Antistolling bij de oudere patiënt met atriumfibrilleren

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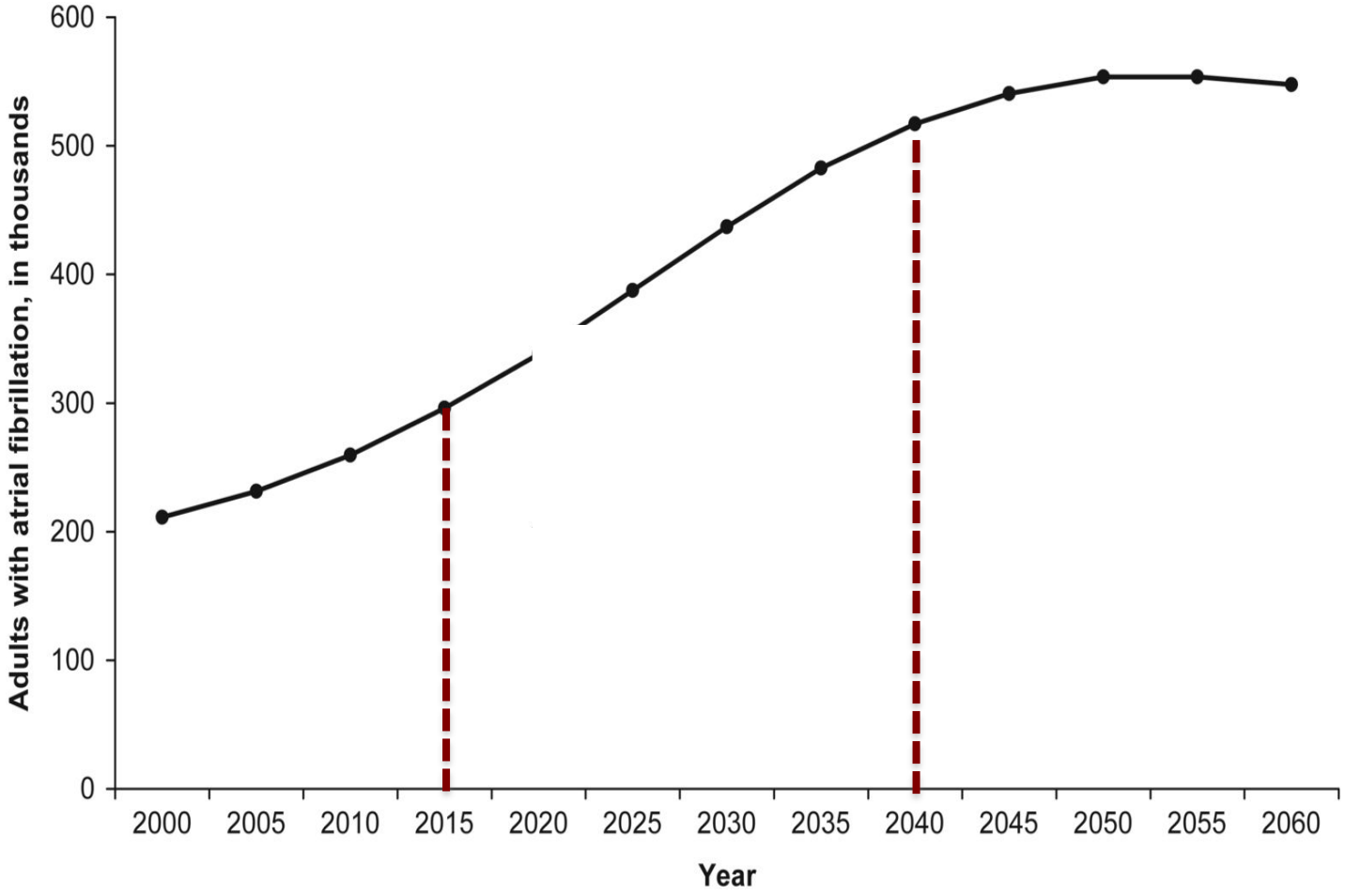
Epidemiologie van atriumfibrilleren (AF)

- Meest voorkomende ritmestoornis in de westerse wereld
- Gemiddeld heeft 2% van de bevolking AF
- In Nederland 340.000 bekende patiënten met AF
- Toenemend voorkomen van AF met de leeftijd:
  - 0,5% <65 jaar
  - 5% > 65 jaar
  - 10% > 80 jaar

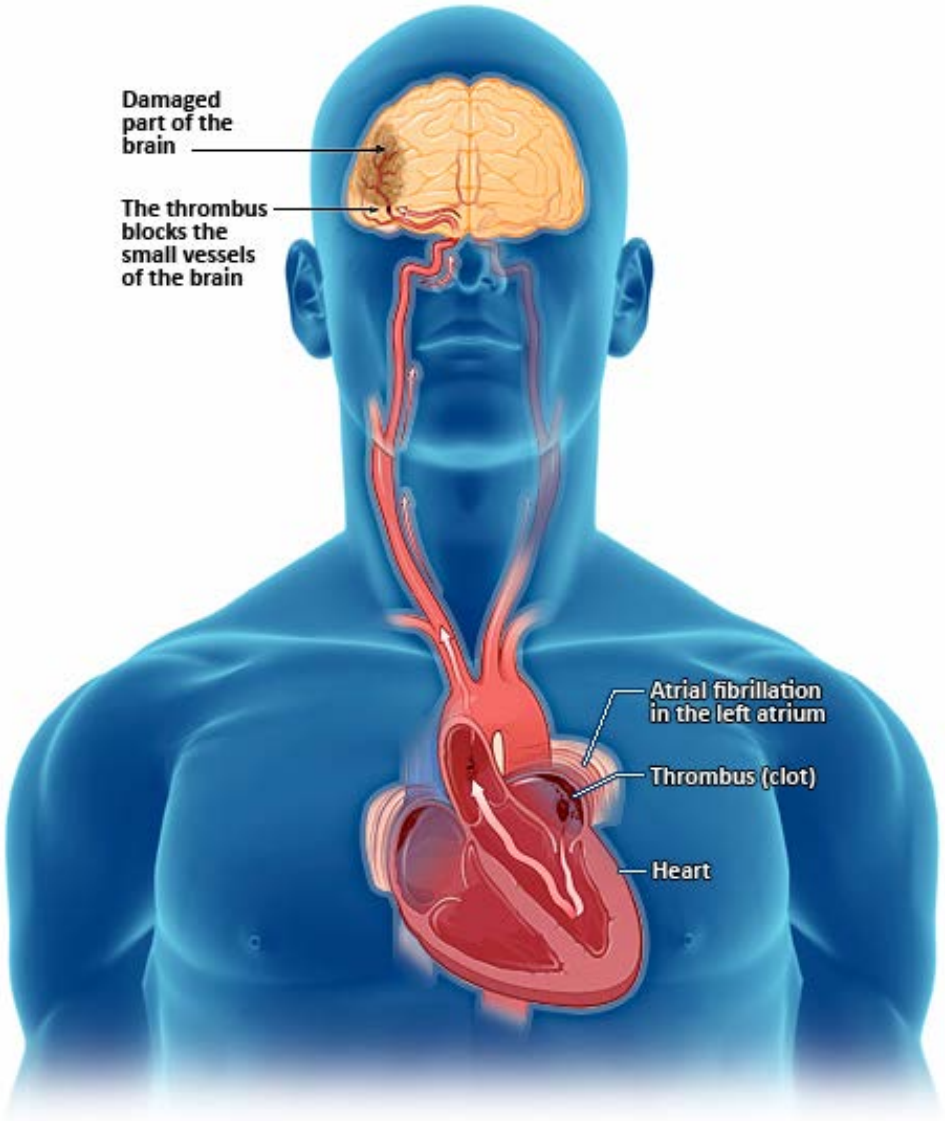
Atriumfibrilleren en vergrijzing



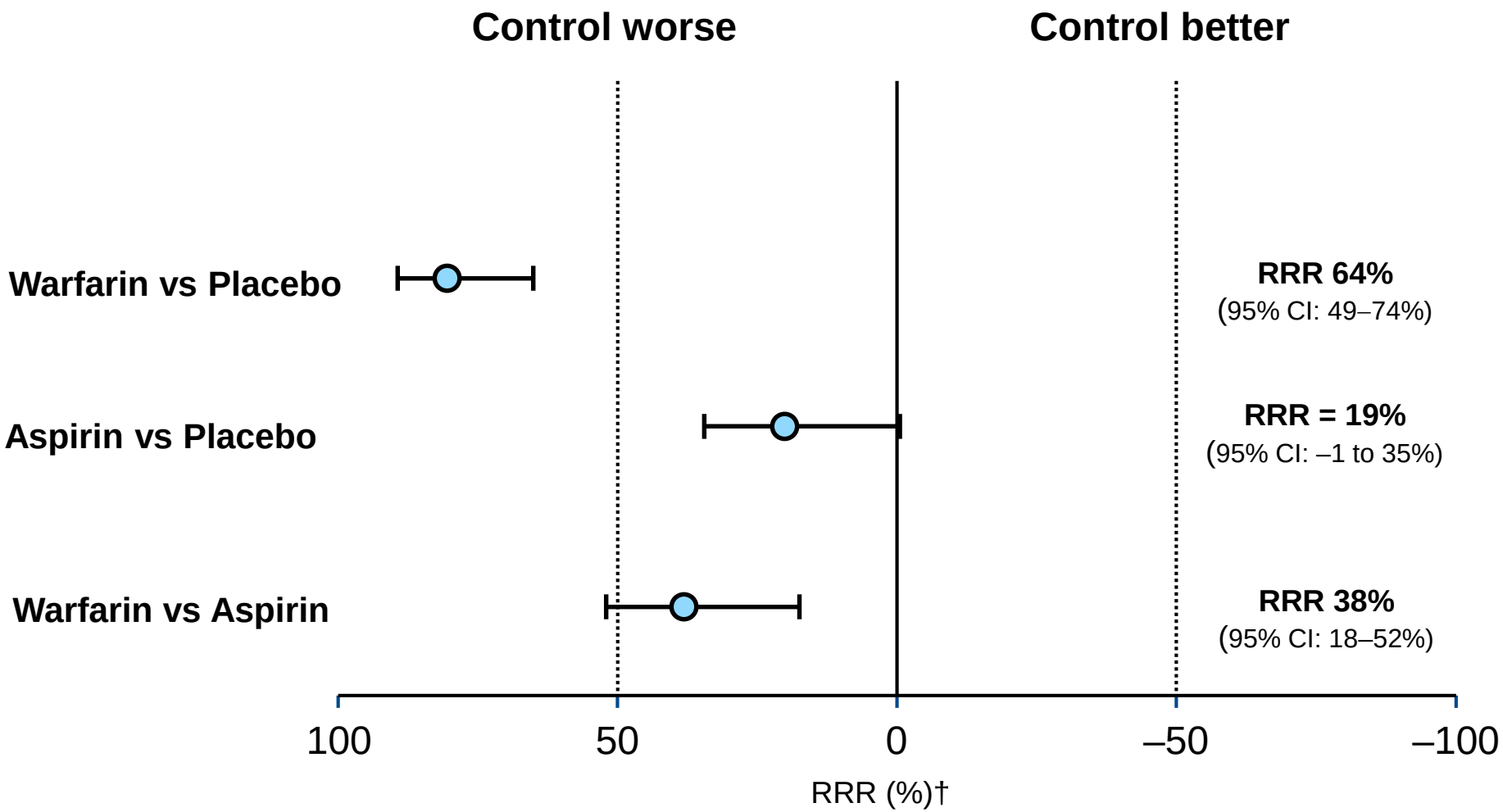
Krijthe et al. 2013

Beroerte (CVA) de belangrijkste complicatie van atriumfibrilleren

- AF 5x vergroot risico op een CVA
- AF -> 5% CVA per jaar
- CVA bij AF zijn ernstig
  3x hogere morbiditeit
  2x hogere mortaliteit
- **Goed te voorkomen met antistolling**



Warfarin reduces the risk of stroke in patients with AF



†Relative risk reduction (RRR) for all strokes (ischaemic and haemorrhagic)

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

Antistolling in AF
CVA risico versus bloedingsrisico

CHA_2DS_2-VASc score	
RISK FACTORS	SCORE
Congestive heart failure	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thromo-embolism	2
Vascular disease	1
Age 65-74	1
Sex category female	1

HAS-BLED score	
RISK FACTORS	SCORE
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age>65)	1
Drugs	1
Alcohol	1

Antistolling voor patiënten met AF

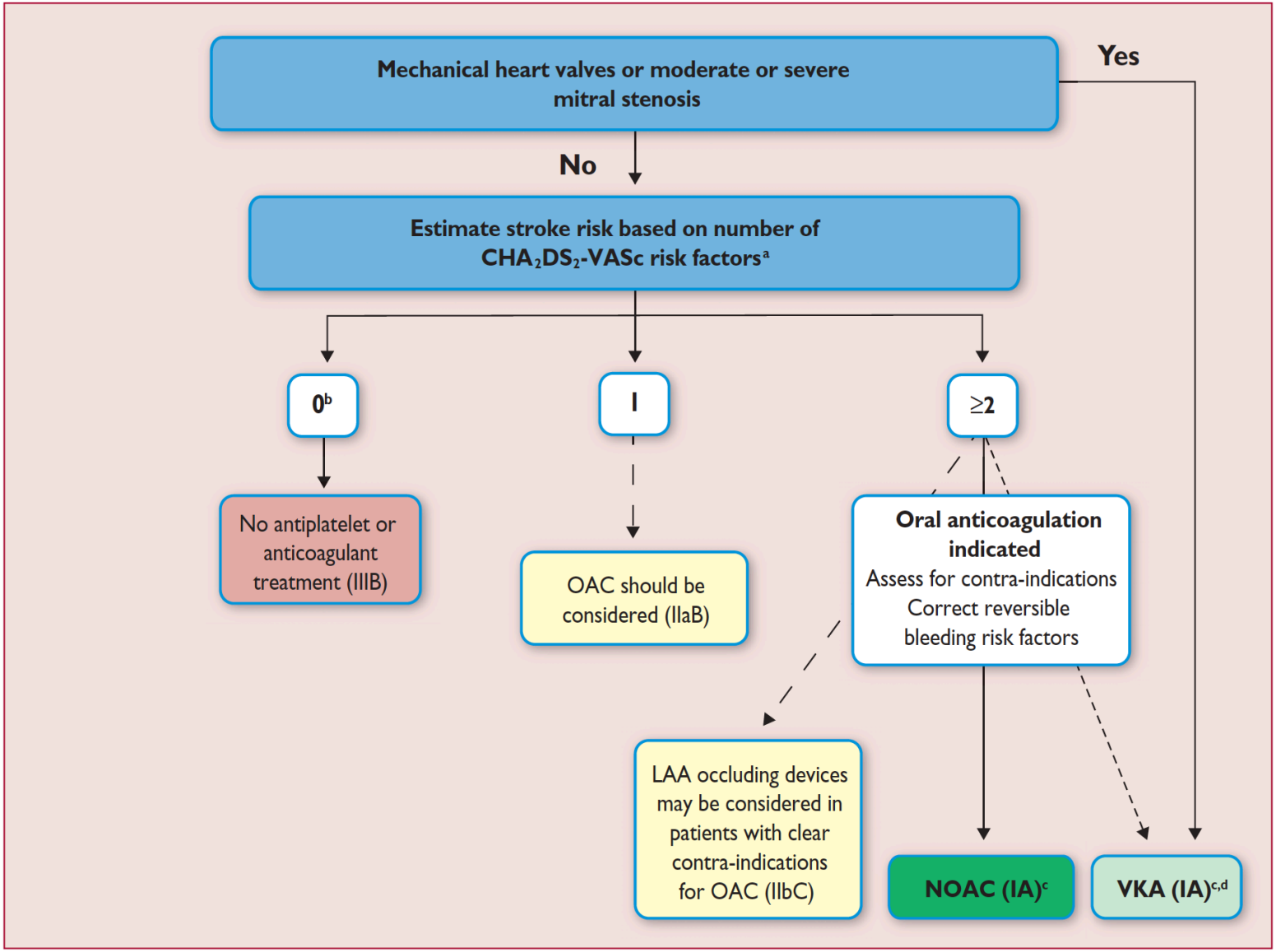
ESC richtlijn

- CHADSvasc ≥ 1 schrijf antistolling voor
  (geen plaats voor aspirine)

- HAS-BLED ≥ 3 ‘voorzichtigheid geboden’
  (≠ contra-indicatie, maar opdracht:)
  behandel corrigeerbare factoren!

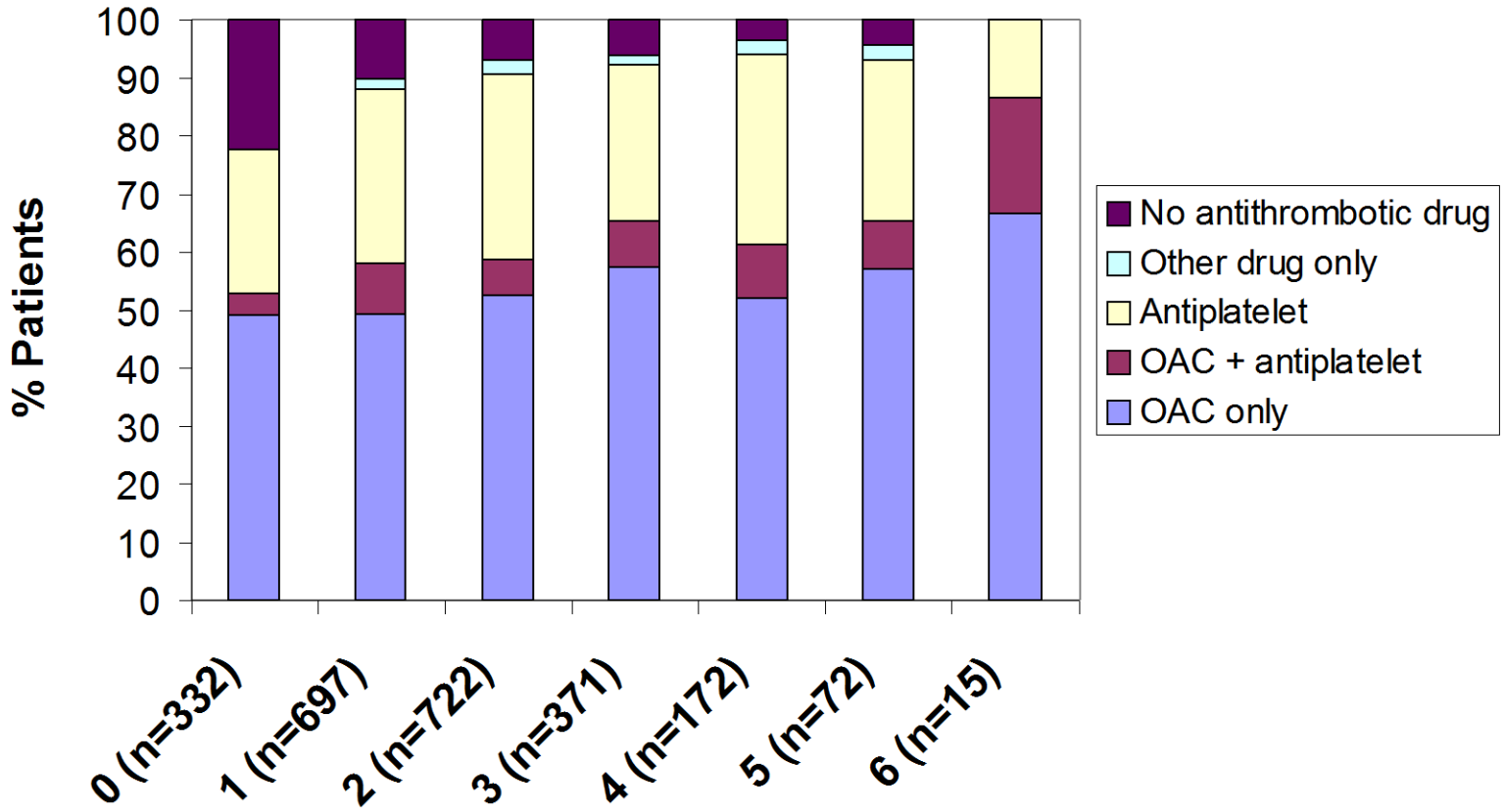
ESC AF Guidelines EHJ 2010, 2012

Antistolling voor patienten met AF



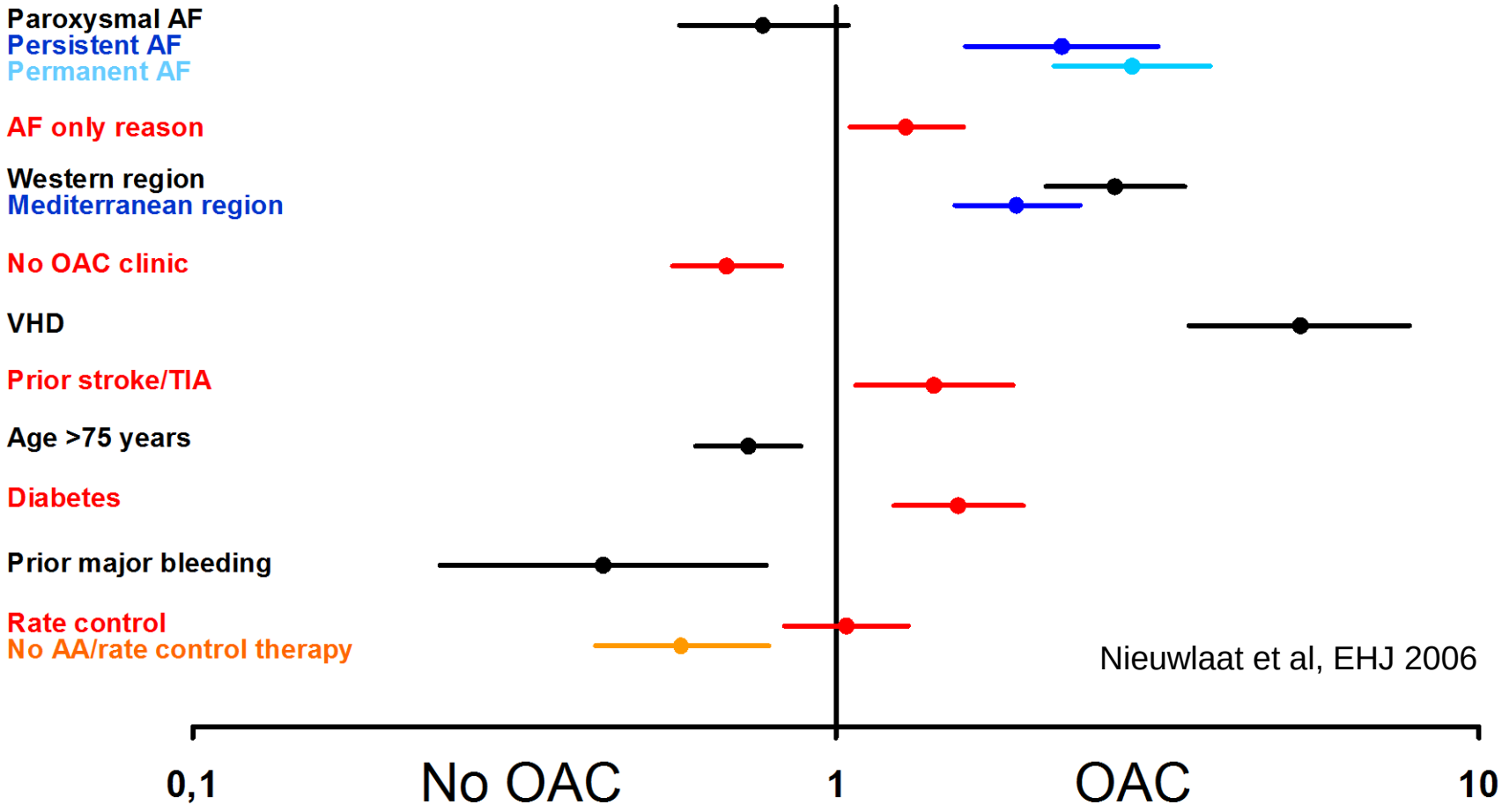
ESC AF Guidelines EHJ 2016

Antithrombotics according to CHADS2 score



Nieuwlaat et al, EHJ 2006

Determinants of oral anticoagulation prescription



EORP-AF registry
Anticoagulation treament versus stroke risk

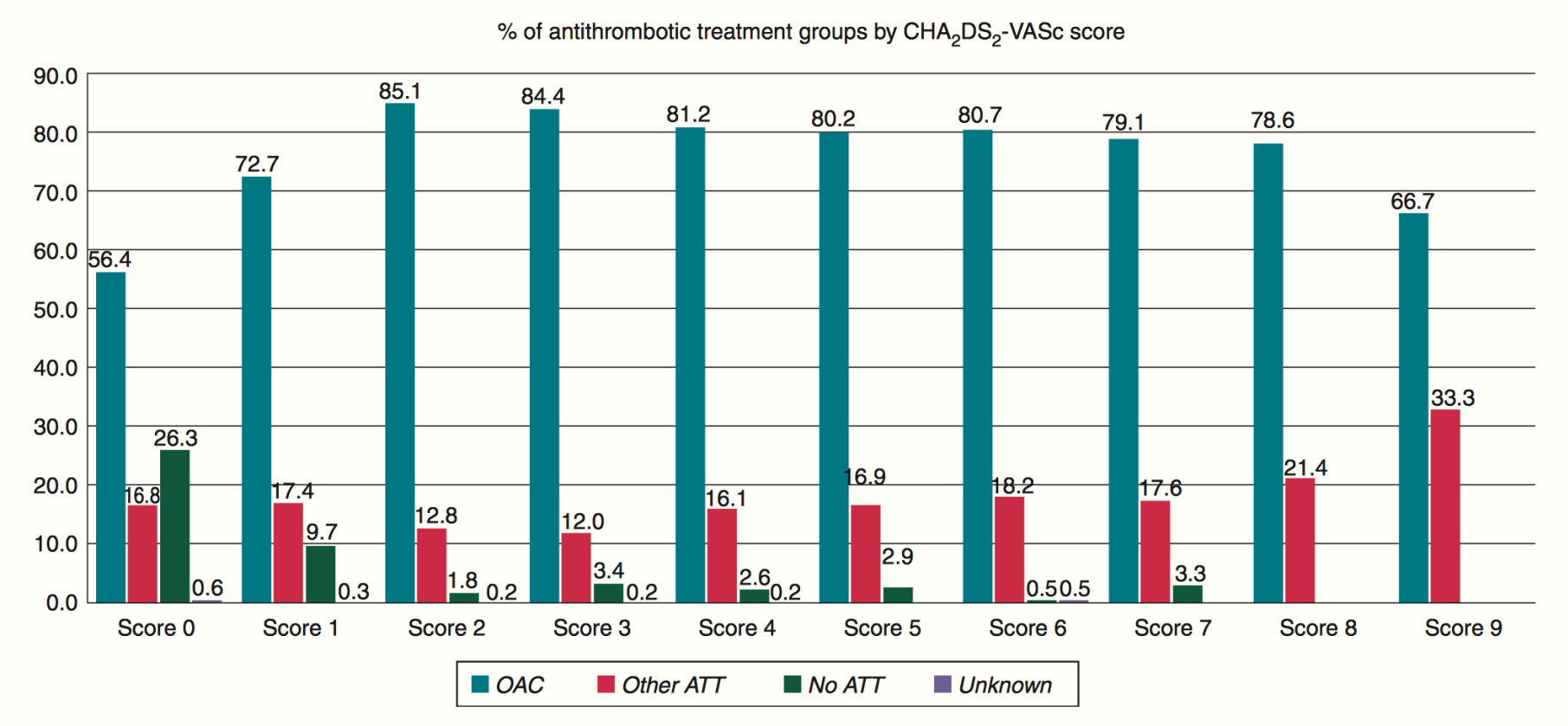


Figure 1 Proportions of patients treated with antithrombotic drugs by CHA_2DS_2-VASc score.

Lip et al. Europace 2014

EORP-AF registry
Anticoagulation treament versus bleeding risk

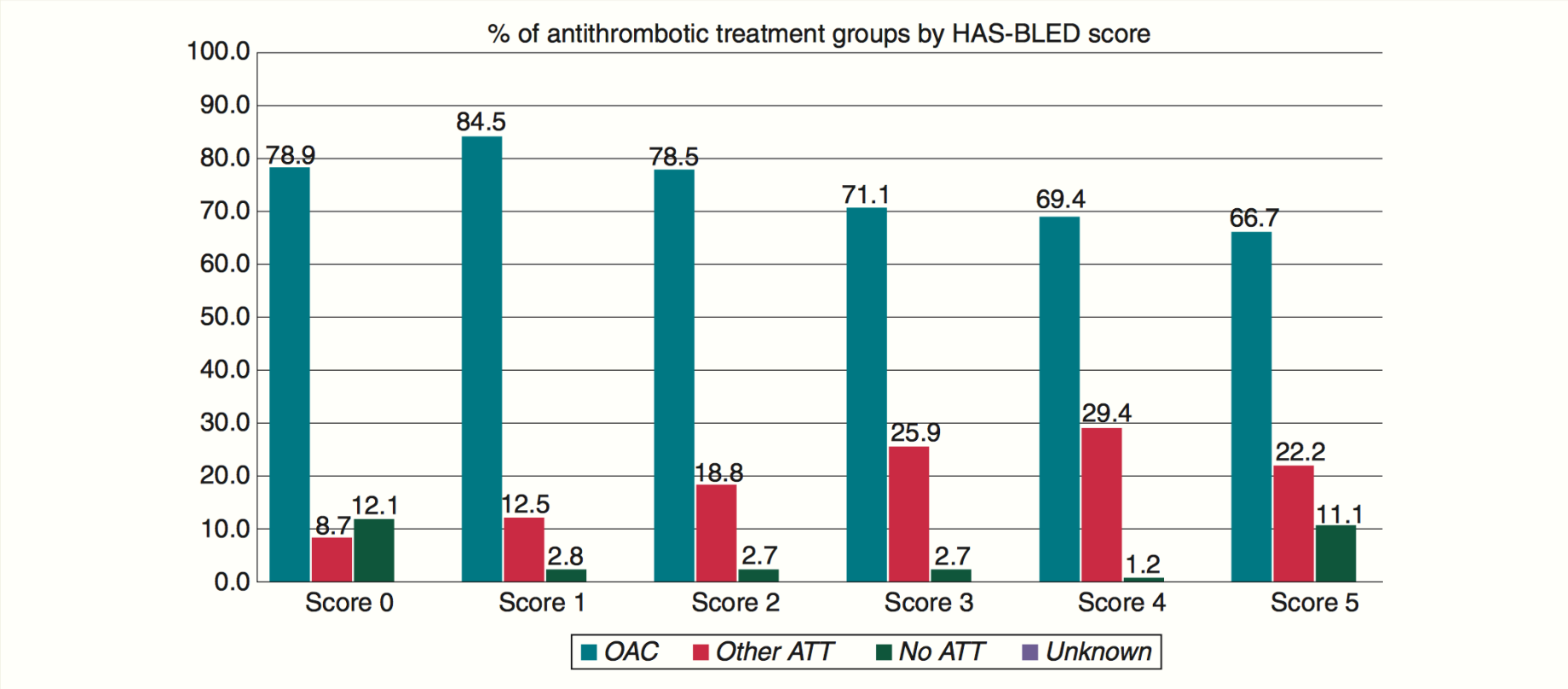


Figure 2 Proportions of patients treated with antithrombotic drugs by HAS-BLED score.

Lip et al. Europace 2014

EORP-AF registry

Table 7 Independent predictors of OAC use: multivariable analysis

Variable	OR	95% CI	*P* value
Age <70 years by 10 years	1.44	1.20–1.73	0.0003
Female gender	0.65	0.51–0.83	0.0005
BMI (per increase by 5 kg/m^2)	1.22	1.05–1.42	0.01
SBP (per increase by 20 mmHg)	0.83	0.71–0.98	0.03
CHA_2DS_2-VASC: <2 vs. ≥2	0.43	0.30–0.62	<0.0001
HAS-BLED score >2 vs. ≤2	0.47	0.35–0.63	<0.0001
Hyperthyroidism	2.82	1.11–7.17	0.03
Previous ischaemic/ thrombo-embolic events	1.67	1.14–2.46	0.009
Chronic kidney disease	0.70	0.50–0.97	0.03

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure.

Lip et al. Europace 2014

BAFTA: Warfarine vs aspirine in older AF pts

- Open label gerandomiseerde study met geblindeerde eindpunt bepaling
- 234 huisarts praktijken in UK
- Patiënten ≥ 75 jaar met AF
- 488 warfarine (INR 2.0-3.0) versus 486 aspirine (75 mg)
- Gemiddelde follow-up duur 2.7 jaar
- Gecombineerd eindpunt:
  CVA, intracraniële bloeding en perifere embolie

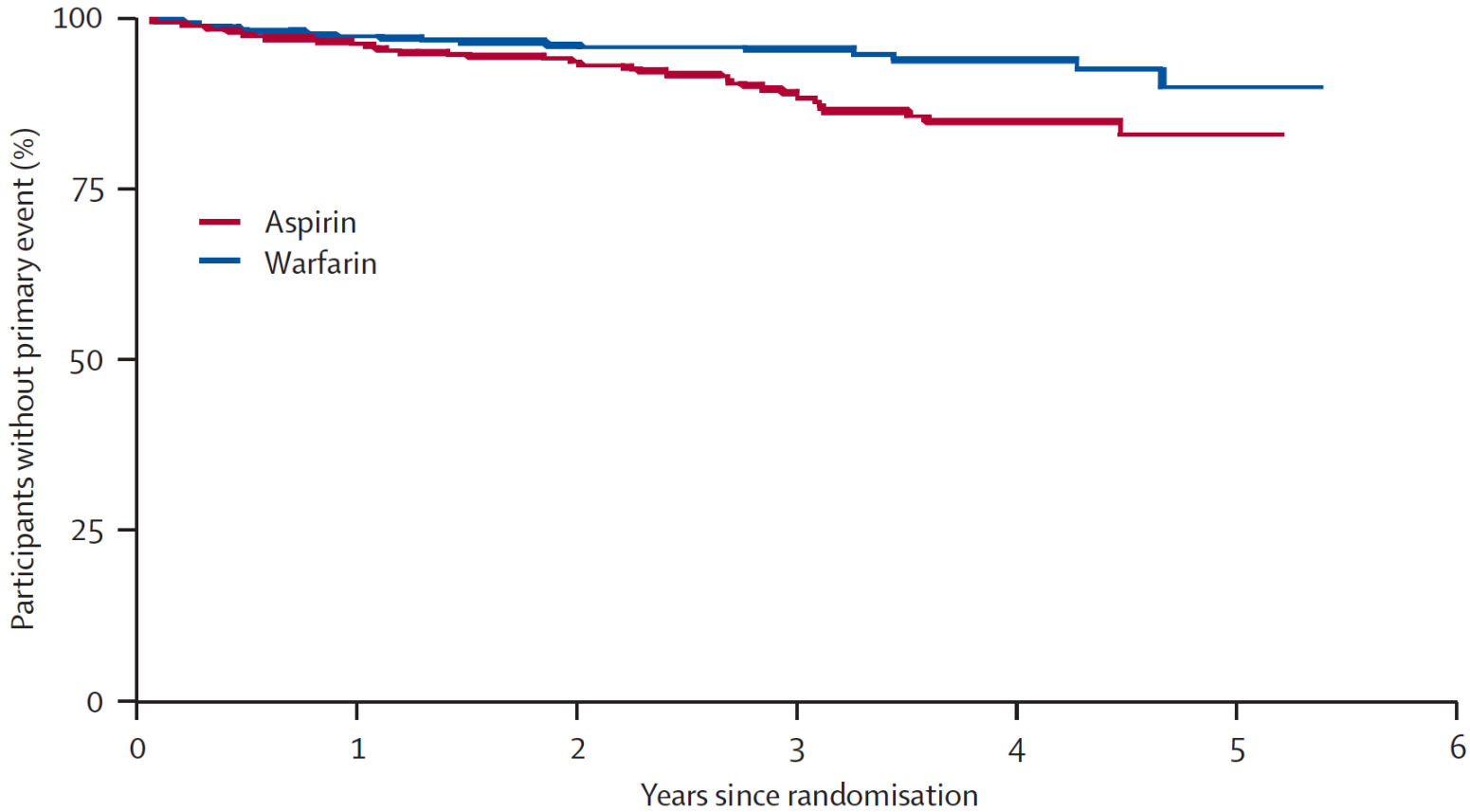
Mant et al. Lancet 2007

Warfarine versus aspirine: BAFTA

	Warfarin	Aspirin
Number of patients	488	485
Age (years)	81·5 (4·3)	81·5 (4·2)
Age group		
75–79	197 (40%)	200 (41%)
80–84	196 (40%)	190 (39%)
≥85	95 (19%)	95 (20%)
Male	267 (55%)	264 (54%)

Mant et al. Lancet 2007

Warfarine versus aspirine: BAFTA



Number at risk

Warfarin	488	450	383	169	77	19
Aspirin	485	447	378	146	72	14

Mant et al. Lancet 2007

Antistolling versus aspirine: BAFTA

	Warfarin		Aspirin		Warfarin *vs* aspirin	
	N	Risk per year	N	Risk per year	RR (95% CI)	p
Death						
All causes	107	8·0%	108	8·4%	0·95 (0·72–1·26)	0·73
Fatal primary endpoint	15	1·1%	23	1·8%	0·63 (0·31–1·26)	0·16
Other vascular death*	41	3·1%	34	2·7%	1·16 (0·72–1·88)	0·53
Non-vascular death*	51	3·8%	51	4·0%	0·96 (0·64–1·45)	0·84
Secondary vascular outcomes (fatal and non-fatal)						
All strokes	33	2·5%	61	4·9%	0·52 (0·33–0·80)	0·002
All strokes plus TIA	40	3·1%	70	5·7%	0·55 (0·36–0·82)	0·002
Myocardial infarction	15	1·1%	15	1·2%	0·96 (0·44–2·11)	0·91
Heart failure	38	2·9%	23	1·8%	1·59 (0·92–2·79)	0·08
Other vascular events†	34	2·6%	45	3·7%	0·71 (0·44–1·13)	0·13
All non-stroke vascular events	78	6·1%	76	6·3%	0·97 (0·70–1·35)	0·84
Haemorrhage (fatal and non-fatal)						
Major extracranial haemorrhage	18	1·4%	20	1·6%	0·87 (0·43–1·73)	0·67
Other hospital admission for haemorrhage	24	1·8%	19	1·5%	1·22 (0·64–2·36)	0·52
All major haemorrhages (including intracranial and haemorrhagic stroke)	25	1·9%	25	2·0%	0·96 (0·53–1·75)	0·90
Composite outcomes						
Major vascular events (stroke, myocardial infarction, pulmonary embolus,‡ vascular death)	76	5·9%	100	8·1%	0·73 (0·53–0·99)	0·03
Primary events plus major haemorrhage	39	3·0%	64	5·1%	0·59 (0·38–0·89)	0·008

Analyses are censored at first event, so the composite outcomes are not the sum of the individual categories of event. *Includes deaths that occurred after non-fatal primary endpoints, including four deaths from stroke (as 'other vascular death'). †Other events leading to hospital admission or death, such as angina, deep vein thrombosis, acute bowel ischaemia, pulmonary embolism, acute arrhythmia, and elective vascular surgery. ‡There were five pulmonary emboli, one in the warfarin group and four in the aspirin group.

Table 5: **Risk of secondary and composite outcomes by treatment allocation for different patient subgroups**

Mant et al. Lancet 2007

And what about NOACs?

Patients aged more than 75 years: Stroke or systemic embolism

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1 Rivaroxaban						
ROCKET-AF, 2011	125	3,082	154	3,082	28.6%	0.80 [0.63, 1.02]
Subtotal (95% CI)		**3,082**		**3,082**	**28.6%**	**0.80 [0.63, 1.02]**
Total events	125		154			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.2 Apixaban						
ARISTOTLE, 2011	79	2,743	109	2,752	26.2%	0.72 [0.54, 0.97]
AVERROES, 2011	20	909	66	983	17.2%	0.31 [0.19, 0.52]
Subtotal (95% CI)		**3,652**		**3,735**	**43.4%**	**0.49 [0.22, 1.10]**
Total events	99		175			
Heterogeneity: Tau² = 0.30; Chi² = 7.75, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 1.73 (P = 0.08)						
1.3 Dabigatran						
RE-LY, 2009	156	4,828	101	2,360	28.0%	0.75 [0.58, 0.96]
Subtotal (95% CI)		**4,828**		**2,360**	**28.0%**	**0.75 [0.58, 0.96]**
Total events	156		101			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.24 (P = 0.03)						
Total (95% CI)		**11,562**		**9,177**	**100.0%**	**0.65 [0.48, 0.87]**
Total events	380		430			
Heterogeneity: Tau² = 0.06; Chi² = 11.19, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: Chi² = 1.37, df = 2 (P = 0.51), I² = 0%						

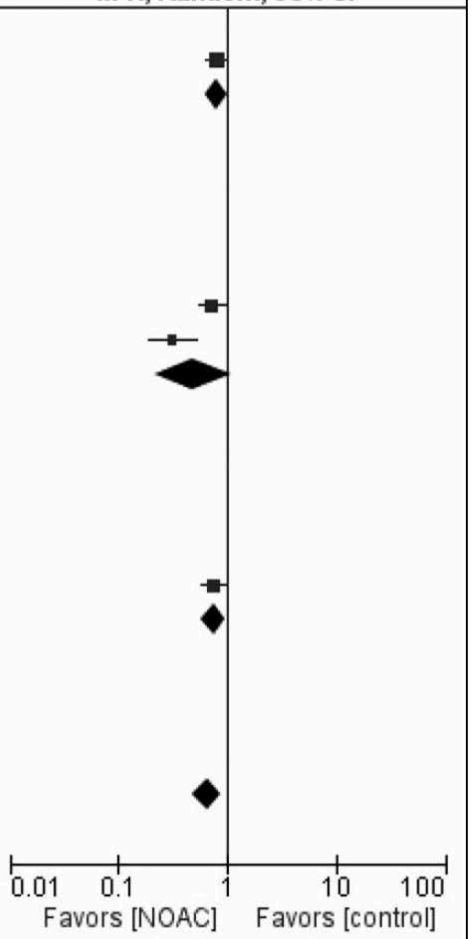


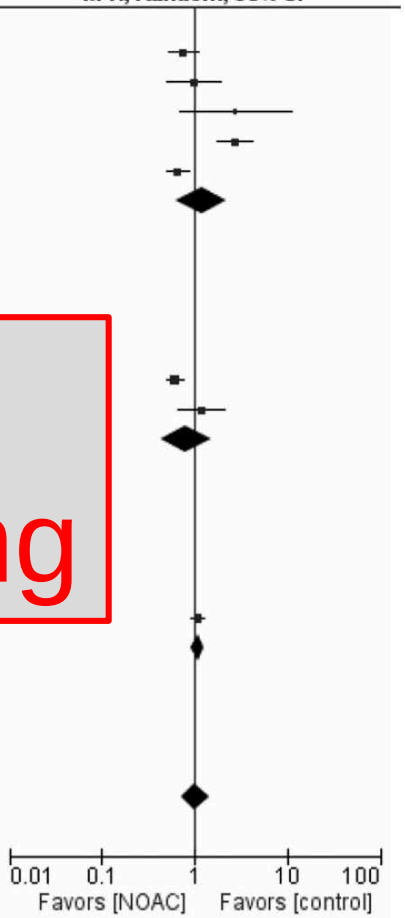
Figure 3. New oral anticoagulants versus conventional therapy for participants aged 75 and older: stroke or systemic embolism.

Sadar et al J Am Geriatr Soc 2014

And what about NOACs?

Patients aged more than 75 years: Major or clinically relevant bleeding

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1 Rivaroxaban						
EINSTEIN PE, 2012	58	440	67	401	13.9%	0.76 [0.52, 1.11]
EINSTEIN, 2010	19	215	20	223	10.2%	0.98 [0.51, 1.90]
EINSTEIN-Extension, 2010	7	88	3	98	4.4%	2.74 [0.69, 10.93]
MAGELLAN, 2013	75	1,530	29	1,548	13.1%	2.70 [1.75, 4.17]
ROCKET-AF, 2011	82	3,073	124	3,077	15.0%	0.65 [0.49, 0.87]
Subtotal (95% CI)		**5,346**		**5,347**	**5,6.7%**	**1.18 [0.64, 2.19]**
Total events	241		243			
Heterogeneity: Tau² = 0.39; Chi² = 32.62, df = 4 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 0.52 (P = 0.60)						
Subtotal (95% CI)		**4,828**		**2,360**	**16.1%**	**1.07 [0.90, 1.28]**
Total events	450		206			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**13,625**		**11,083**	**100.0%**	**1.02 [0.73, 1.43]**
Total events	868		697			
Heterogeneity: Tau² = 0.17; Chi² = 50.25, df = 7 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi² = 0.87, df = 2 (P = 0.65), I² = 0%						



50% reduction of intracranial bleeding

Figure 2. New oral anticoagulants versus conventional therapy for participants aged 75 and older: major or clinically relevant bleeding. CI = confidence interval.

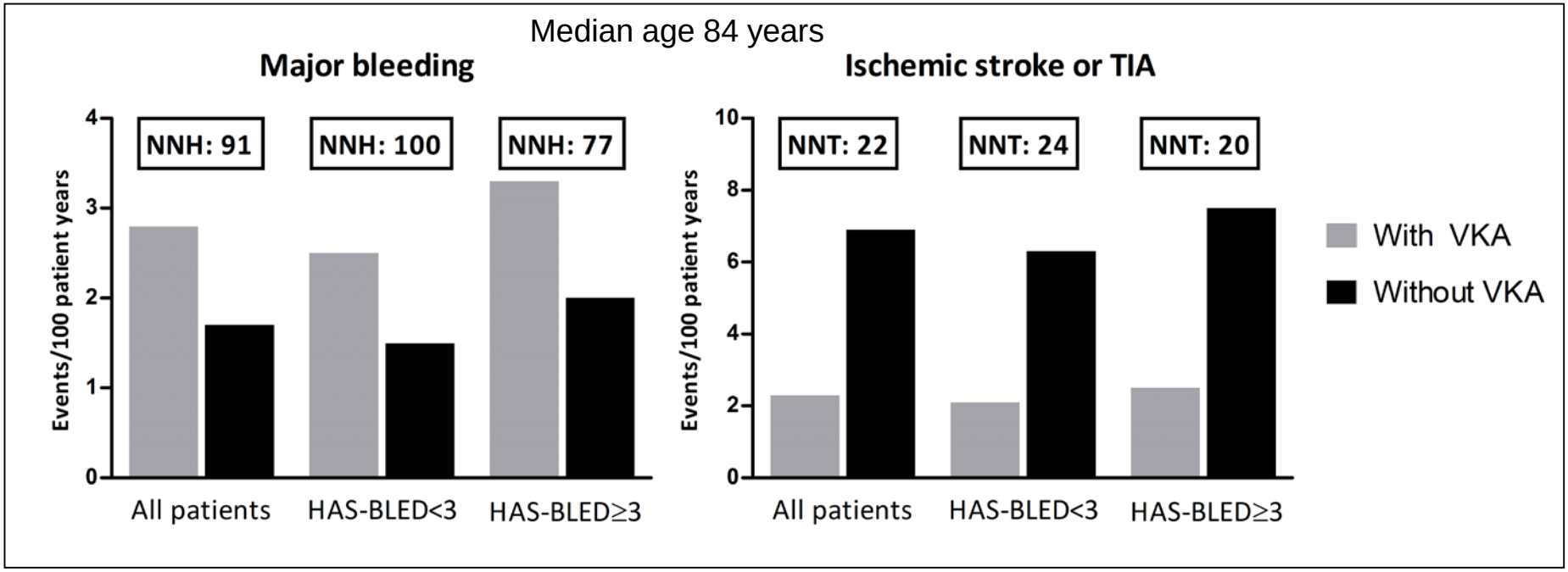
Sadar et al J Am Geriatr Soc 2014

Antistolling in de oudere AF patiënt

- Ondanks ‘evidence’ is de arts terughoudend met (N)OAC
- Primum non nocere!
- Oudere patiënten meer fragiel, meer co-morbiditeit, meer vallen, meer cognitieve disfunctie, etc en hebben daarmee een hoog bloedingsrisico
- Negatieve feedback door ervaringen met bloedingen
- We zien niet het aantal CVAs dat we voorkomen hebben!

Ondanks hoog bloedingsrisico: behandelen!!

- Oudere patiënten hebben een hoog bloedingsrisico maar een nog hoger CVA risico!



Jaspers Fox et al J throm hemostasis 2016

- Tegenover elke bloeding door een vitamine-K antagonist staan 4 CVAs die voorkomen worden

Hoog bloedingsrisico: corrigeren!!!

Hoog bloedingsrisico: behandelen!!!

Neem geen genoegen met hoog bloedingsrisico

- Verlaag de RR in geval van syst RR > 160 mmHg
- Voorkom alcohol abusus
- Voorkom NSAIDs, voorzichtig met aspirine/ clopidogrel
- Valpreventie programma’s (fysiotherapie/ rollator/ etc)
- Gezond maag-darm kanaal (PPI, pro-biotica, etc)

Conclusie

- Een hoge leeftijd en een hoog bloedingsrisico zijn geen reden om af te zien van antistolling bij AF
- Behandeling met een NOAC verdient waar mogelijk de voorkeur, gezien de betere effectiviteit/veiligheids-ratio en de 50% reductie in intracraniële bloedingen
- Laat U niet leiden door ervaring, maar door de wetenschap!