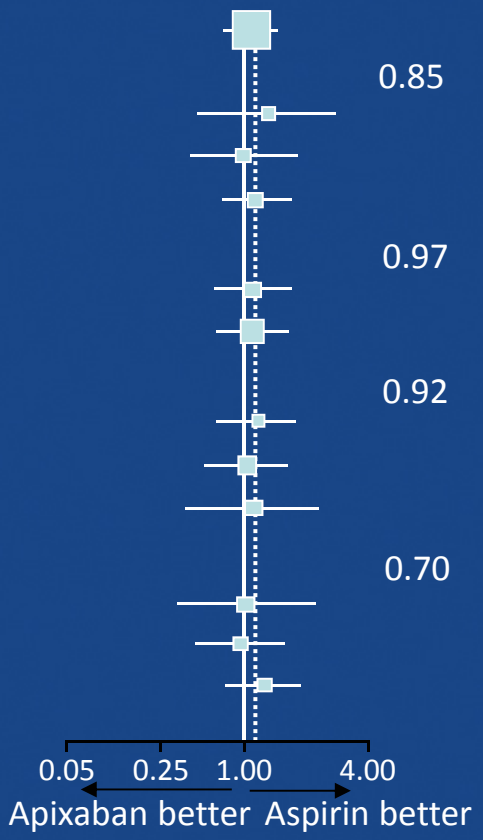
Major bleeding



AVERROES

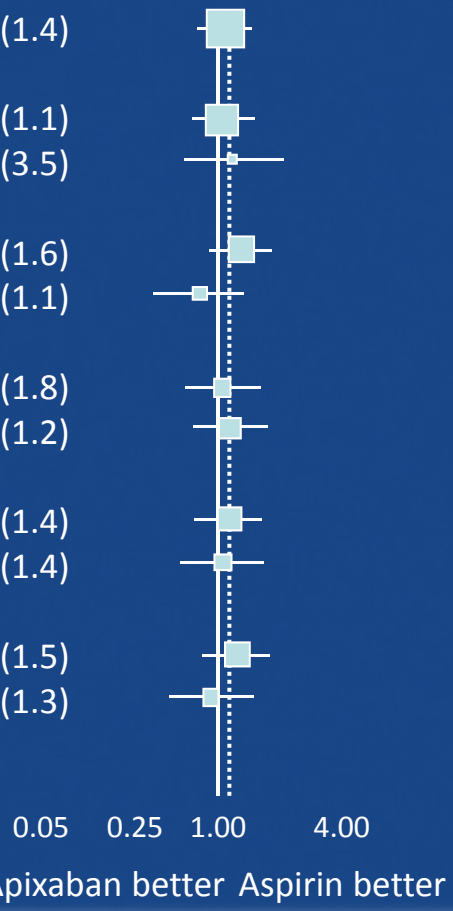
Major bleeding (1)

Characteristic	No. of patients	Aspirin *no. of events (%/yr)*	Apixaban *no. of events (%/yr)*
Overall	5599	39 (1.2)	44 (1.4)
Age			
<65 yr	1714	5 (0.5)	7 (0.7)
65 to <75 yr	1987	10 (1.0)	11 (0.9)
≥75 yr	1897	24 (2.2)	26 (2.6)
Sex			
Female	2321	17 (1.3)	19 (1.5)
Male	3277	22 (1.2)	25 (1.4)
Estimated GFR			
<50 ml/min	1198	16 (2.5)	20 (3.2)
50 to <80 ml/min	2374	17 (1.3)	17 (1.3)
≥80 ml/min	2021	6 (0.5)	7 (0.6)
$CHADS_2$ score			
0–1	2026	6 (0.5)	6 (0.5)
2	1999	14 (1.3)	14 (1.2)
≥3	1570	19 (2.1)	24 (2.9)



Major bleeding (2)

Characteristic	No. of patients	Aspirin *no. of events (%/yr)*	Apixaban *no. of events (%/yr)*	Hazard ratio with Apixaban (95% CI)	P value for interaction
Overall	5599	39 (1.2)	44 (1.4)		
Prior stroke or TIA					0.73
No	4835	28 (1.0)	30 (1.1)		
Yes	764	11 (2.7)	14 (3.5)		
Study aspirin dose					0.14
<162 mg daily	3602	22 (1.1)	32 (1.6)		
≥162 mg daily	1978	17 (1.5)	12 (1.1)		
Previous VKA use					0.74
Yes	2216	21 (1.7)	22 (1.8)		
No	3383	18 (1.0)	22 (1.2)		
Patient refused VKA					0.84
No	3506	24 (1.2)	28 (1.4)		
Yes	2092	15 (1.3)	16 (1.4)		
Heart failure					0.36
No	3428	22 (1.1)	28 (1.5)		
Yes	2171	17 (1.4)	16 (1.3)		



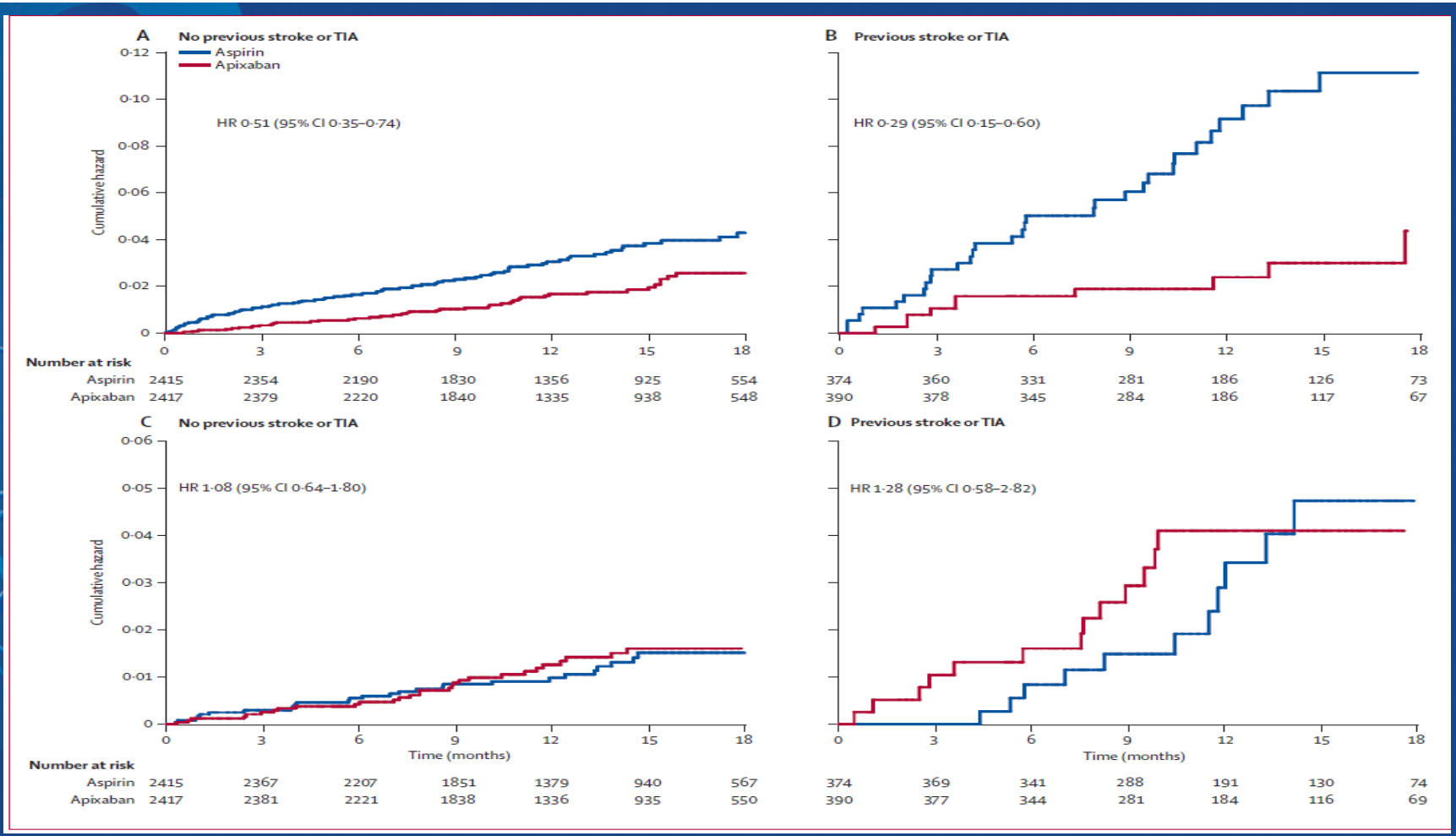
Phase III AVERROES: discontinuation of study medication

- Annual rate of permanent discontinuation (at 2 years)
  - 17.9% with apixaban
  - 20.5% with ASA

- 12% lower risk of permanent discontinuation with apixaban vs ASA
  - HR 0.88%; 95% CI 0.78–0.99; P=0.03

Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial

*Hans-Christoph Diener, John Eikelboom, Stuart J Connolly, Campbell D Joyner, Robert G Hart, Gregory Y H Lip, Martin O'Donnell, Stefan H Hohnloser, Graeme J Hankey, Olga Shestakovska, Salim Yusuf, for the AVERROES steering committee and investigators**



The Lancet Neurology, 11;225 - 231, 2012

Clinical Implications

- In patients with AF considered unsuitable for warfarin, or refuse taking warfarin, apixaban significantly reduced the risk of stroke or systemic embolism compared to ASA.
- The risk of bleeding was similar with aspirin and apixaban.
- Apixaban was also associated with a significant reduction in the need for CV hospitalizations.

Clinical Implications

- Most AF patients deemed unsuitable for warfarin are suitable to the new generation anticoagulants
- When warfarin is undesirable because of bleeding risk, apixaban is superior to ASA

Which NOAC?

1. Dabigatran 110 mg bid
2. Rivaroxaban 15 mg qd
3. Apixaban 5 mg bid

HEART DISEASE AND STROKE PREVENTION

ADDRESSING THE NATION'S LEADING KILLERS

Bar-Ilan University
Faculty of Medicine

אוניברסיטת בר-אילן
הפקולטה לרפואה