



Is there a role for aspirin in stroke prevention in AF 2015?

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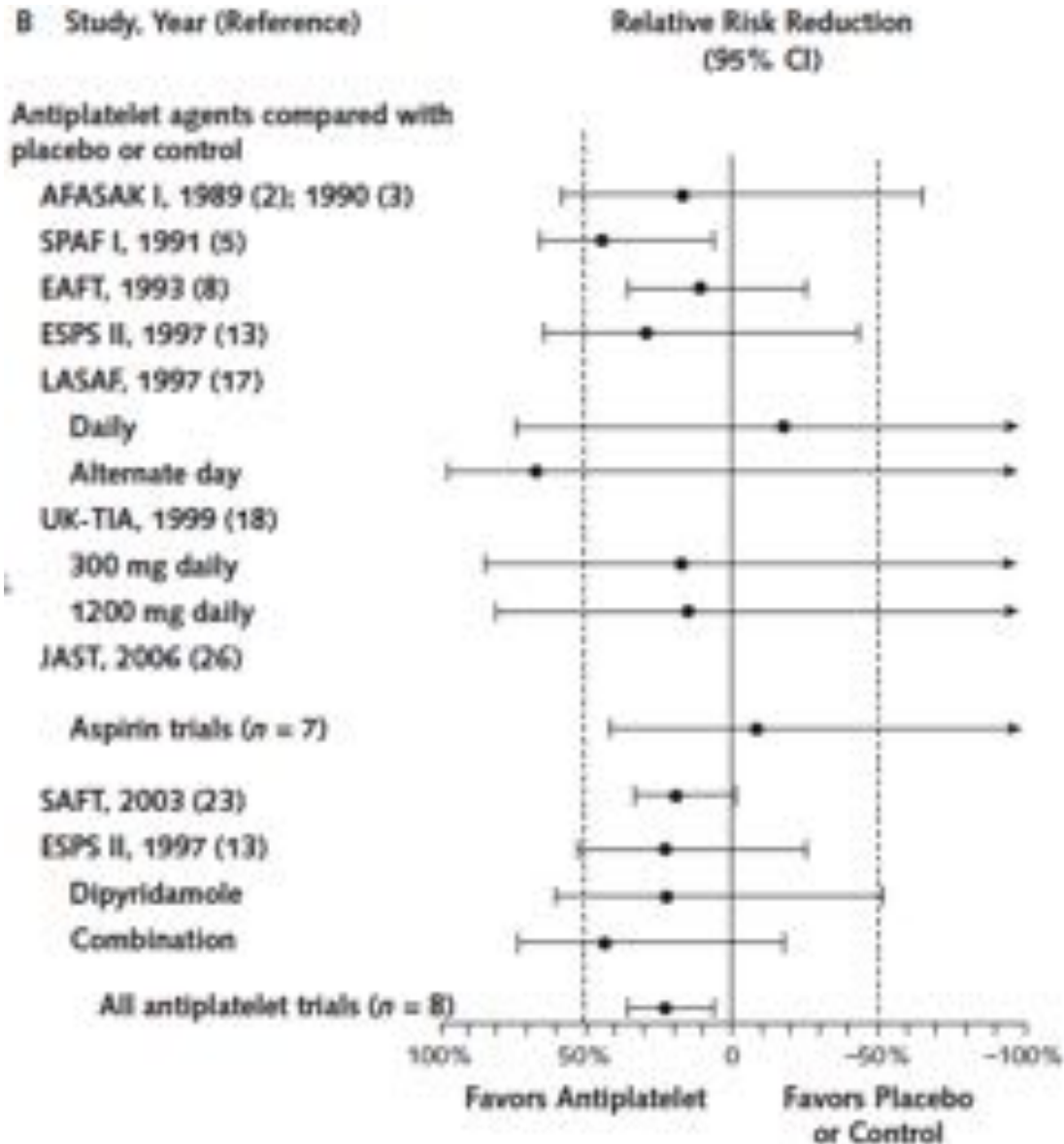
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MY CONFLICTS OF INTEREST ARE

Consultant and lecture fees from
Bayer, Boehringer-Ingelheim, Bristol-
Myers Squibb, and Pfizer



Aspirin vs placebo or control in AF



Aspirin vs placebo or no treatment

Study, Year (Reference)	Secondary Prevention, %†	Participants, n	Dosage	Strokes/Patients/Patient-Years; Antiplatelet vs. Placebo or No Treatment, n/n/n‡	Relative Risk Reduction (95% CI), %§
Aspirin vs. placebo					
AFASAK I, 1989 (2); 1990 (3)	6	672	75 mg/d	16/336/409 vs. 19/336/398	17
SPAF I, 1991 (5)	7	1120	325 mg/d	25/552/723 vs. 44/568/734	44
EAFT, 1993 (8)	100	782	300 mg/d	88/404/853 vs. 90/378/734	11
ESPS II, 1997 (13)	100	211	50 mg/d	17/104/123 vs. 23/107/111	29
UK-TIA, 1999 (18)**	100	28	300 mg/d	3/13/52 vs. 4/15/60	17
	100	36	1200 mg/d	5/21/84 vs. 4/15/60	14
5 aspirin-placebo trials	41	2834	-	154/1430/2244 vs. 184/1419/2097	22 (2 to 39)
Aspirin vs. no treatment					
LASAF, 1997 (17)	0	196	125 mg/d	4/104/145 vs. 3/91/135	-17
	0	181	125 mg qod	1/90/148 vs. 3/91/135	67
IAST, 2006 (26)	3	871	150 mg/d	20/426/895 vs. 19/445/935	-10
In total, 7 aspirin trials	30	3990	-	179/2050/3432 vs. 209/2046/3302	19 (-1 to 35)

Warfarin vs antiplatelets

C Study, Year (Reference)

Relative Risk Reduction
(95% CI)

Adjusted-dose warfarin compared
with antiplatelet agents

AFASAK I, 1989 (2); 1990 (3)

AFASAK II, 1998 (14)

Chinese ATAFS, 2006 (30)

EAFT, 1993 (8)

PATAF, 1999 (16)

SPAF II, 1994 (10)

Age ≤ 75 y

Age >75 y

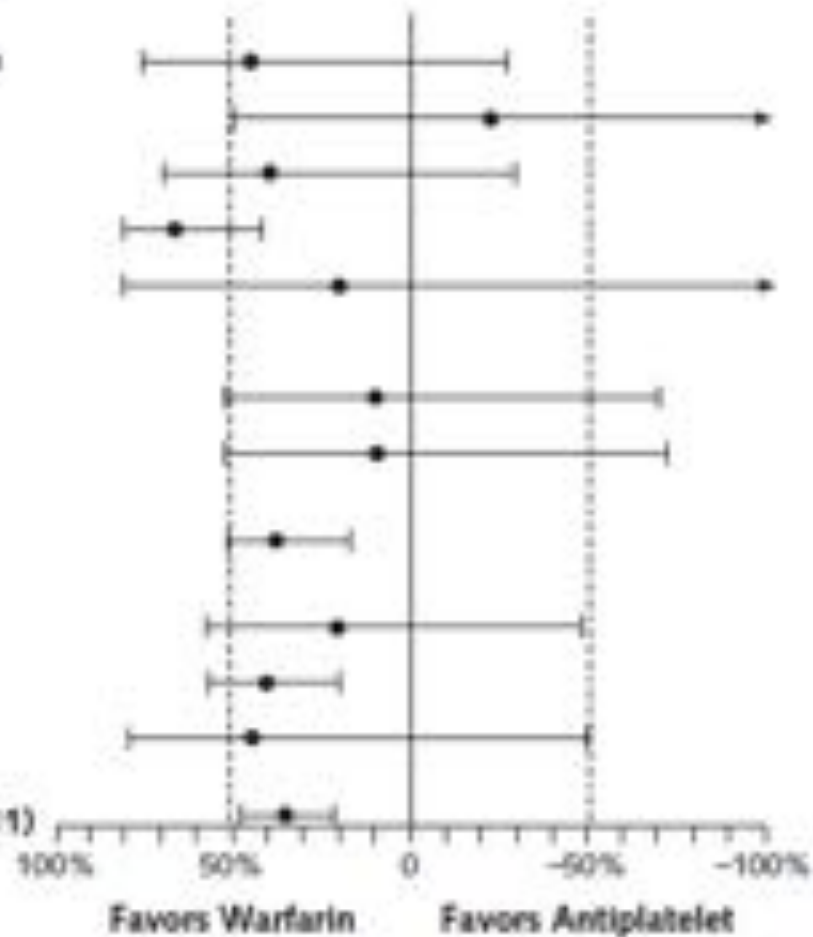
Aspirin trials (n = 8)*

SIFA, 1997 (12)

ACTIVE-W, 2006 (28)

NASPEAF, 2004 (25)

All antiplatelet trials (n = 11)



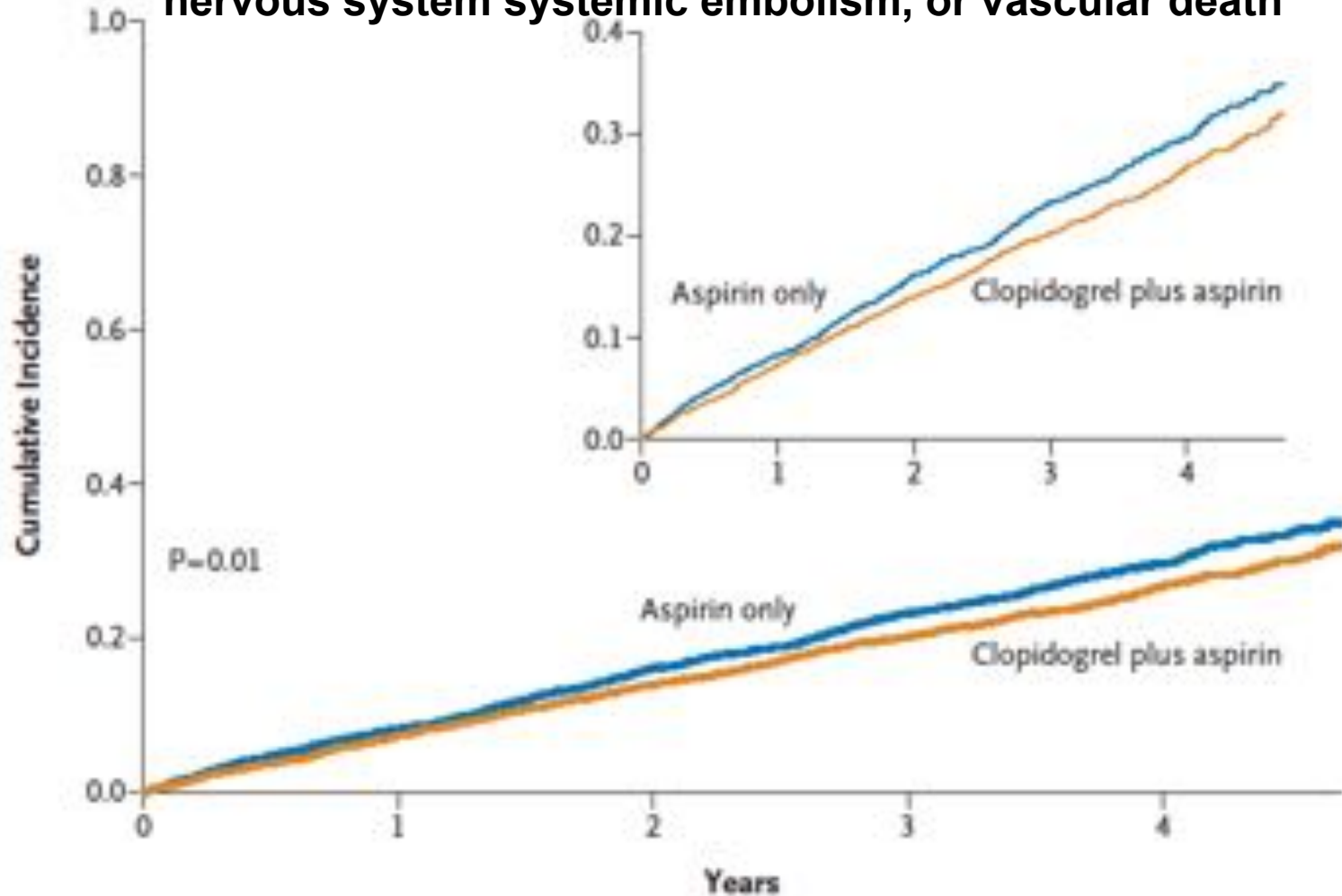
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Warfarin Compared with Antiplatelet Therapy

Study, Year (Reference)	Secondary Prevention, %†	Participants, n	Target INR	Strokes/Patients/Patient-Years: Adjusted-Dose Warfarin vs. Antiplatelet, n/n/n	Relative Risk Reduction (95% CI), %‡
Adjusted-dose warfarin vs. aspirin					
AFASAK I, 1989 (2); 1990 (3)	6	671	2.8–4.2	9/335/413 vs. 16/336/409	45
SPAF II, 1994 (10) (patients age <75 y)	6	715	2–4.5	19/358/1099 vs. 21/357/1083	10
SPAF II, 1994 (10) (patients age >75 y)	9	385	2–4.5	20/197/394 vs. 21/188/377	10
EAFI, 1993 (8)§	100	455	2.5–4	20/225/507 vs. 52/230/477	67
AFASAK II, 1998 (14)	8	339	2–3	11/170/355 vs. 9/169/365	–23
PATAF, 1999 (16)	0	272	2.5–3.5	3/131/401 vs. 4/141/392	20
Vermos et al., 2006 (27)	0	31	1.6–2.5	0/16/5 vs. 2/15/5	100
Chinese ATAFS, 2006 (30)§	19	704	2–3	9/335/530 vs. 17/369/583	43
WASPO, 2007 (31)	0	75	2–3	0/36/36 vs. 0/39/39	NC
8 aspirin trials	21	3647	–	91/1803/3740 vs. 142/1844/3730	38 (18 to 52)
Adjusted-dose warfarin vs. nonaspirin antiplatelet agents					
SIFA, 1997 (12)§	100	916	2–3.5	18/454/450 vs. 23/462/460	21
NASPEAF, 2004 (25)	0	479	2–3	6/237/556 vs. 11/242/576	45
ACTIVE-W, 2006 (28)§	15	6706	2–3	65/3371/4200 vs. 106/3335/4180	40
11 aspirin trials	22	11748	–	180/5865/8946 vs. 282/5883/8946	37 (23 to 48)
Adjusted-dose warfarin vs. low- and fixed-dose warfarin plus aspirin**					
SPAF III, 1996 (11)	38	1044	2–3	14/523/581 vs. 48/521/558	73
AFASAK II, 1998 (14)	10	341	2–3	11/170/355 vs. 11/171/377	–1
In total, 12 aspirin trials	24	12963	–	205/6558/9982 vs. 341/6575/9881	39 (22 to 52)

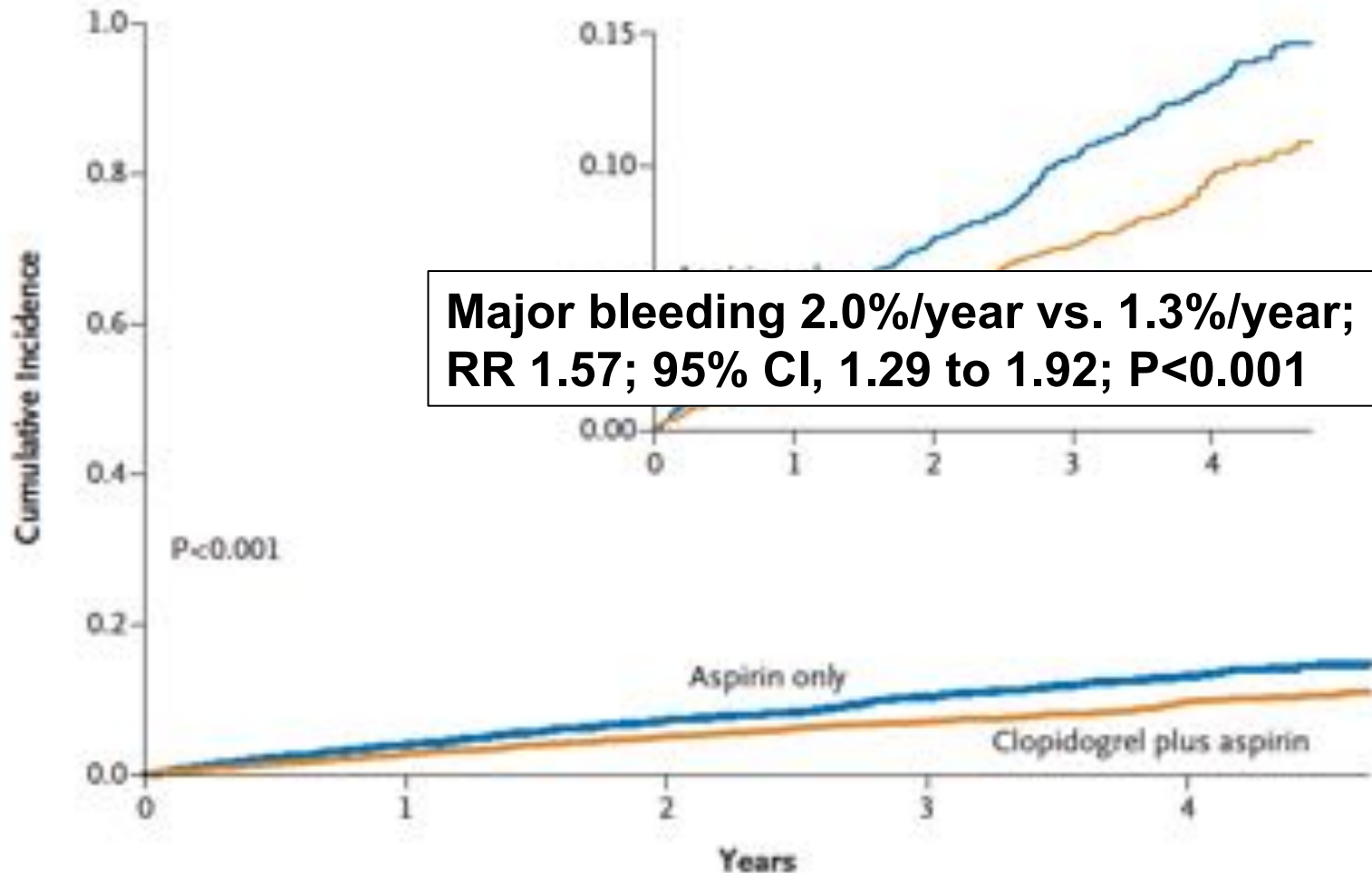
Aspirin + Clopidogrel vs. Aspirin

Primary outcome: Stroke, myocardial infarction, non-central nervous system systemic embolism, or vascular death

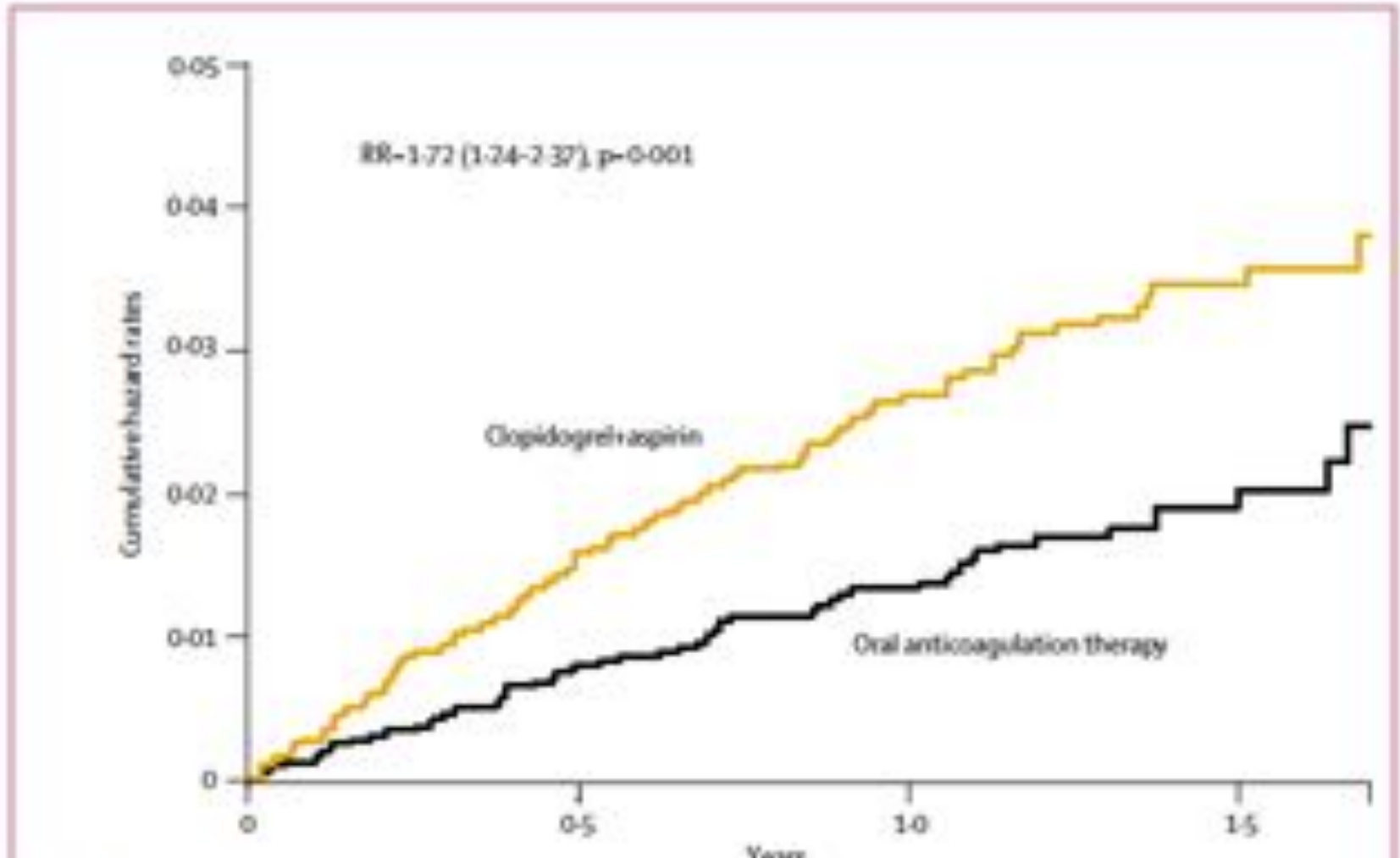


Aspirin + Clopidogrel vs. Aspirin

Ischemic stroke



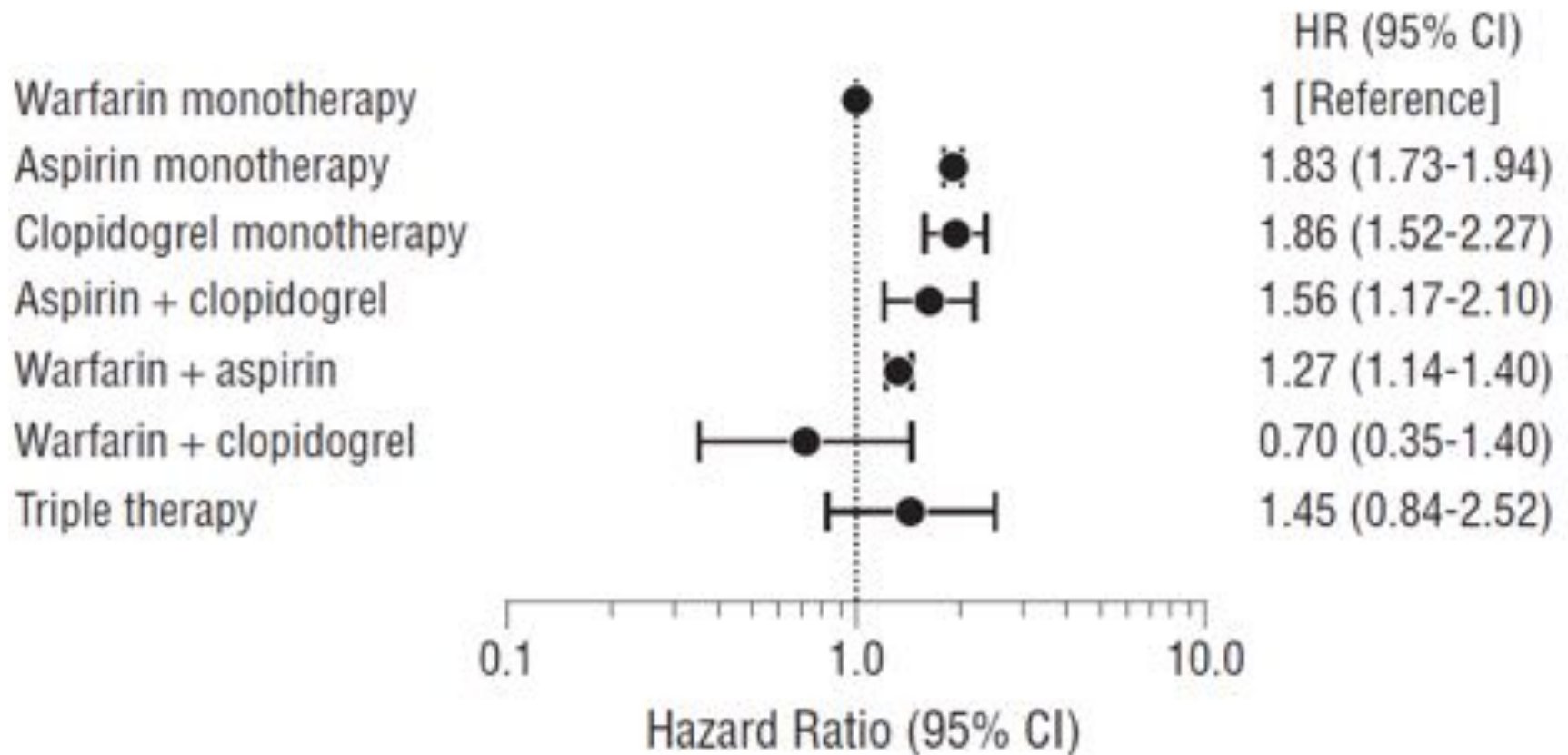
ACTIVE W: Warfarin vs. Clopidogrel + ASA Risk of Stroke



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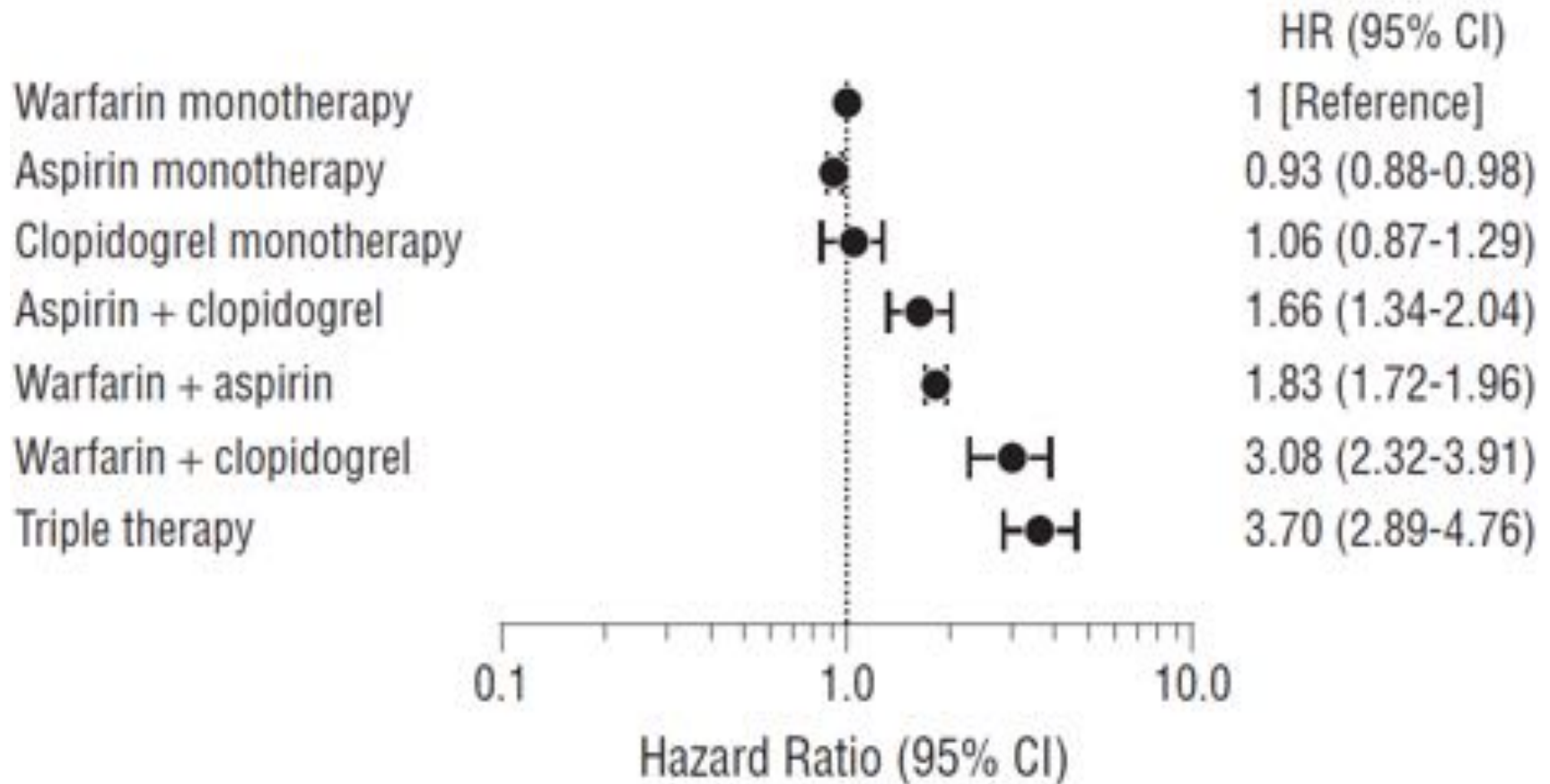
Ischemic stroke associated with warfarin, aspirin, clopidogrel in patients with AF

n=82 854

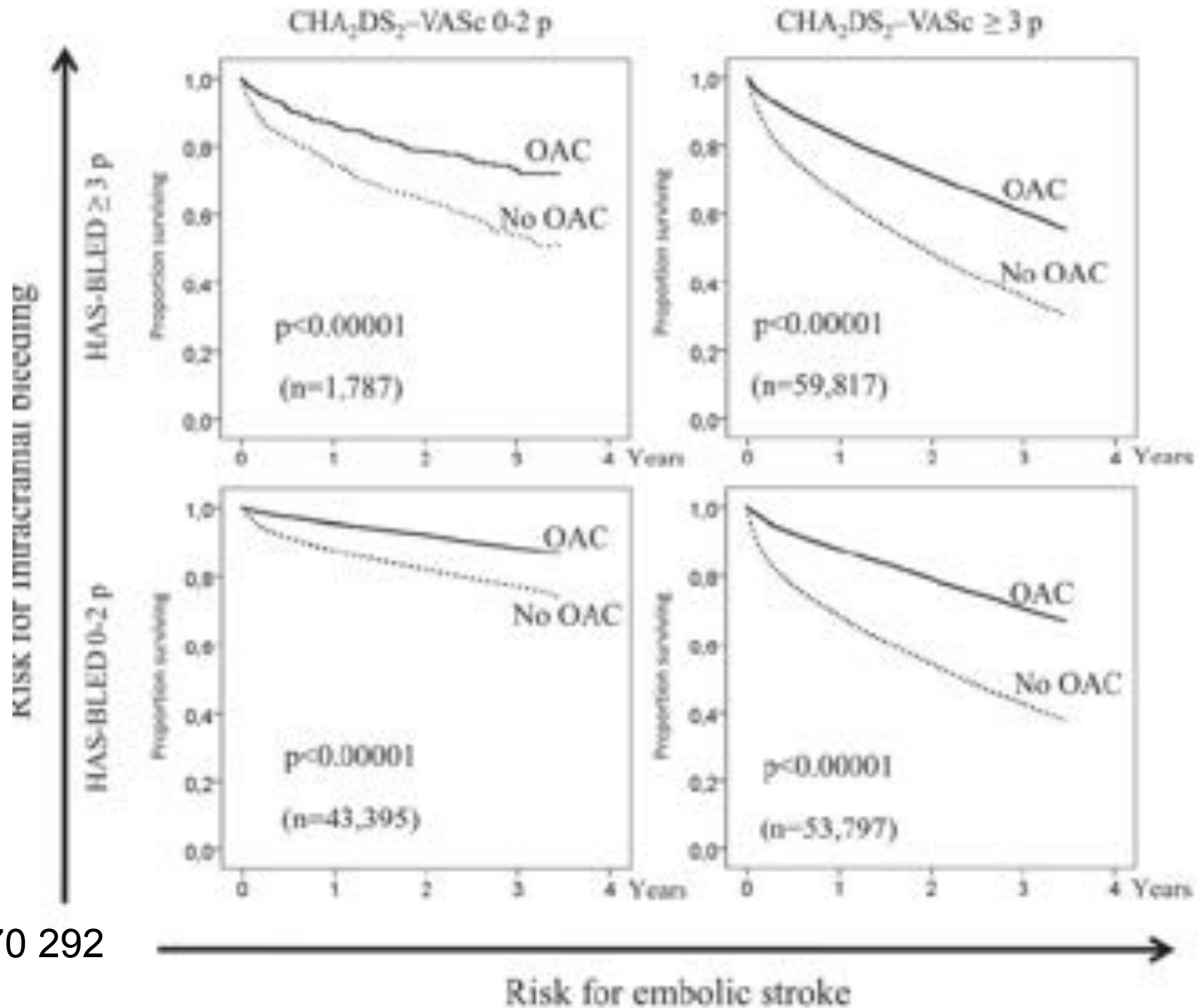


Bleeding associated with warfarin, aspirin, clopidogrel in patients with AF

n=82 854



Mortality, ischemic stroke and intracranial bleeds



N = 170 292



Net clinical benefit with warfarin or aspirin in patients with AF

Hazard ratios (95% CI), n=132 372

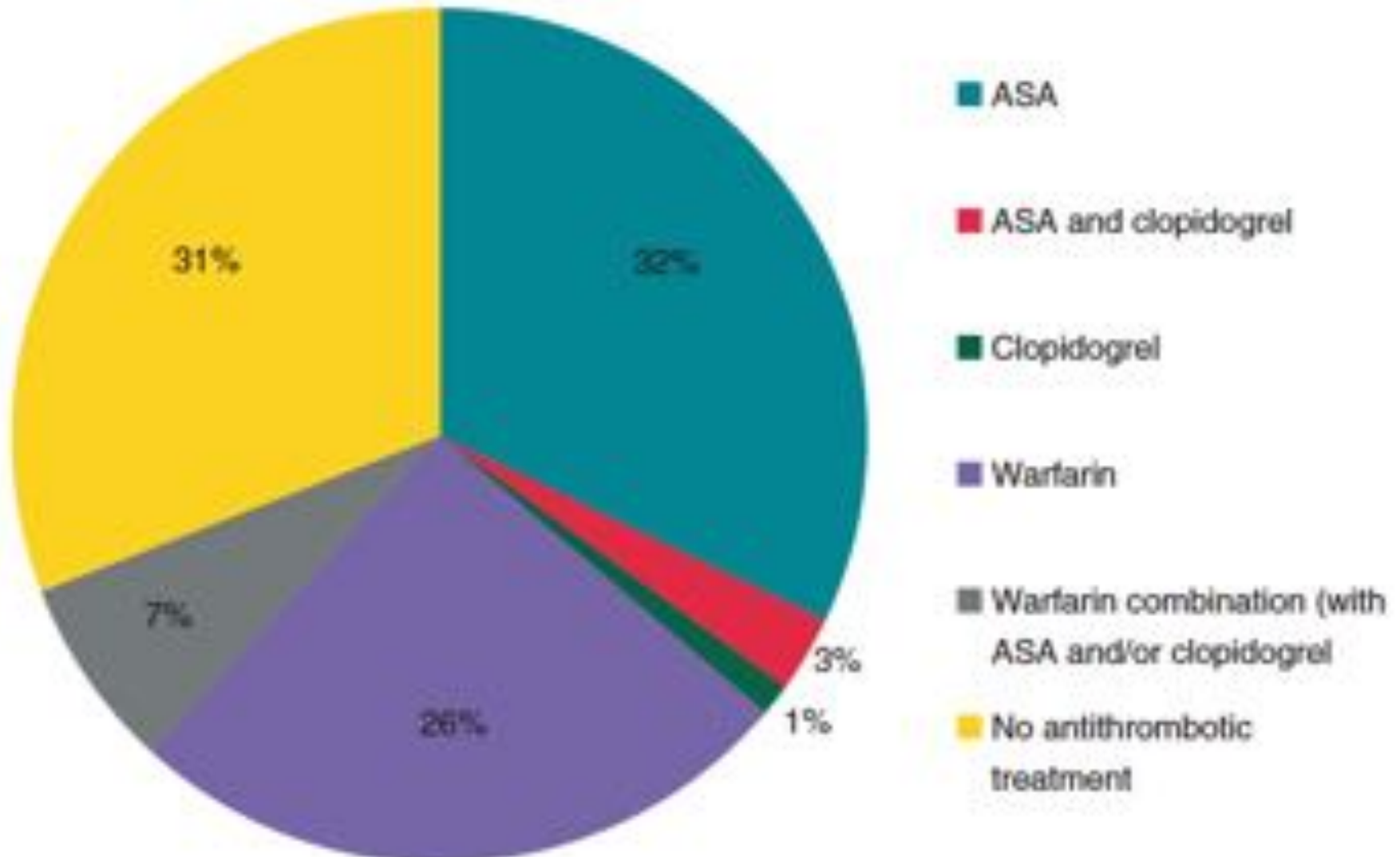
	Stroke				VKA		ASA	
	Ischaemic		Haemorrhagic		HAS-BLED score		HAS-BLED score	
	N (%)	Person to years at risk	N (%)	Person to years at risk	Score ≤2	Score ≥3	Score ≤2	Score ≥3
CHADS₂								
Score 0	323 (1.0)	157,279	184 (0.6)	157,511	-0.02 (-0.09 to 0.06)	0.19 (-1.39 to 1.77)	-0.10 (-0.20 to -0.00)	0.37 (-0.74 to 1.48)
Score 1	1,853 (3.9)	169,755	436 (0.9)	170,606	0.84 (0.70 to 0.99)	0.56 (0.16 to 0.95)	-0.26 (-0.44 to -0.07)	0.21 (-0.18 to 0.60)
Score 2-6	5,034 (7.9)	180,237	761 (1.2)	182,250	1.95 (1.70 to 2.20)	2.68 (2.33 to 3.04)	0.21 (-0.14 to 0.55)	0.30 (-0.08 to 0.68)
CHA₂DS₂-VASc								
Score 0	46 (0.4)	66,020	32 (0.3)	66,076	-0.11 (-0.20 to -0.03)	-	-0.00 (-0.09 to 0.08)	-
Score 1	170 (0.9)	86,370	108 (0.6)	86,474	-0.02 (-0.15 to 0.11)	0.25 (-0.86 to 1.36)	-0.02 (-0.15 to 0.11)	0.14 (-0.89 to 1.17)
Score 2-9	6,994 (6.2)	354,881	1,241 (1.1)	357,817	1.19 (1.07 to 1.32)	2.21 (1.93 to 2.50)	-0.04 (-0.22 to 0.14)	0.23 (-0.06 to 0.53)

Net clinical benefit = (ischaemic stroke rate with no treatment – ischaemic stroke rate on treatment) – 1.5*(ICH rate on treatment – ICH rate with no treatment)



Aspirin versus no treatment in AF

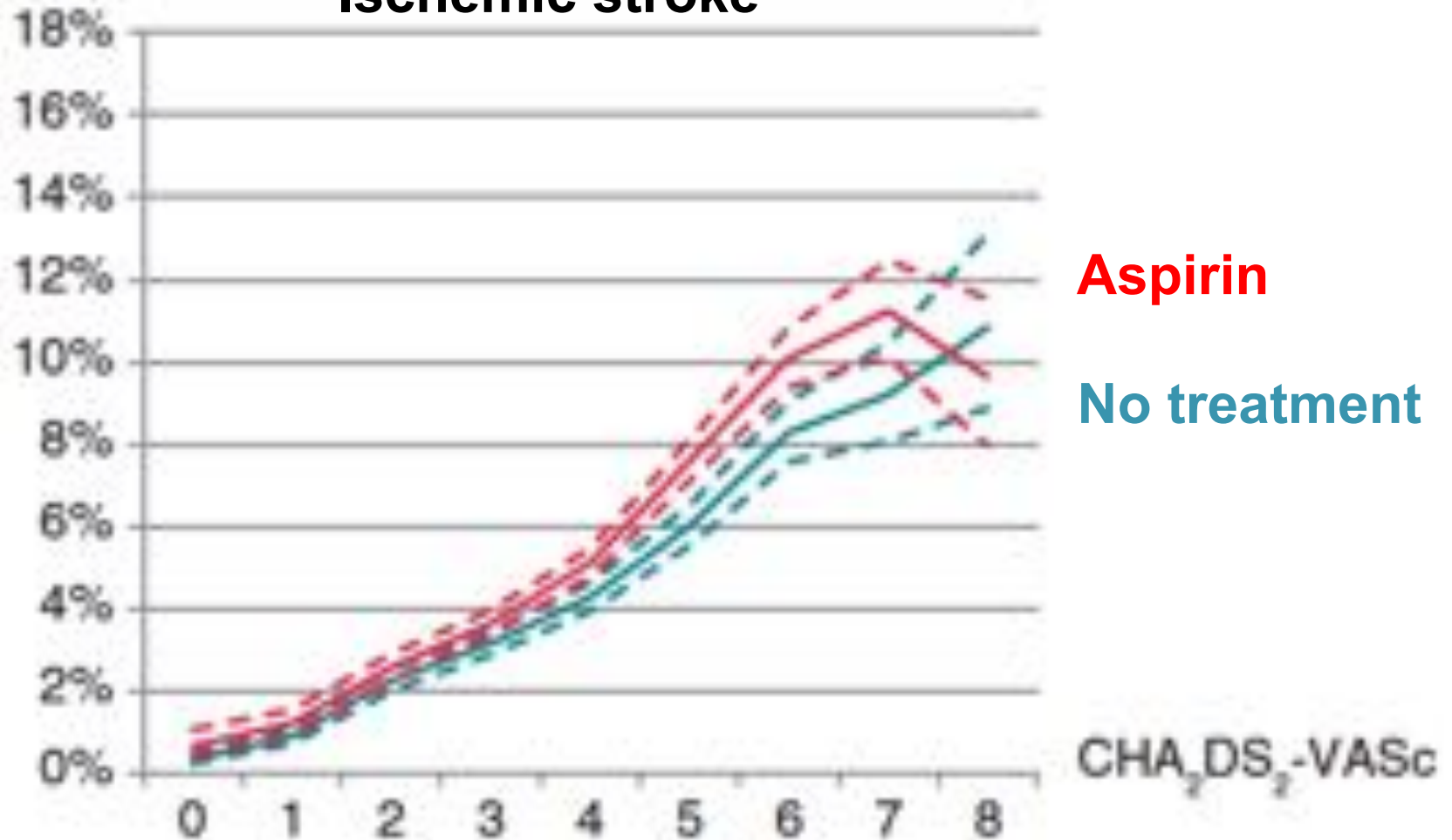
Swedish registry data 2005-2009; 58 671 aspirin monotherapy, 56 514 no treatment



Aspirin versus no treatment in AF

Swedish registry data 2005-2009; 58 671 aspirin monotherapy, 56 514 no treatment

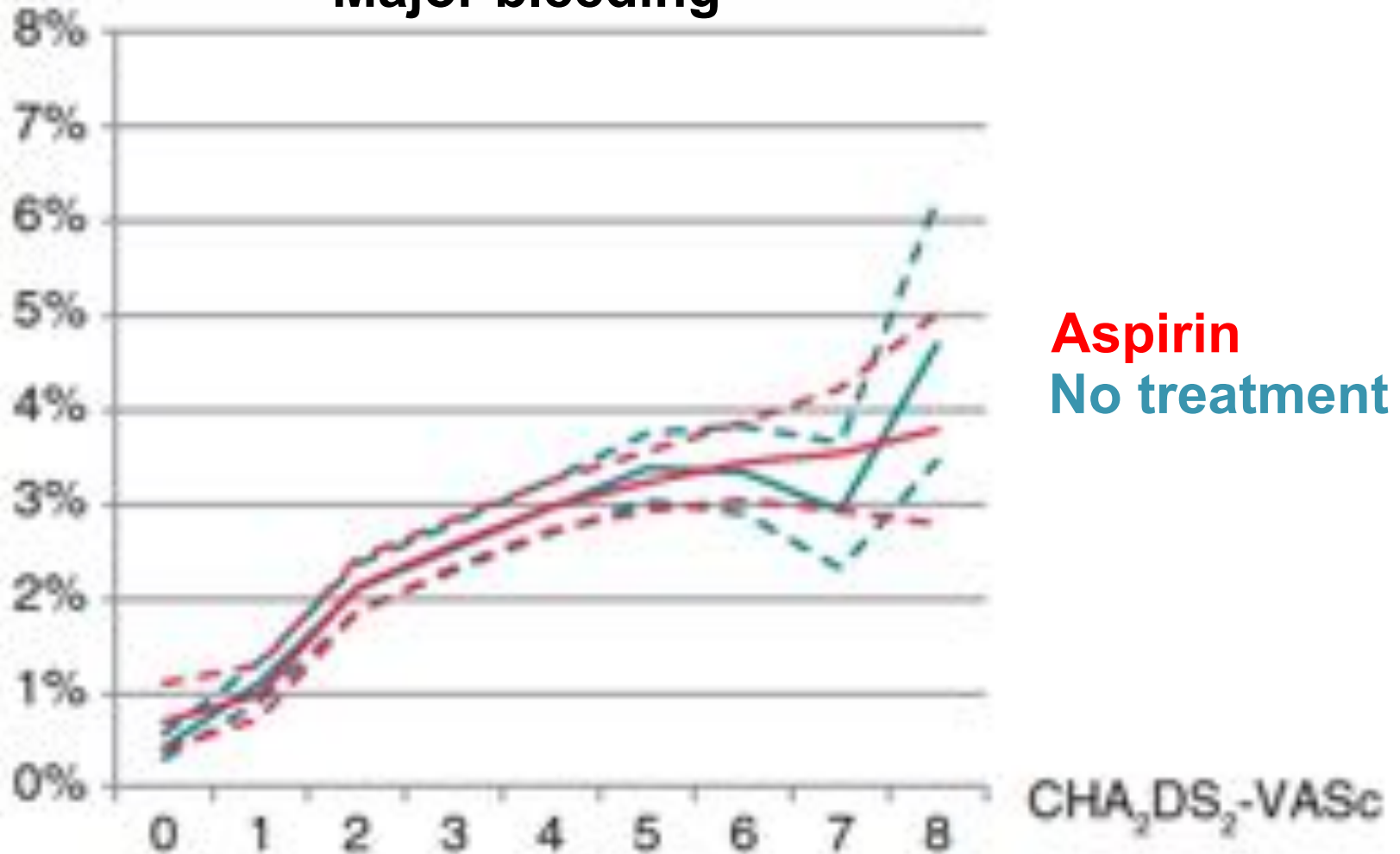
Ischemic stroke



Aspirin versus no treatment in AF

Swedish registry data 2005-2009; 58 671 aspirin monotherapy, 56 514 no treatment

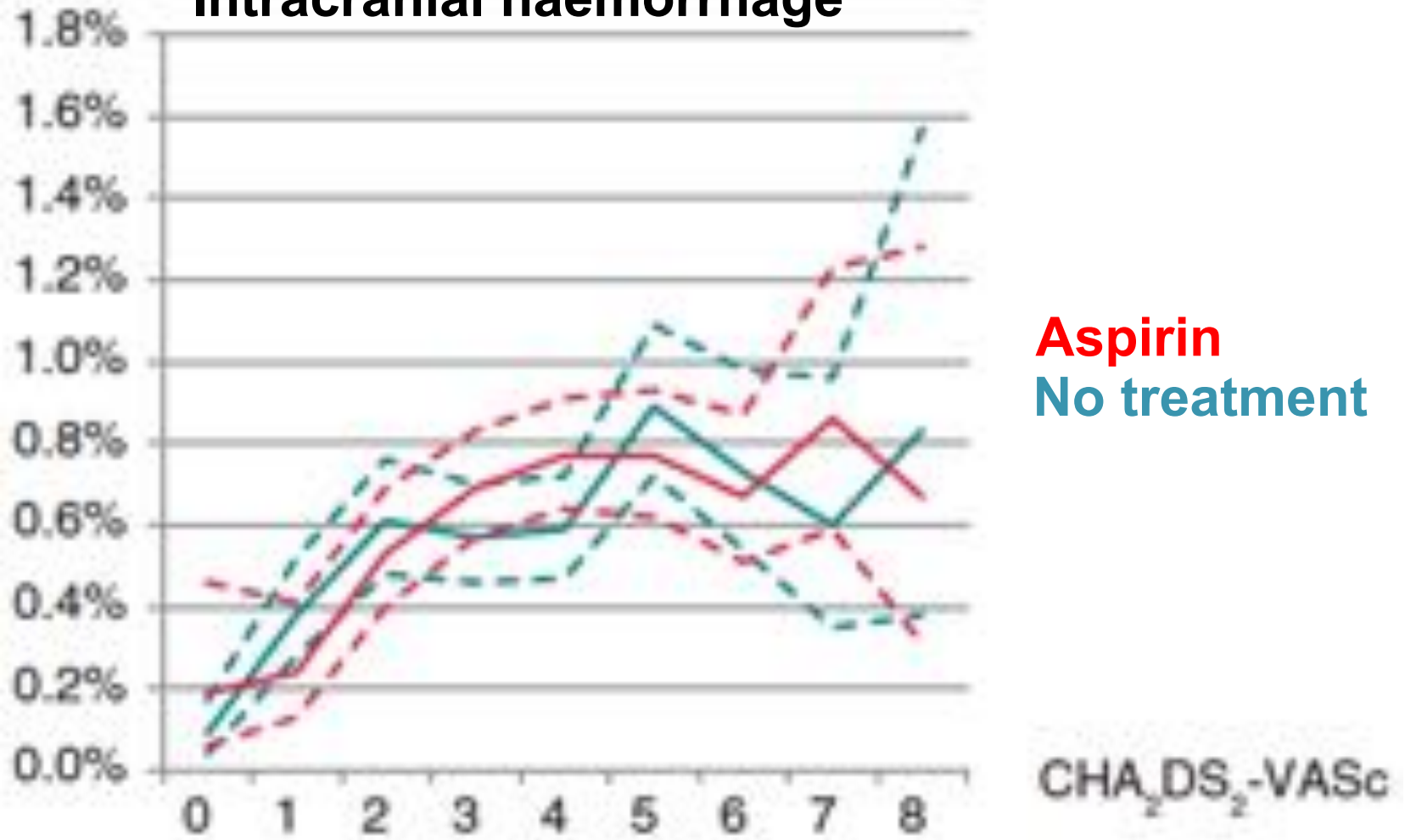
Major bleeding



Aspirin versus no treatment in AF

Swedish registry data 2005-2009; 58 671 aspirin monotherapy, 56 514 no treatment

Intracranial haemorrhage



Aspirin versus no treatment in AF

Swedish registry data 2005-2009; 58 671 aspirin monotherapy, 56 514 no treatment

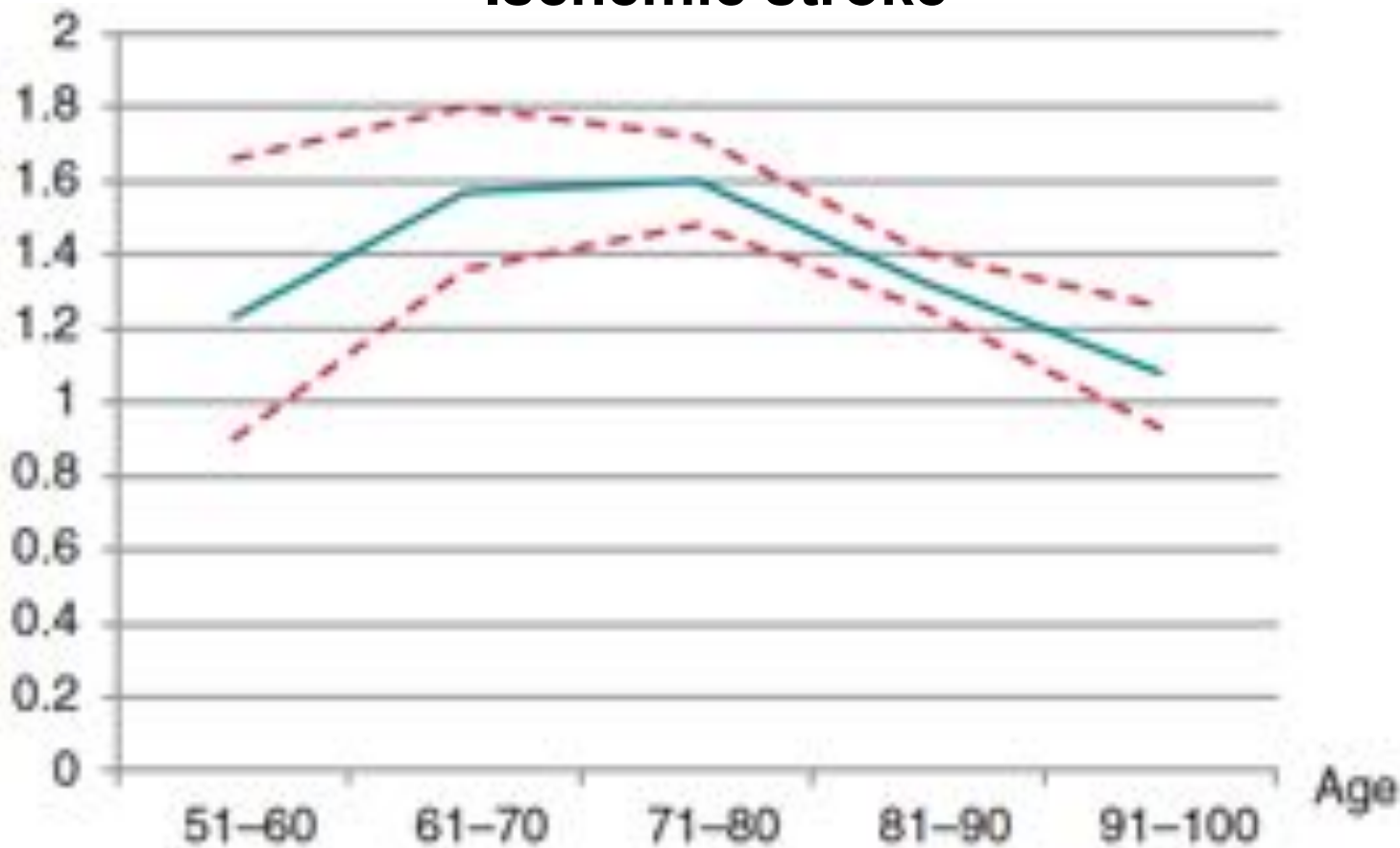
Annualized incidence (95% CI) of outcome events in relation to treatment strategy, according to propensity score matching

	ASA	No antithrombotic treatment	P
Ischaemic stroke	7.37% (7.11–7.63)	6.61% (6.37–6.86)	<0.001
Thrombo-embolic event	10.60% (10.29–10.92)	9.53% (9.24–9.83)	<0.001
Intracranial haemorrhage	0.95% (0.87–1.05)	1.00% (0.91–1.10)	0.46
Major bleeding	3.85% (3.67–4.03)	4.06% (3.87–4.25)	0.12

Aspirin versus no treatment in AF

Swedish registry data 2005-2009; 58 671 aspirin monotherapy, 56 514 no treatment

Adjusted HR for aspirin vs no antithrombotic treatment in relation to age
Ischemic stroke

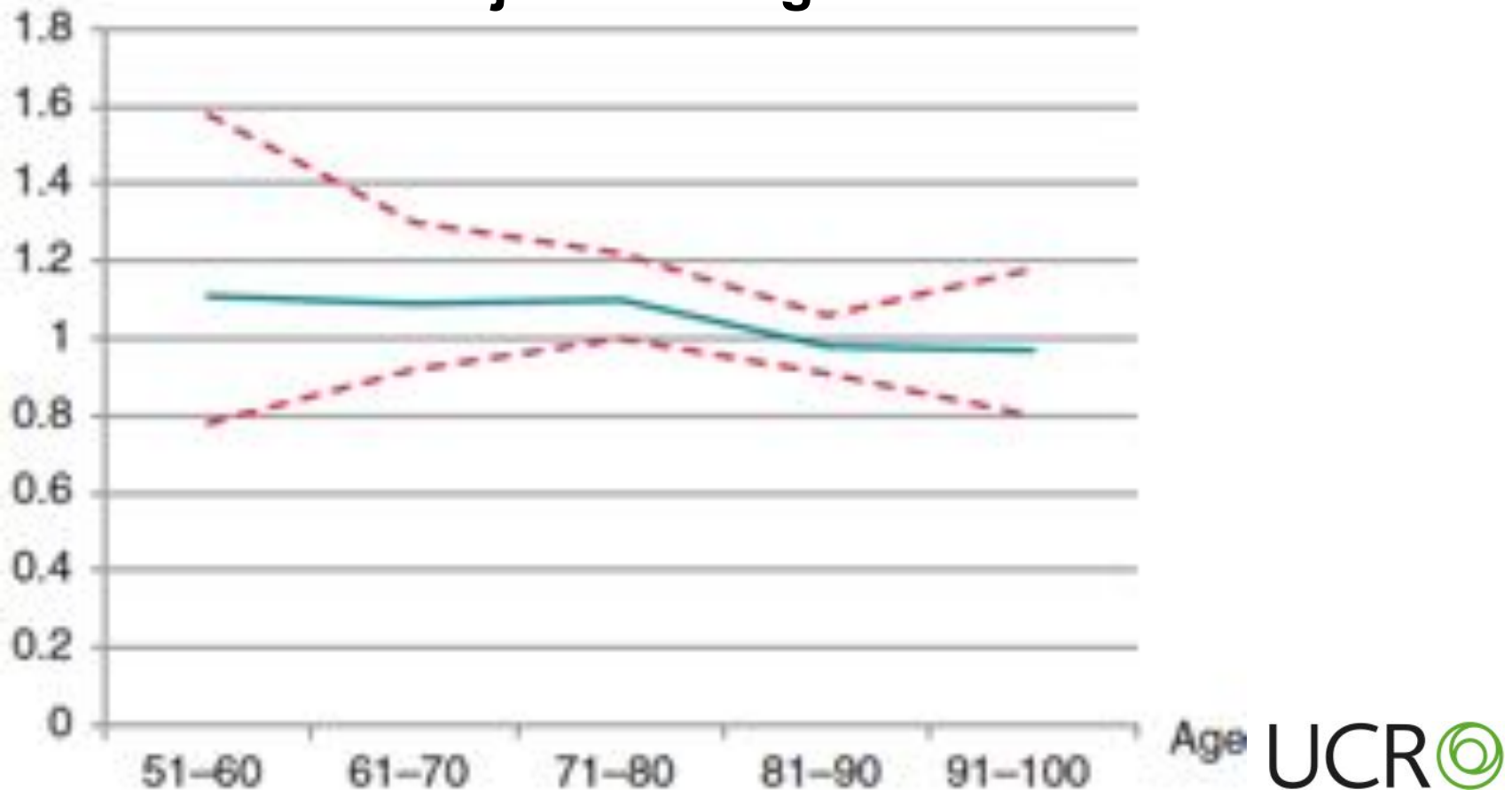


Aspirin versus no treatment in AF

Swedish registry data 2005-2009; 58 671 aspirin monotherapy, 56 514 no treatment

Adjusted HR for aspirin vs no antithrombotic treatment in relation to age

Major bleeding



NOAC studies in Atrial Fibrillation

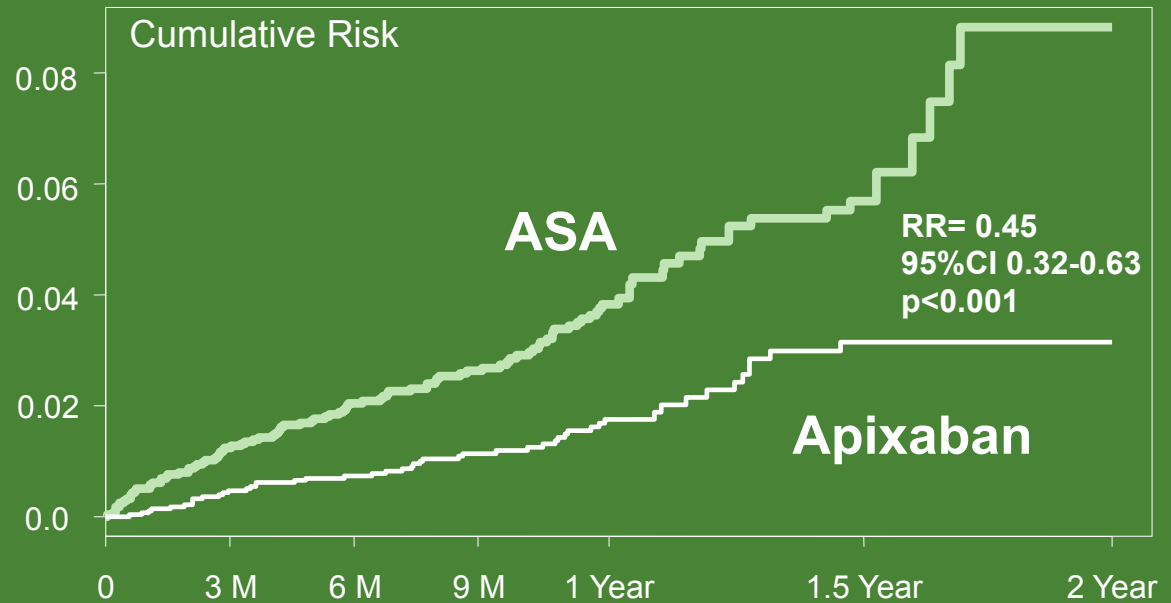
	<i>RE-LY</i>	<i>ROCKET- AF</i>	<i>ARISTOTLE</i>	<i>ENGAGE- TIMI 48</i>	<i>AVVEROES</i>
Control	Warfarin	Warfarin	Warfarin	Warfarin	ASA 81–324 mg
Study drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Apixaban
Dose (mg)	150, 110 X 2	20 (15*) X 1	5 (2.5*) X 2	60**, 30** X 1	5 (2.5*) X 2
No of pts.	18.113	14.266	18.206	21.105	5.599
Design	PROBE	Double-blind	Double-blind	Double-blind	Double-blind

*reduced dose for selected patients

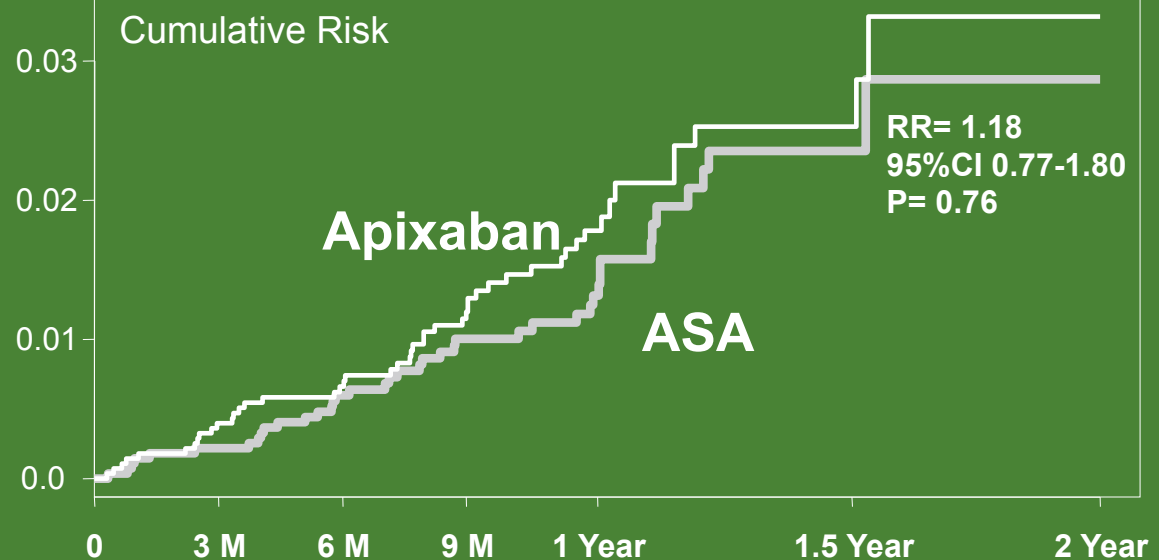
**halved dose for selected patients

Apixaban compared to aspirin in AF

Stroke/SE



Major bleeding

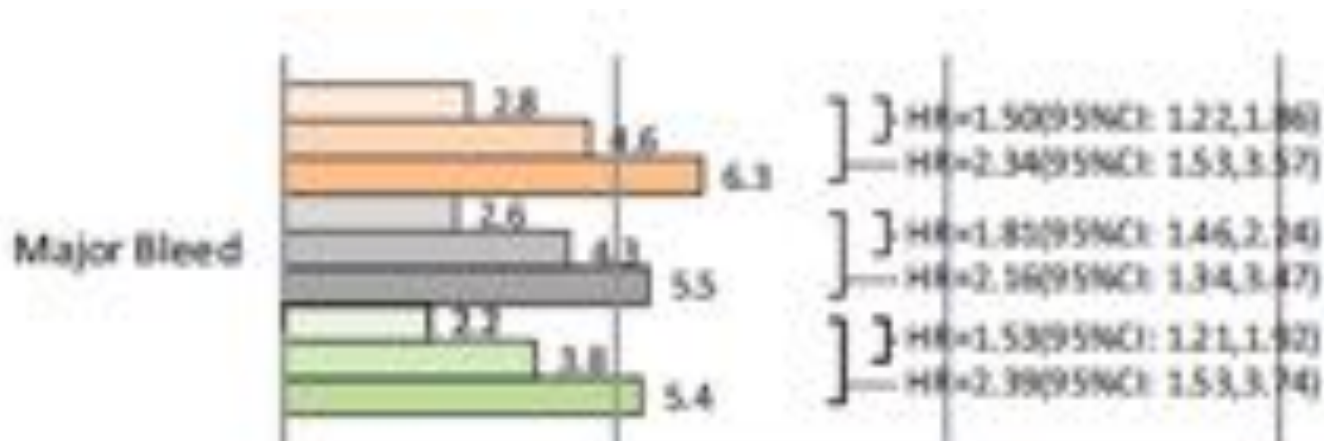




**Is there a role for aspirin
in combination with OAC for
stroke prevention in AF 2015?**

NOACs and antiplatelets

Results from RELY



PATIENTS ON WARFARIN

- NO ANTIPLATELET (n=3696)
- SINGLE ANTIPLATELET (n=2046)
- DUAL ANTIPLATELET (n=280)

PATIENTS ON DE 150

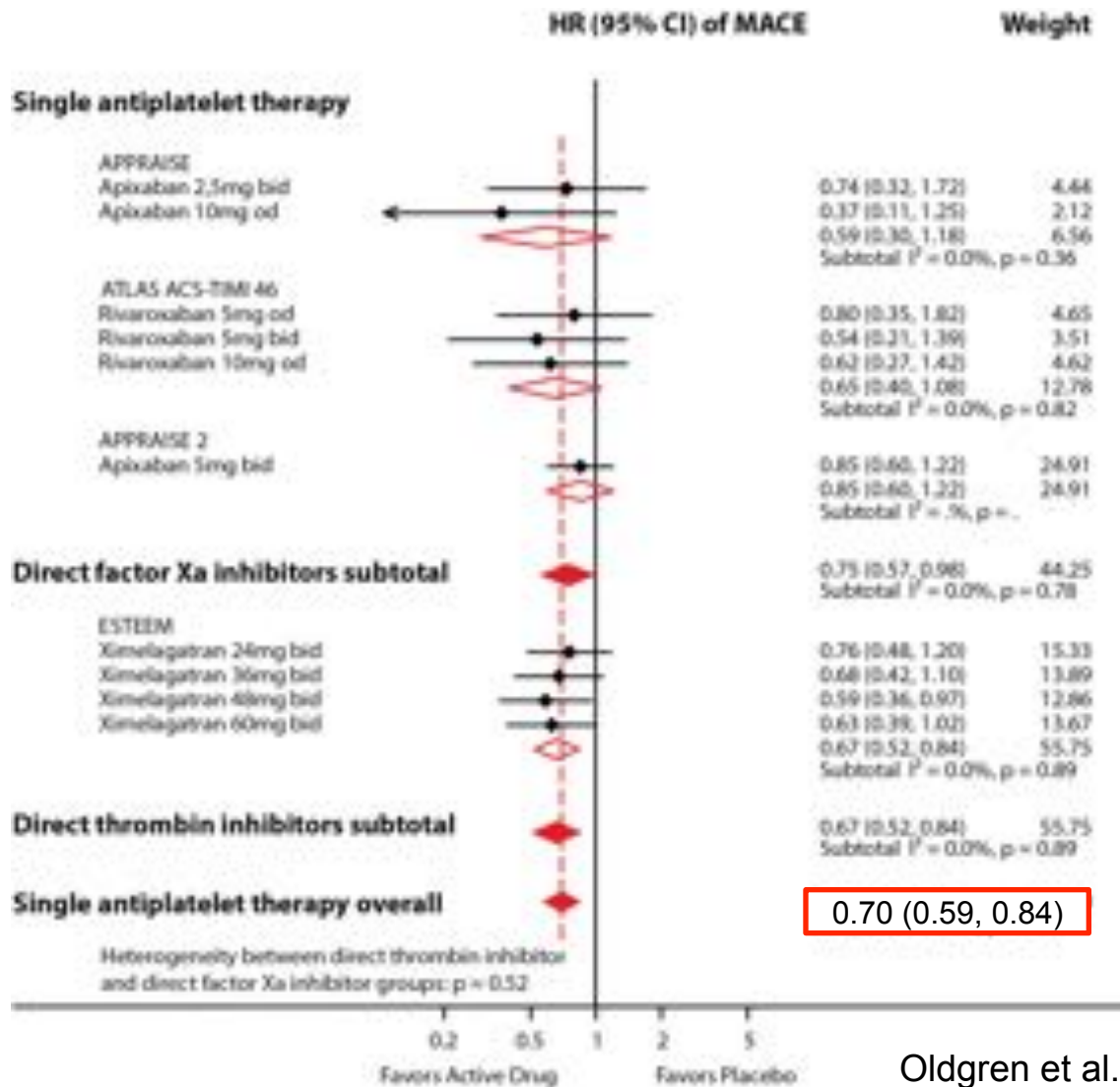
- NO ANTIPLATELET (n=3772)
- SINGLE ANTIPLATELET (n=2040)
- DUAL ANTIPLATELET (n=264)

PATIENTS ON DE 110

- NO ANTIPLATELET (n=3696)
- SINGLE ANTIPLATELET (n=2046)
- DUAL ANTIPLATELET (n=280)



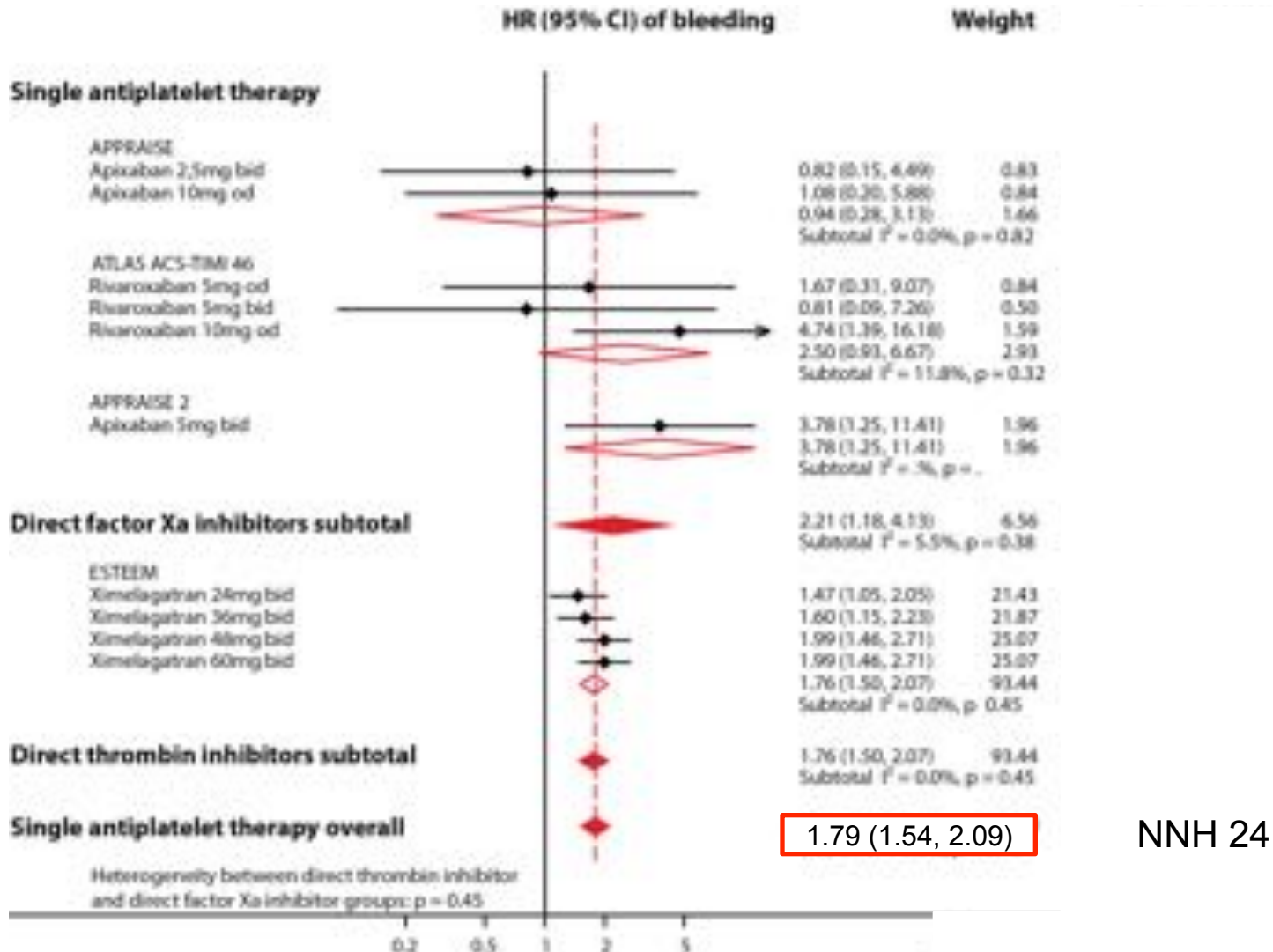
MACE (all-cause death, MI, stroke) OAC and single antiplatelet therapy post ACS



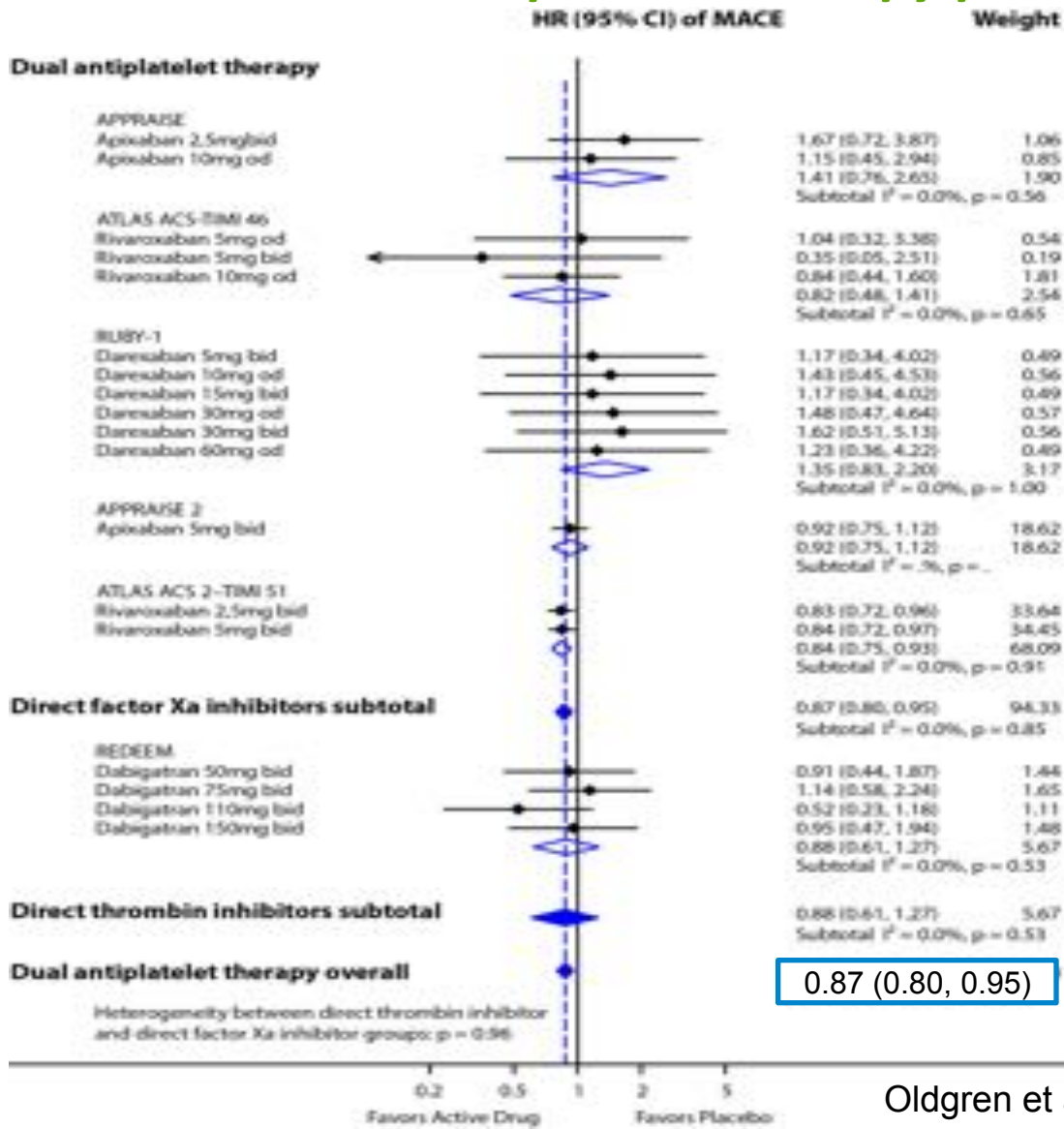
NNT 32

Clinically significant bleeding

OAC and single antiplatelet therapy post ACS

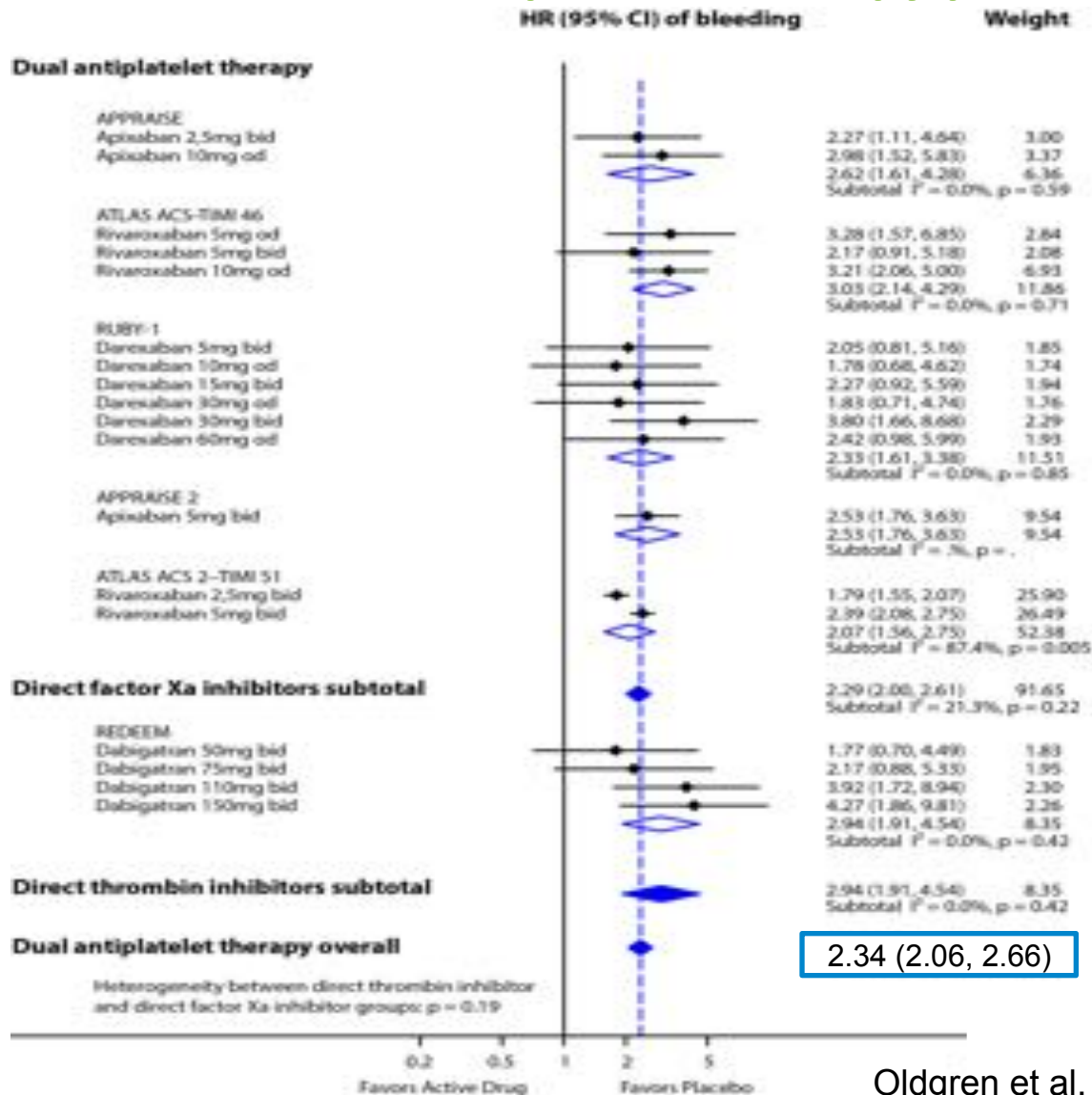


MACE (all-cause death, MI, stroke) OAC and dual antiplatelet therapy post ACS



Clinically significant bleeding

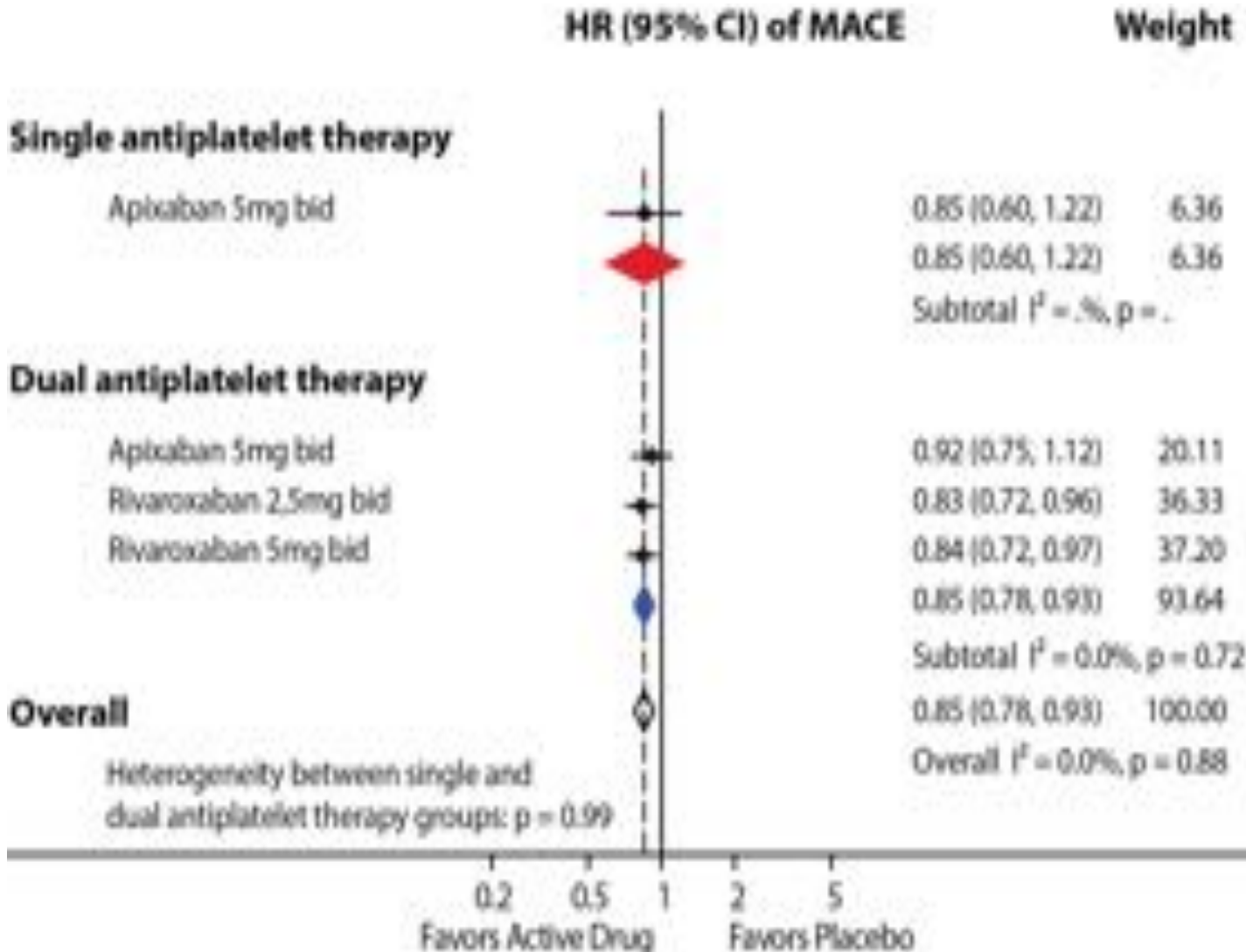
OAC and dual antiplatelet therapy post ACS



NNH 23

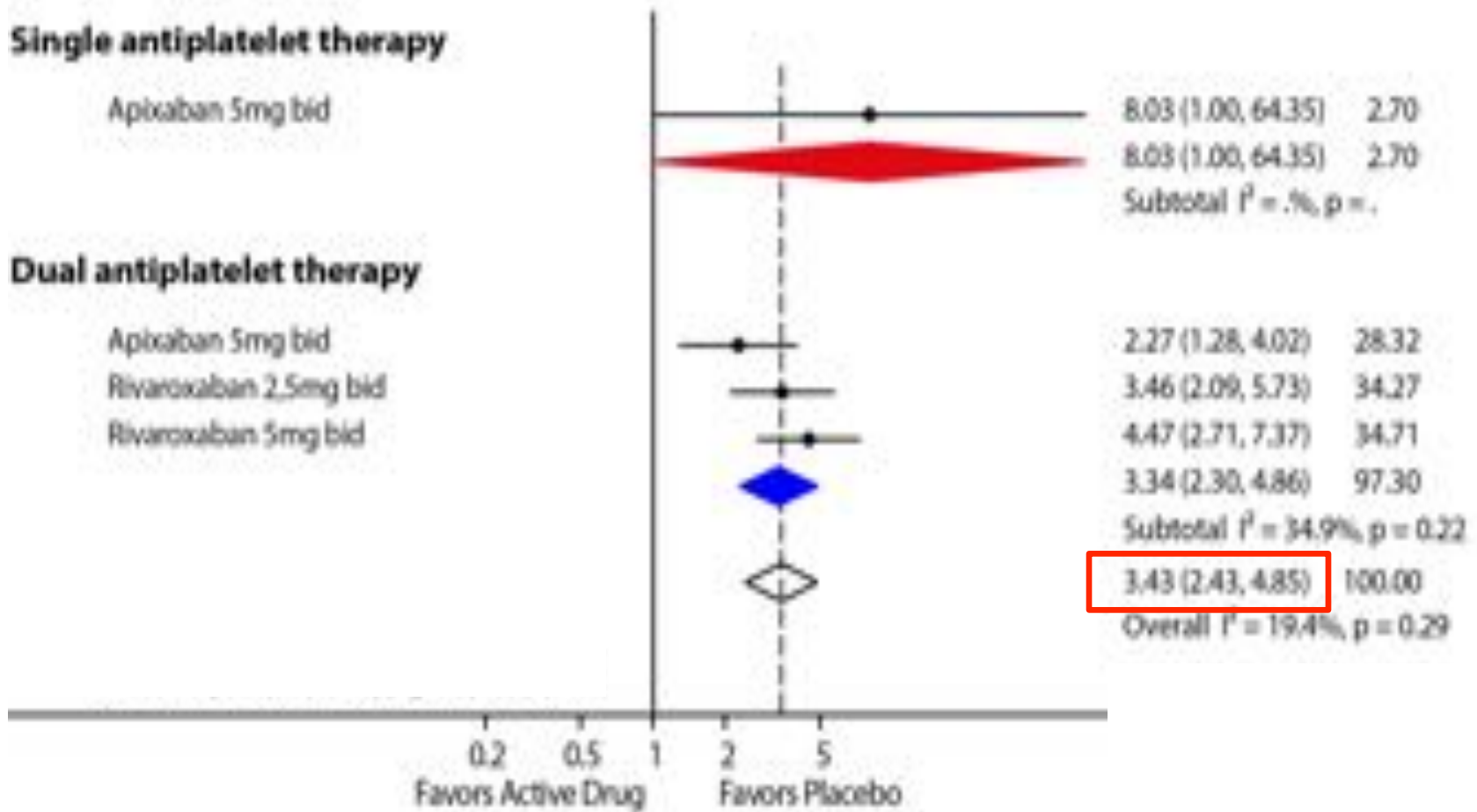
MACE (all-cause death, MI, stroke)

OAC and antiplatelets in phase III post ACS studies

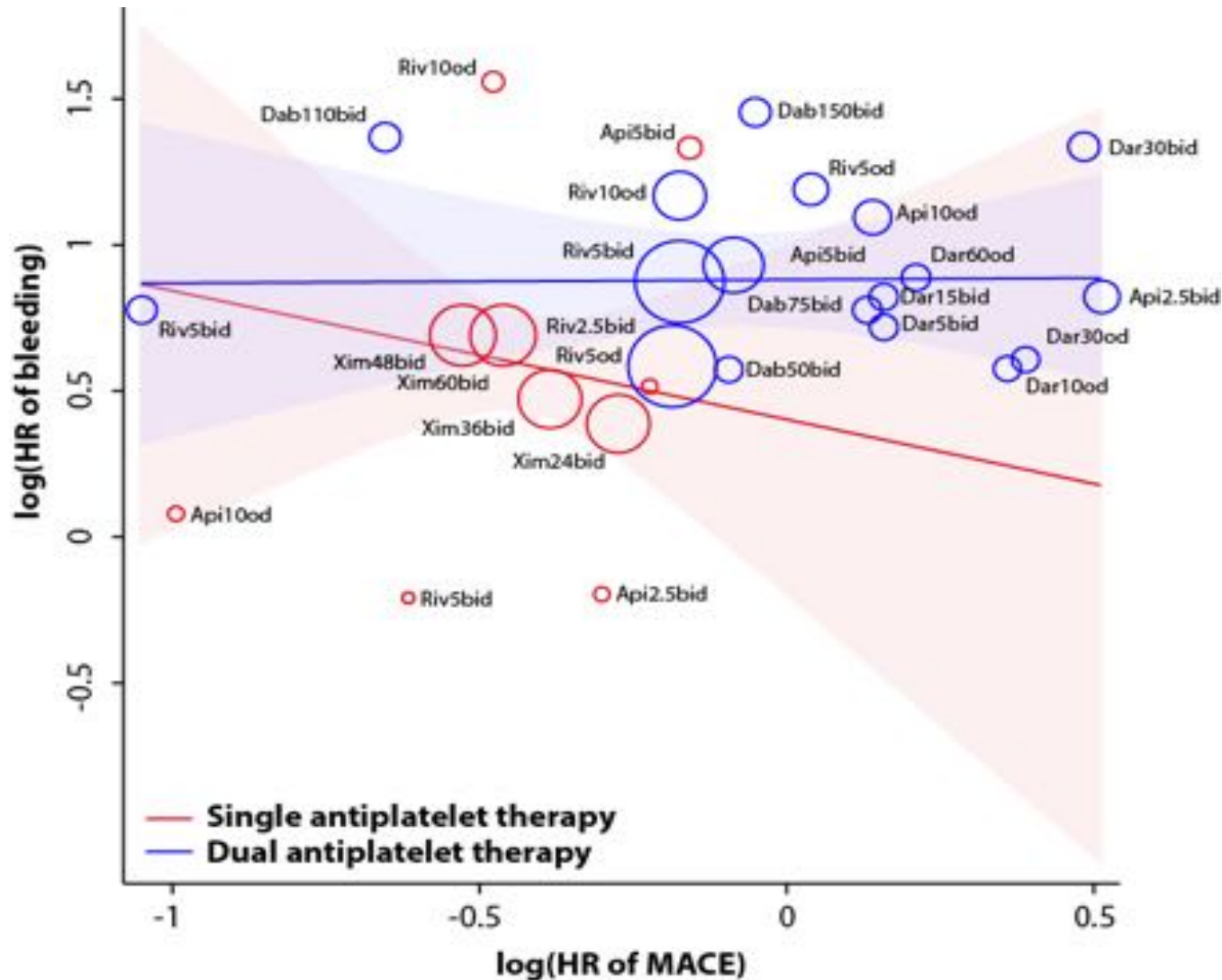


Major bleeding events NOAC

OAC and antiplatelets in phase III post ACS studies



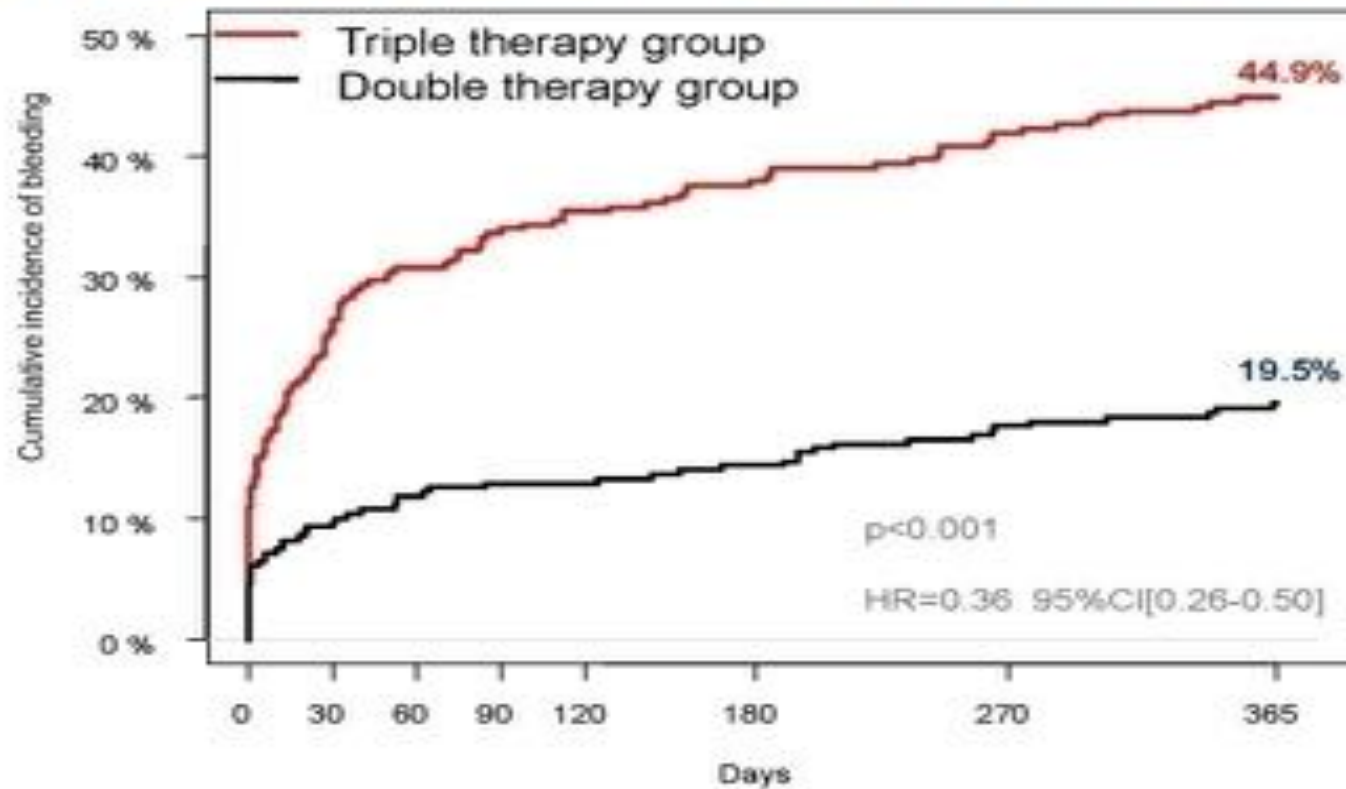
Association of effects on MACE with effects on bleeding rate when adding NOAC to single or dual antiplatelets post ACS



WOEST trial: Omission of aspirin reduces bleeding

WOEST

Primary Endpoint: Total number of TIMI bleeding events



n at risk: 284 210 194 186 181 173 159 140
279 253 244 241 241 236 226 208

Summary

- Aspirin monotherapy for stroke prevention in AF should generally not be used
- Aspirin + Clopidogrel is better than aspirin alone, with increased risk for major bleeding
- Aspirin + Clopidogrel is non-inferior to OAC
- Treatment with antiplatelets in combination with OAC increase bleeding risk, the ideal combinations and treatment durations are yet to be identified

Atrial fibrillation patients do not benefit from acetylsalicylic acid

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EDITORIAL

Acetylsalicylic acid for stroke prevention in atrial fibrillation: a conspiracy that needs to end?

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stroke, and may even increase the risk of ischaemic stroke in elderly patients. Thus, our data support the new European guidelines recommendation that ASA as monotherapy should not be used as stroke prevention in atrial fibrillation.

Keywords

Atrial fibrillation • Stroke • Acetylsalicylic acid