Directe orale antistollingsmiddelen

Pieter Willem Kamphuisen
Internist vasculair geneeskundige
Hoogleraar vasculaire geneeskunde

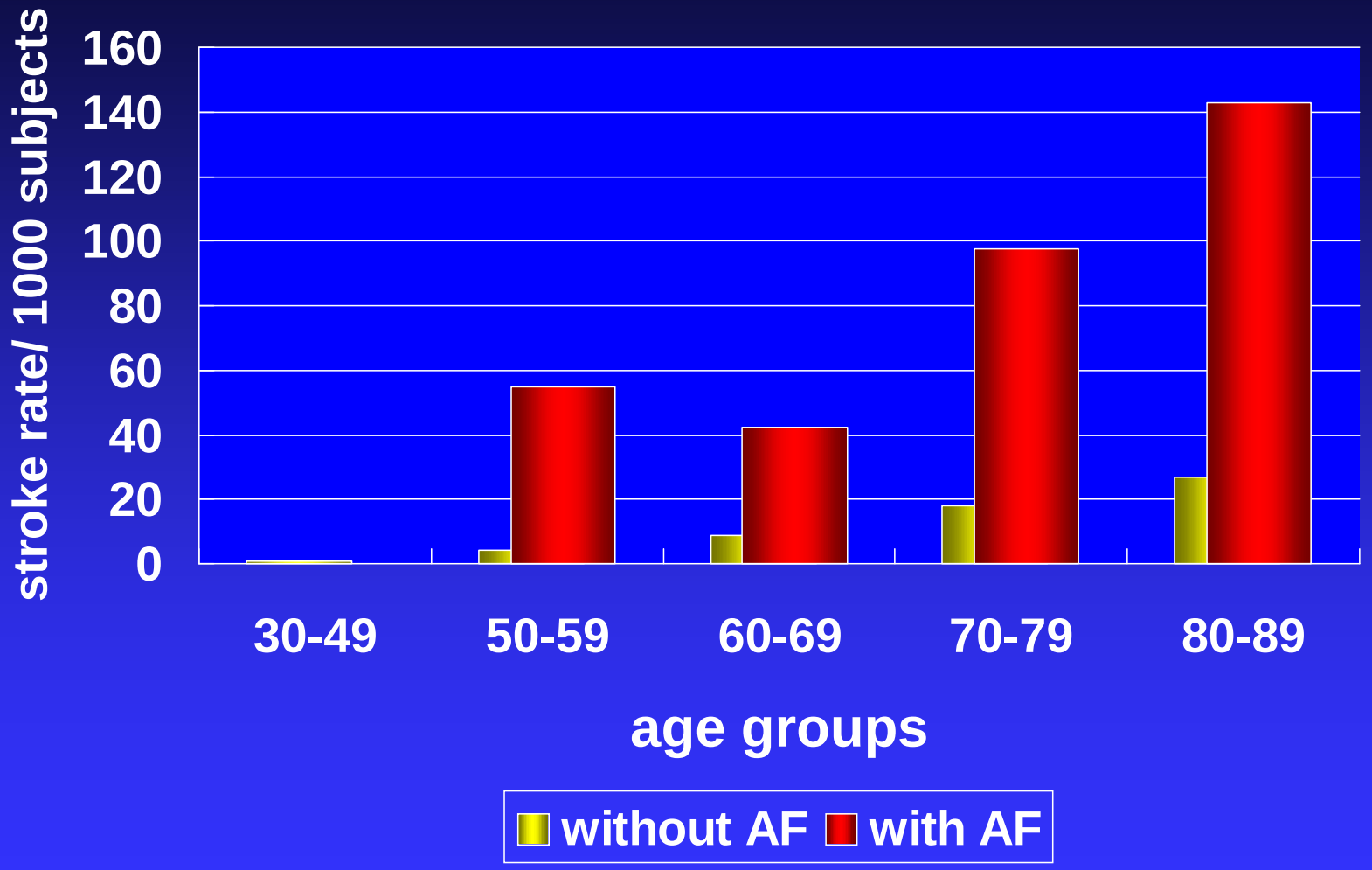
Kerngetallen
Gebruikers orale antistolling Nederland

- 350.000 patiënten
  acenocoumarol (78%)
  fenprocoumon (22%)
  (warfarine)(buitenlandse gasten/toeristen)

- 20 per 1.000 inwoners

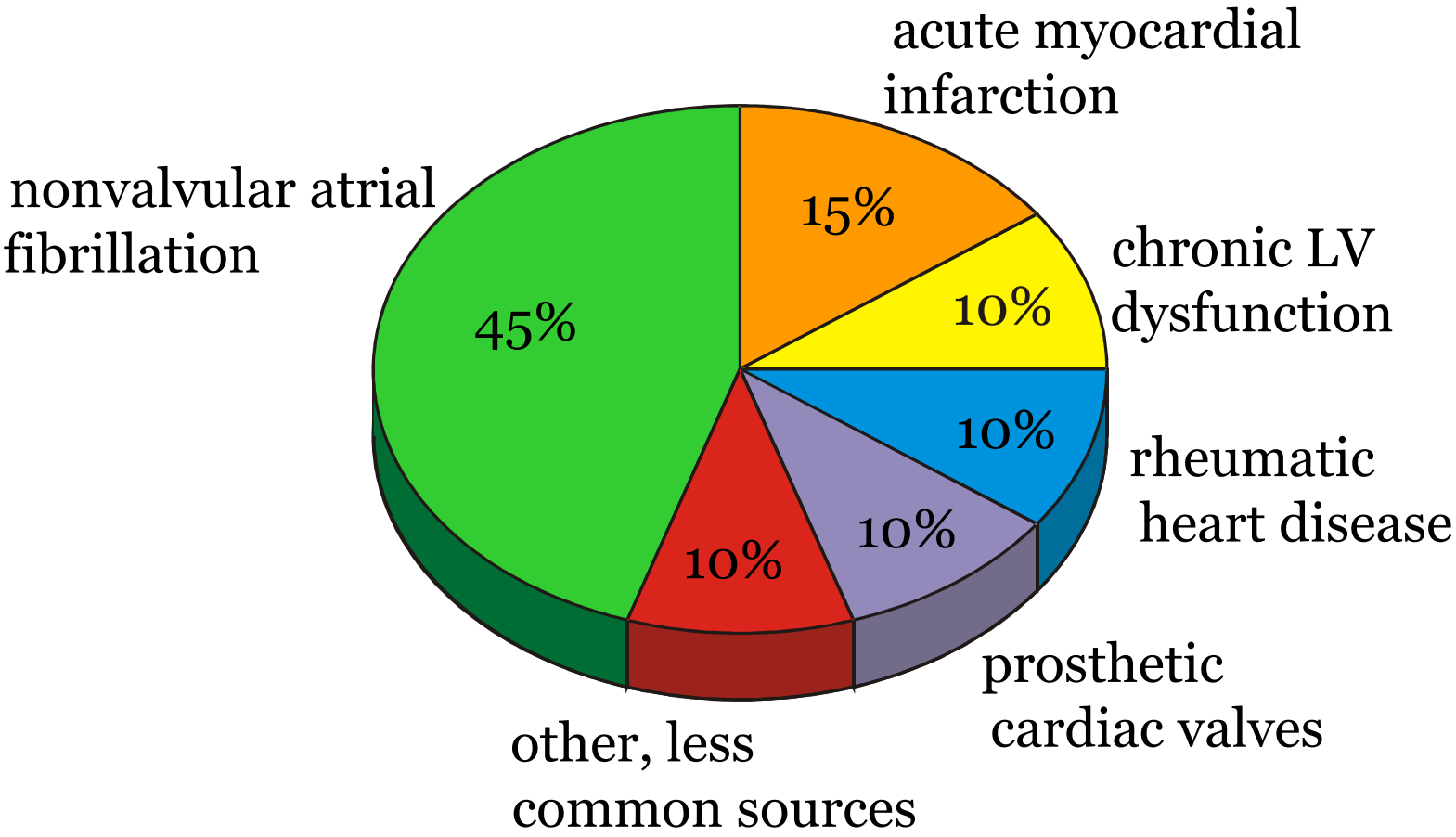
- per HA-praktijk: 50 patiënten

Stroke Incidence in AF
Framingham, 30-year follow-up

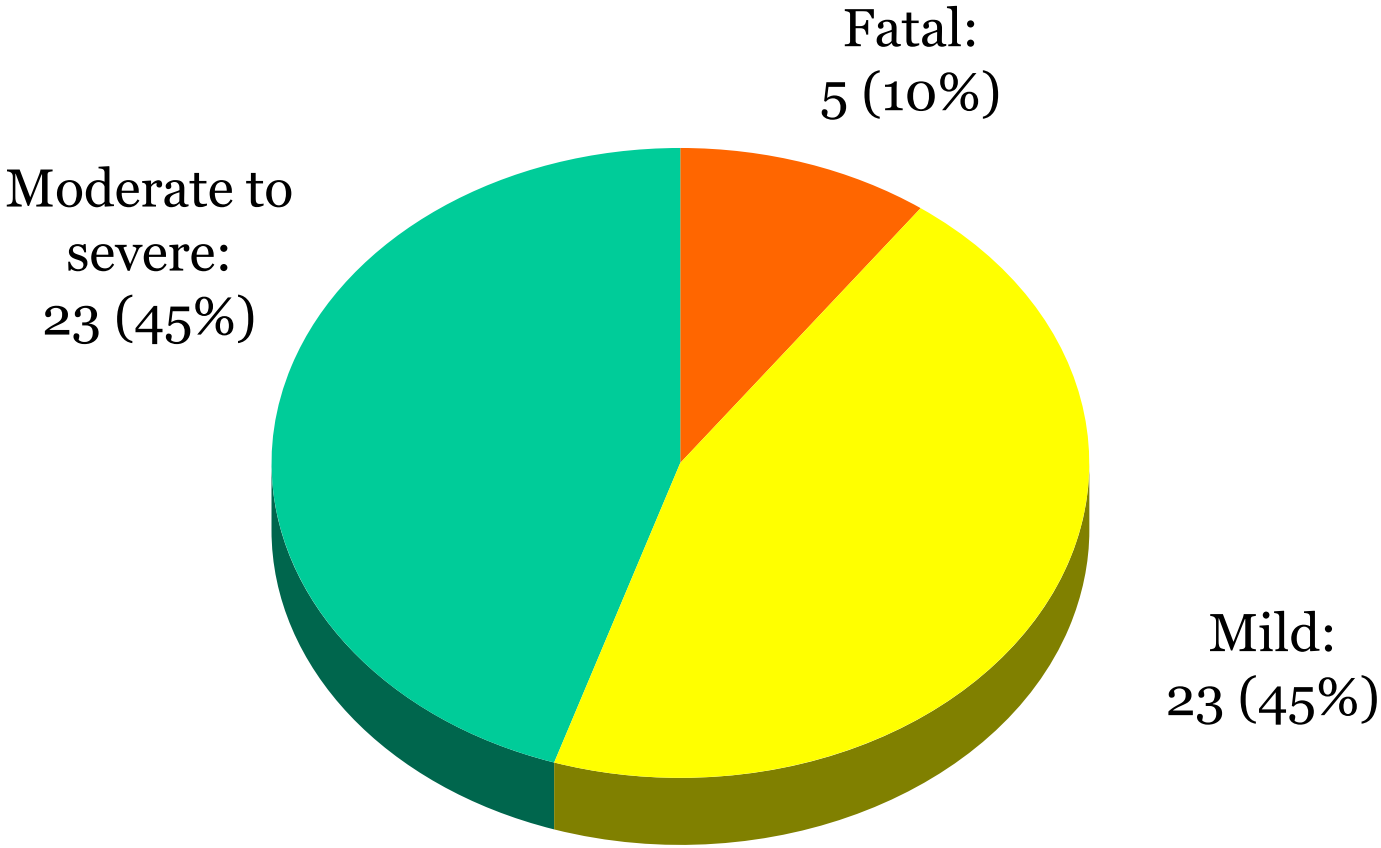


Wolf et al., Arch Int Med 1987;147:1561

Cardiac conditions associated with stroke



Severity of Ischemic Strokes in Atrial Fibrillation



CHA_2DS_2-VASc

tergooi

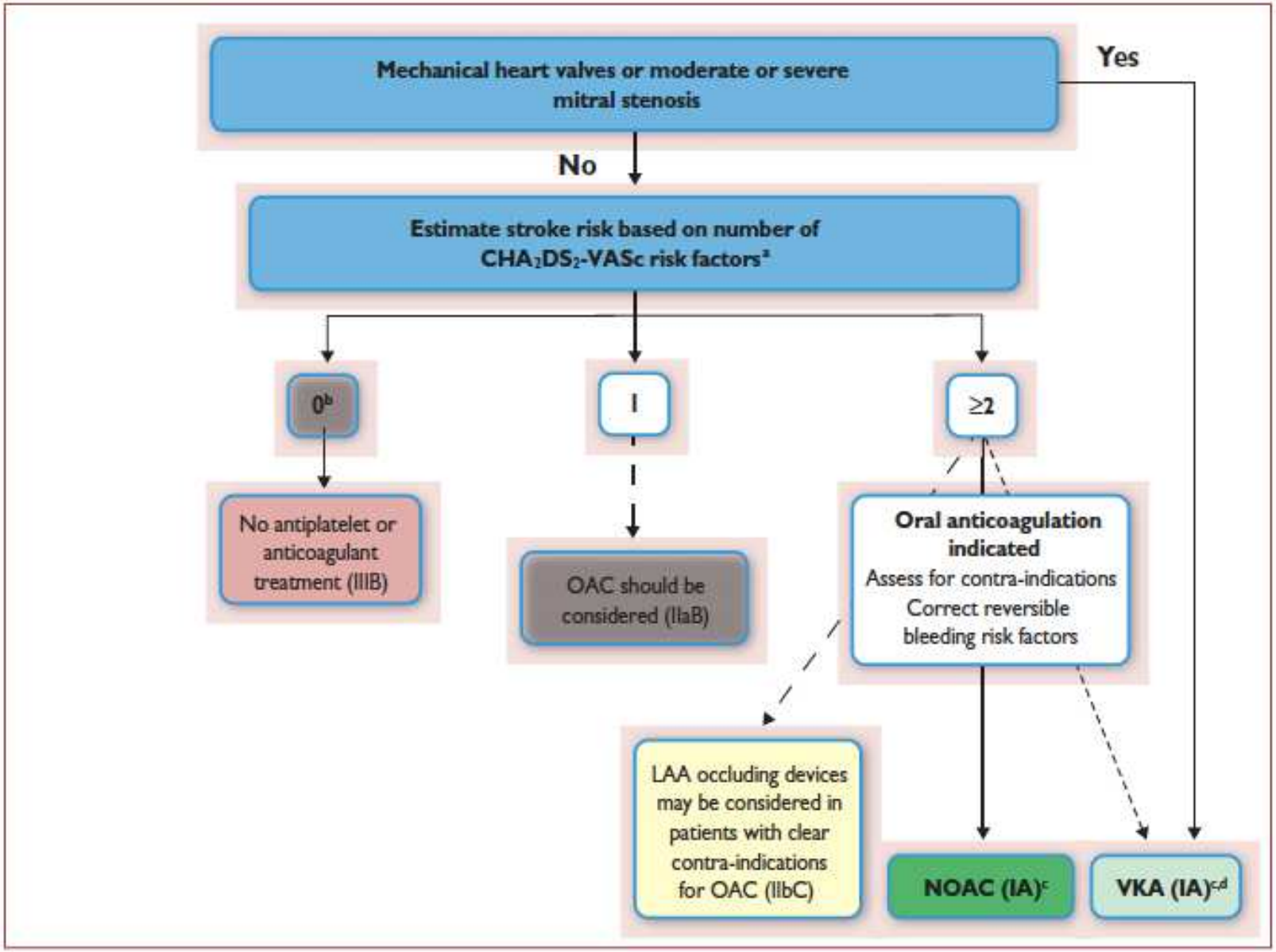
a) The risk factor based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1 or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease[a]	1
Age 65-74	1
Sex category (i.e., female gender)	1
Maximum score	**9**

Stroke, TIA or systemic embolism and age ≥75 years are regarded as major risk factors, and others are described as clinically relevant non-major risk factors

Lip et al Chest 2010
Camm et al EHJ 2010

CHA_2DS_2-VASc Score	#	#TE Events	TE Rate During 1 yr (95% CI)	TE Rate During 1 yr, Adjusted for Aspirin RX
0	103	0	0% (0-0)	0%
1	162	1	0.6% (0.0-3.4)	0.7%
2	184	3	1.6% (0.3-4.7)	1.9%
3	203	8	3.9% (1.7-7.6)	4.7%
4	208	4	1.9% (0.5-4.9)	2.3%
5	95	3	3.2% (0.7-9.0)	3.9%
6	57	2	3.6% (0.4-12.3)	4.5%
7	25	2	8.0% (1.0-26.0)	10.1%
8	9	1	11.1% (0.3-48.3)	14.2%
9	1	1	100% (2.5-100)	100%
Total	1,084	25	*P Value for trend 0.003*	

Nieuwlaat et al Chest 2010



AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.

[a]Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.

[b]Includes women without other stroke risk factors.

[c]IIaB for women with only one additional stroke risk factor.

[d]IB for patients with mechanical heart valves or mitral stenosis.

Veneuze trombo-embolie

Doel behandeling

- Vermindering sterfte
- Vermindering terugkeer ziekte
- 30% van patiënten blijft stolsel aanwezig in vene → stolsels lossen lang niet altijd op
- Voorkomen van langetermijnscomplicaties:
  - Post-trombotisch syndroom
  - Pulmonale hypertensie

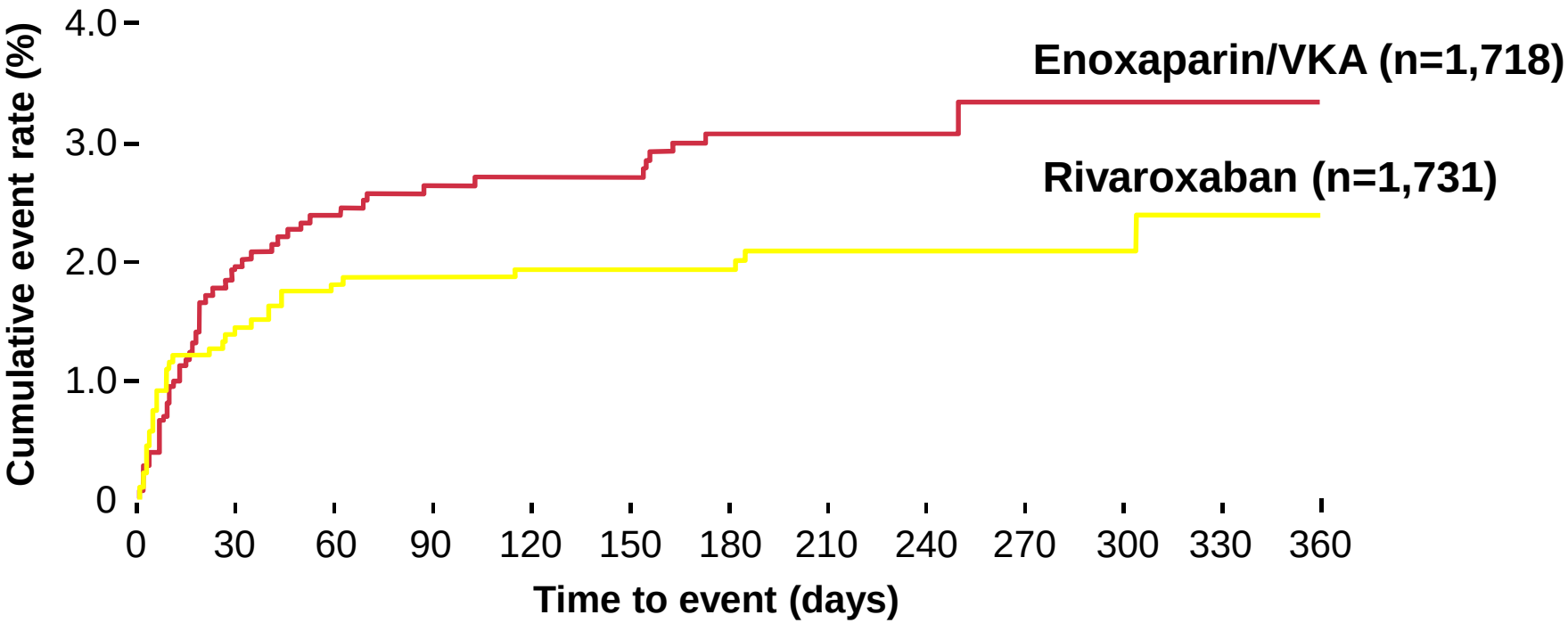
Recidief VTE

Prandoni Ann Int Med 1996;126:743

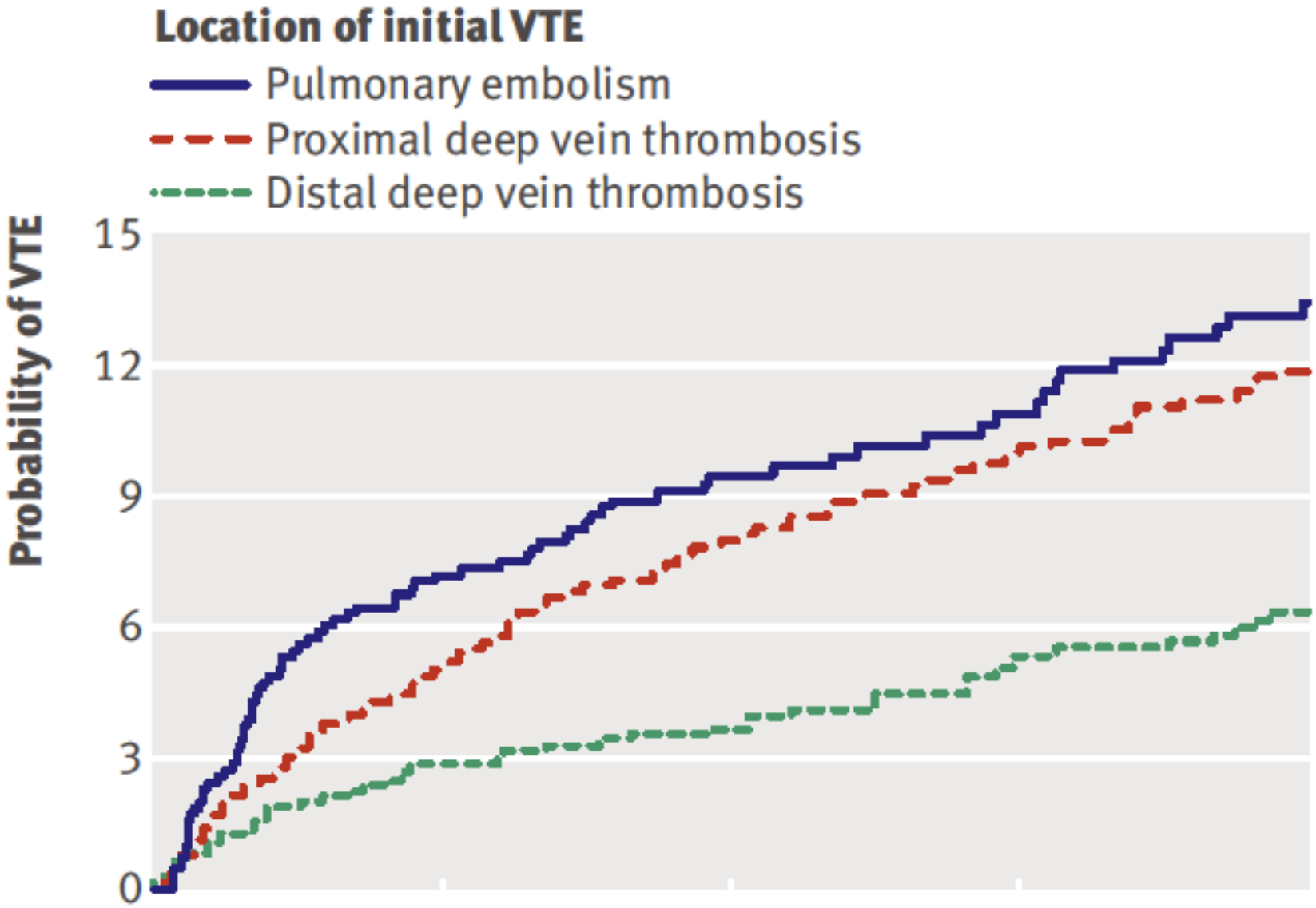
Cumulatieve incidentie bij 355 patienten met een eerste DVT

na 2 jaar: 18 %
na 5 jaar: 25 %
na 8 jaar: 30 %
hoger risico: maligniteit, idiopathische VTE
lager risico: na operatie, recent trauma

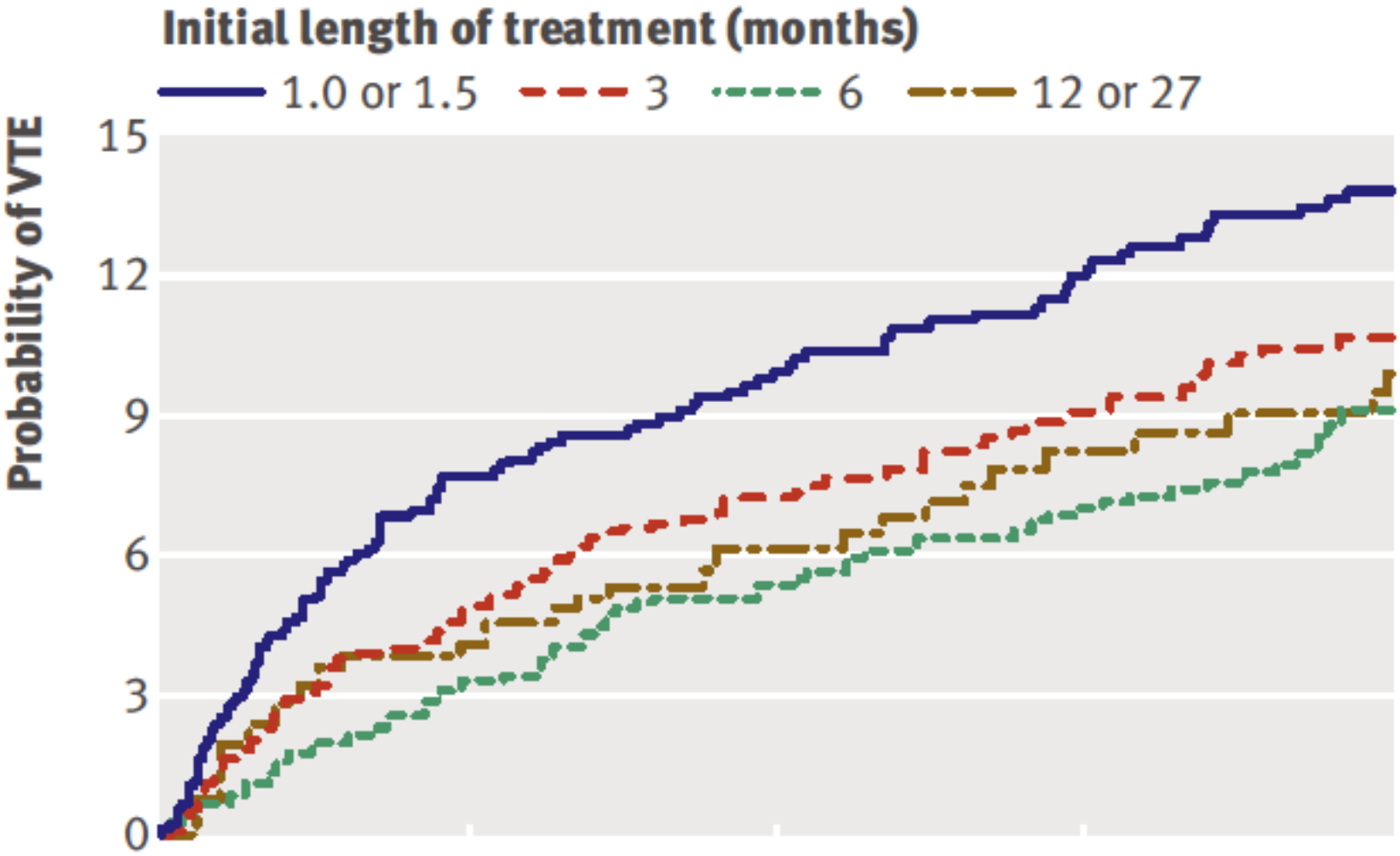
Antistolling is effectief



Number of subjects at risk													
Rivaroxaban	1,731	1,668	1,648	1,621	1,424	1,412	1,220	400	369	363	345	309	266
Enox/VKA	1,718	1,616	1,581	1,553	1,368	1,358	1,186	380	362	337	325	297	264



Boutitie et al. BMJ 2011



Boutitie et al. BMJ 2011

Vitamine K antagonisten

Indication	Therapeutic Range (INR)
Treatment of venous thrombosis Treatment of pulmonary embolism Prevention of systemic embolism Tissue heart valves Valvular heart disease Atrial fibrillation Bileaflet mechanical valve in aortic position	2.0 – 3.0 Target = 2.5
Mechanical prosthetic valves Acute Myocardial infarction	2.5 – 3.5 Target = 3.0

Pharmacokinetics

Absorption

- Rapid absorption
- Food does not affect absorption

Distribution

- 99% protein bound

Metabolism

- Liver
- Cytochrome P450 2C9

Drug Interactions

tergooi

Increase Warfarin Response

NSAIDS, ASA

Acetaminophen > 2g/d

Amiodarone

Quinolones (e.g., Cipro), sulfonamides, metronidazole

Fibrates

Ginkgo, Garlic, Ginseng

Grapefruit

Decrease Warfarin Response

Phenobarbital

Carbamazepine

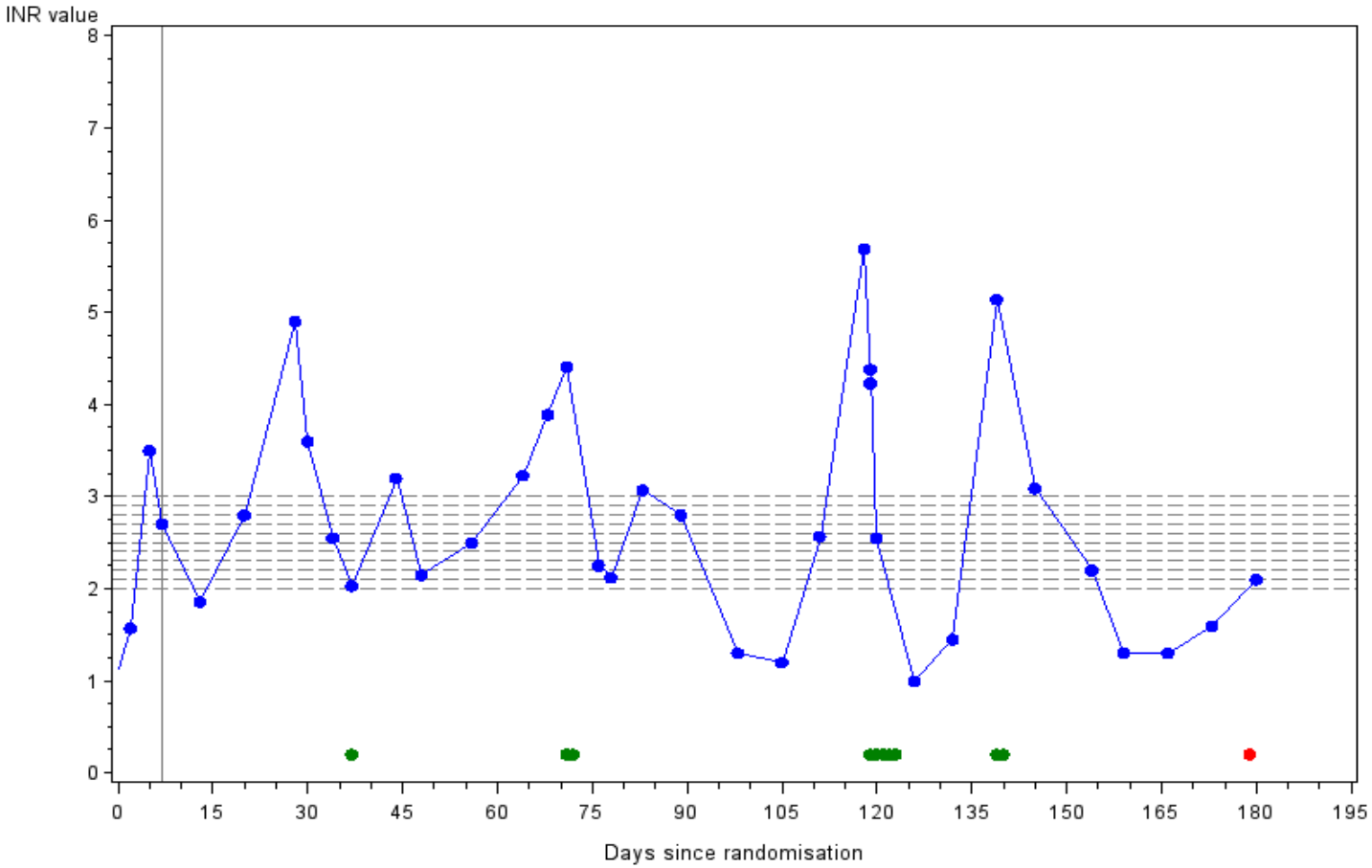
Phenytoin

Vitamin K rich foods

- Green leafy vegetables

Huidige problemen antistollingsbehandeling

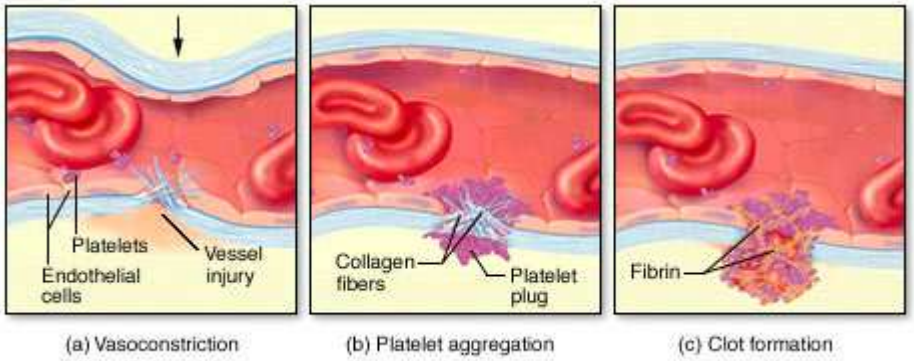
Monitoring en dosis aanpassing van vitamine K antagonisten

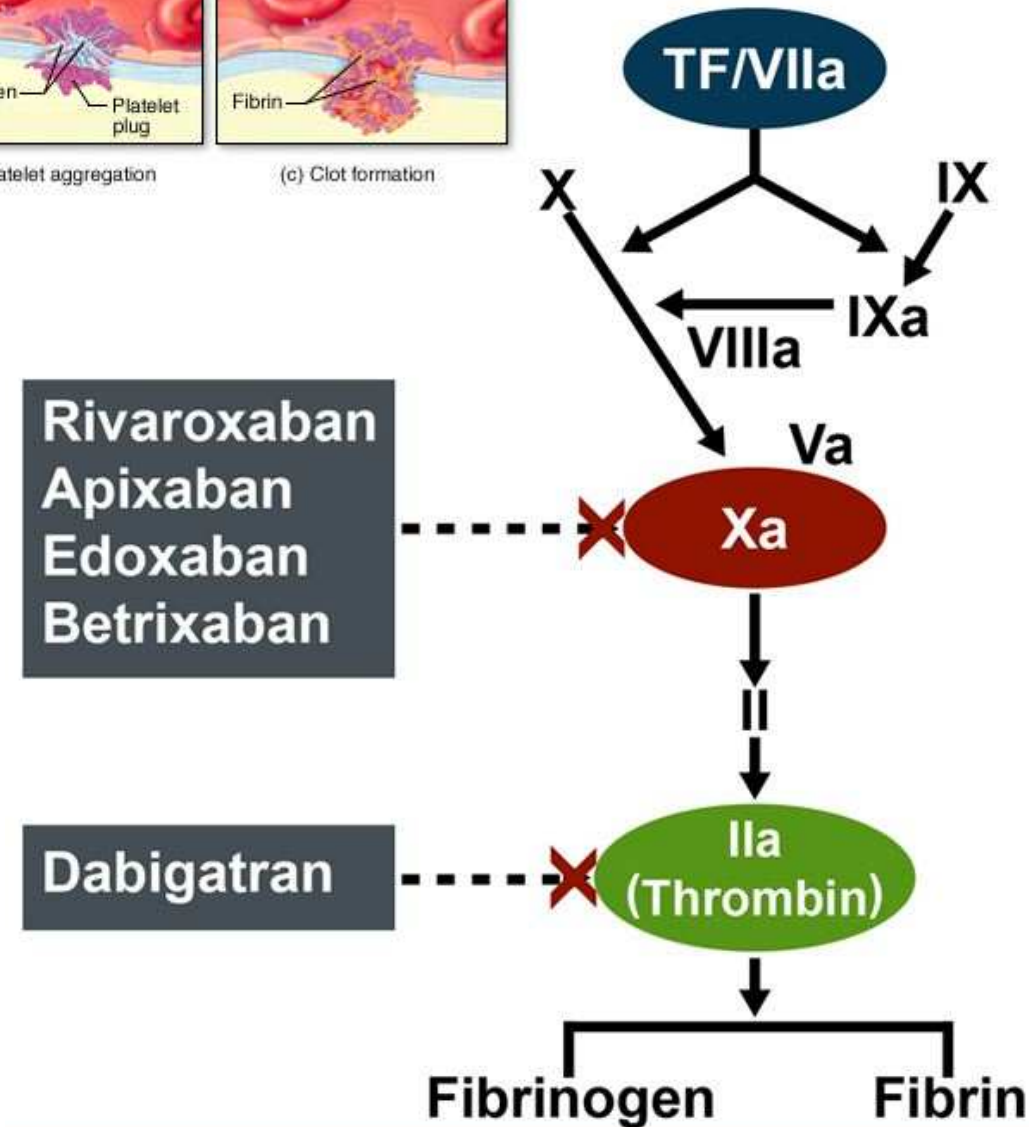


>60 trombosediensten in Nederland

Hospitalisation due to medication complications

omschrijving ATC groep	Aantal	Percentage
Trombocytenaggregatieremmers	29	8,7%
Vitamine K-antagonisten	21	6,3%
NSAID's	17	5,1%
Psychofarmaca (waaronder anxiolytica, hypnotica en sedativa)	17	5,1%
Insulines en analoga	16	4,8%
Orale Bloedglucoseverlagende middelen	15	4,5%
"High ceiling" diuretica/lisdiuretica	15	4,5%
Corticosteroïden, oraal	13	3,9%
Antimicrobiële middelen	11	3,3%
Anti-epileptica	9	2,7%
Vitamine K-antagonist met NSAID	6	1,8%
Combinatie van verschillende geneesmiddelen	99	29,8%
Overige geneesmiddelen	64	19,3%
Totaal	332	100,0%


Platelets
Endothelial cells
Vessel injury
Collagen fibers
Platelet plug
Fibrin
(a) Vasoconstriction
(b) Platelet aggregation
(c) Clot formation


TF/VIIa
X
IX
IXa
VIIIa
Va
Xa
Rivaroxaban
Apixaban
Edoxaban
Betrixaban
II
IIa
(Thrombin)
Dabigatran
Fibrinogen
Fibrin

Voordelen van DOACs

Geen monitoring

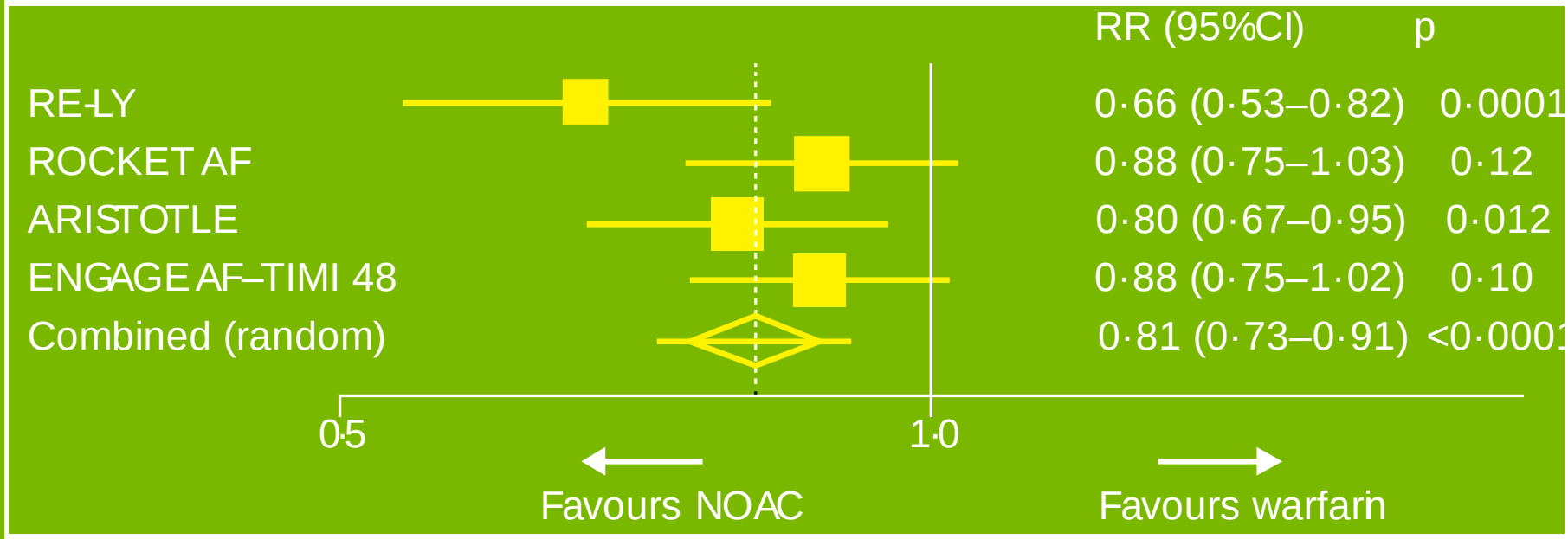
Makkelijk te doseren

Vrijwel geen interactie met voeding/geneesmiddelen

Geen LMWH nodig bij acute VTE (rivaroxaban, apixaban)

Overbruggingstherapie simpeler

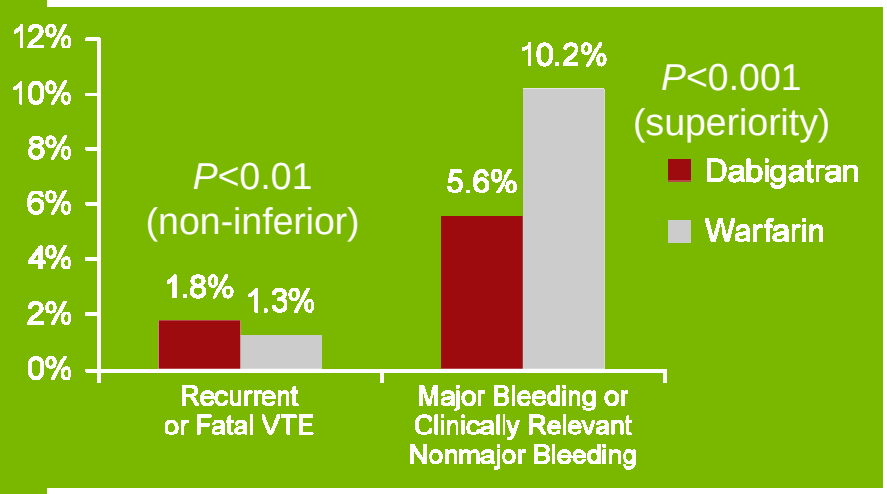
Stroke or systemic embolic events in large NOAC trials, vs warfarin



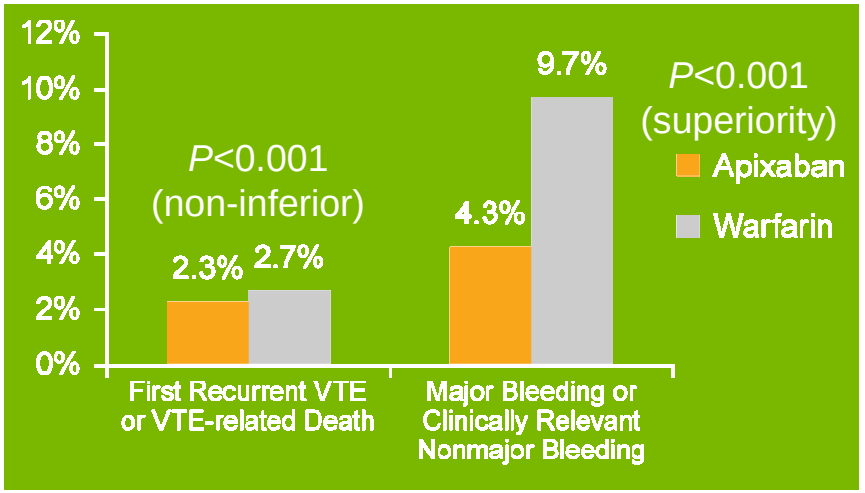
Ruff *et al.*, The Lancet, 2013

VTE Treatment

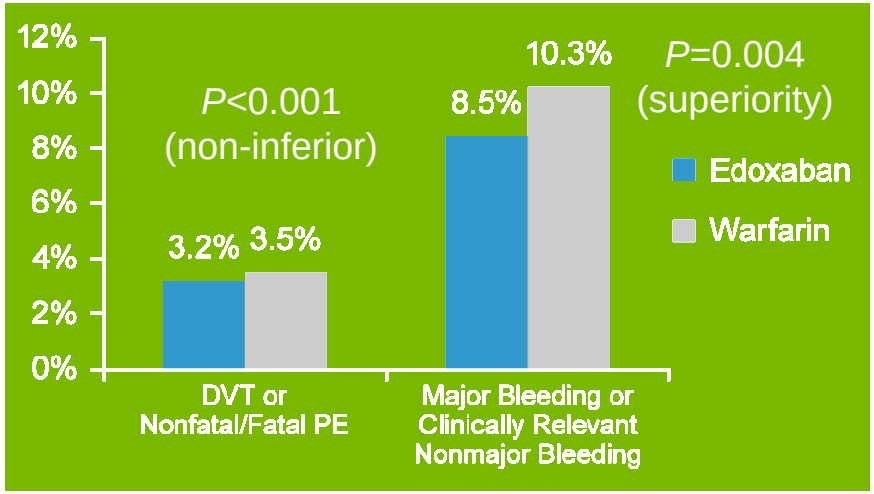
RE-MEDY (Dabigatran)[1,2]



AMPLIFY (Apixaban)[1,3]



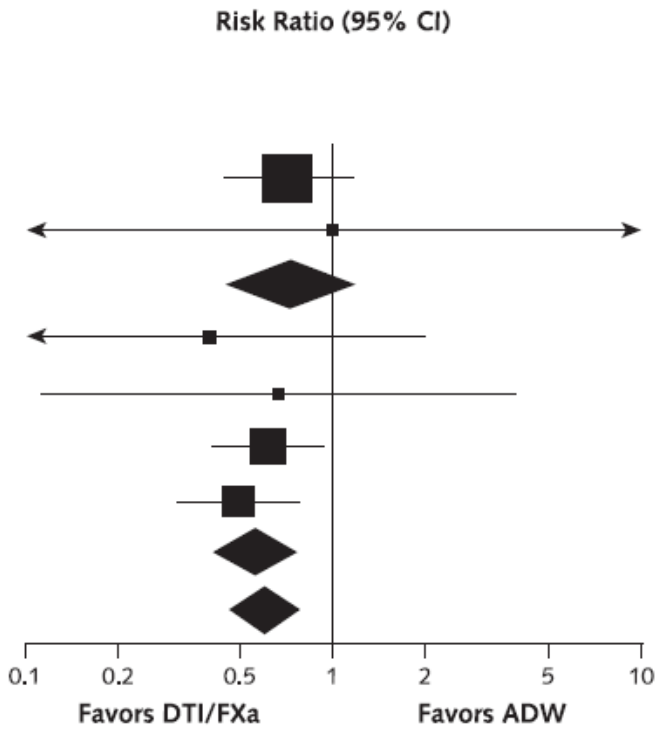
HOKUSAI-VTE (Edoxaban)[1,4]



1. Cavender MA, Giugliano RP. *Hot Topics in Cardiology*. 2013;8:1-14. 2. Schulman S, et al. *N Eng J Med*. 2013;368:709-718.
3. Agnelli G, et al. *N Engl J Med*. 2013; 369:799-808. 4. Hokusai-VTE Investigators. *N Engl J Med*. 2013;369:1406-1415.

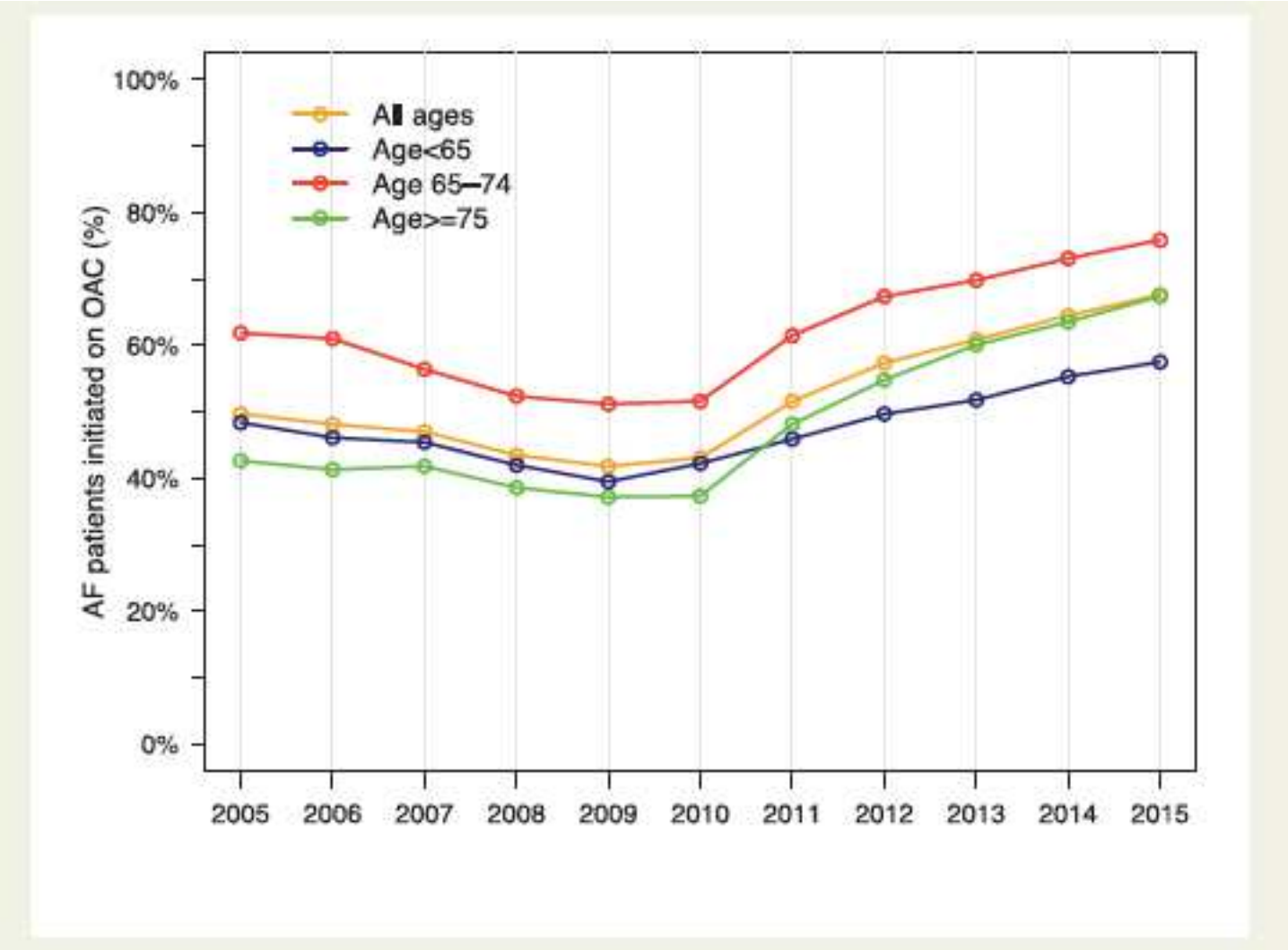
Fatal bleeding

Study, Year (Reference)	Events/Total, *n/N* DTI/FXa	Events/Total, *n/N* Warfarin	Risk Ratio	Lower Limit	Upper Limit
Fatal bleeding					
Connolly et al, 2009 (32)	28/6075	39/6022	0.71	0.44	1.15
Schulman et al, 2009 (35)	1/1273	1/1266	0.99	0.06	15.88
DTI			0.72	0.45	1.16
Bauersachs et al, 2010 (36)	2/1731	5/1718	0.40	0.08	2.04
Büller et al, 2012 (16)	2/2412	3/2405	0.66	0.11	3.97
Granger et al, 2011 (33)	34/9088	55/9052	0.62	0.40	0.94
Patel et al, 2011 (34)	27/7111	55/7125	0.49	0.31	0.78
FXa			0.55	0.41	0.75
Total			0.60	0.46	0.77



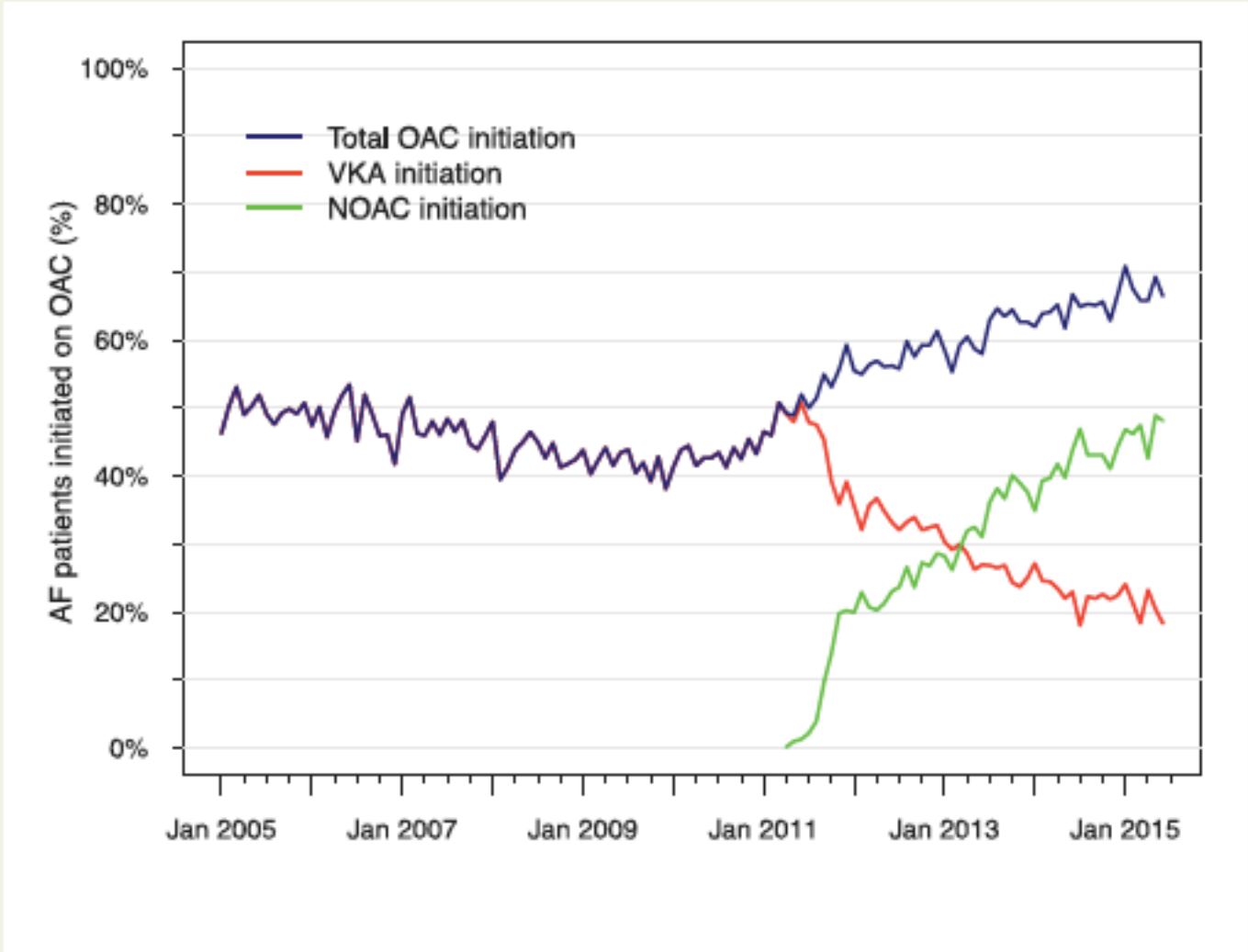
Adam SS. Ann Intern Med 2012;157:796-807

OAC initiation in new AF patients



Gadsbøll et al Eur Heart J 2017

Most patients are started on DOACs



Gadsbøll et al Eur Heart J 2017

Nadelen DOACs

- Renaal geklaard, relatieve contra-indicatie bij eGFR<30 ml/min
- Interactie met Pgp en Cyp3A4
- Compliance
- Antidotum: idarucizumab voor dabigatran, PCC voor Xa remmers

Bij wie geen DOACs

- eGFR<30 ml/min
- Mechanische hartkleppen
- Zwangerschap
- ketoconazol, itraconazol, voriconazol, posaconazol, HIV-proteaseremmers, rifampicine, fenytoïne, carbamazepine, fenobarbital

Nierinsufficientie

Table 14 Dose adjustment for NOACs as evaluated in the PHASE III trials (adapted from Hart *et al.*[316])

	Dabigatran (RE-LY) [318, 425]	Rivaroxaban (ROCKET-AF) [320, 426]	Apixaban (ARISTOTLE) [319, 427]	Edoxaban (ENGAGE AF-TIMI 48) [321]
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 mL/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl 30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 μmol/L) plus age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

CKD = chronic kidney disease; CrCl = creatinine clearance; GFR = glomerular filtration rate; NA = not available.

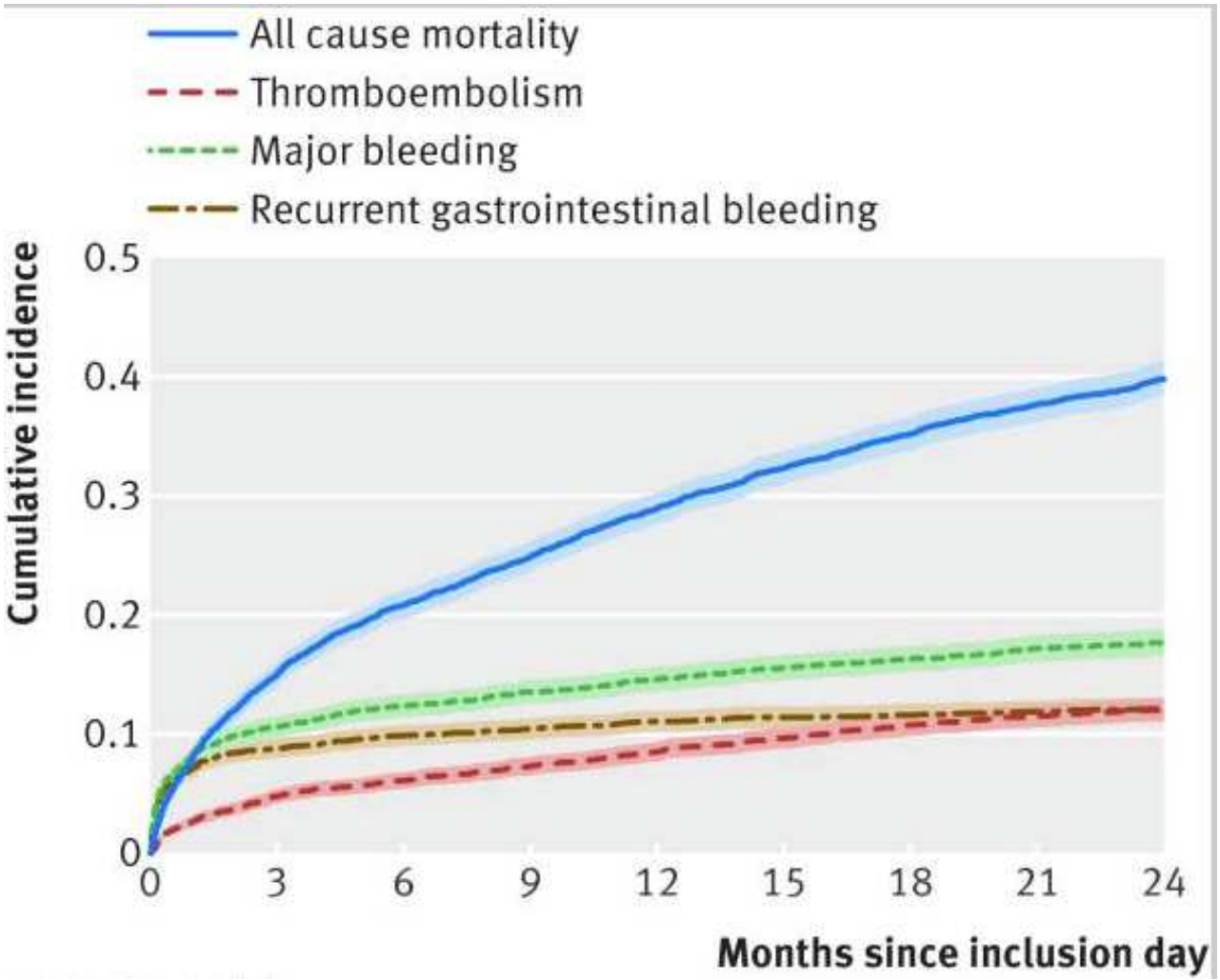
ESC guideline AF 2016

OAC in frail patients

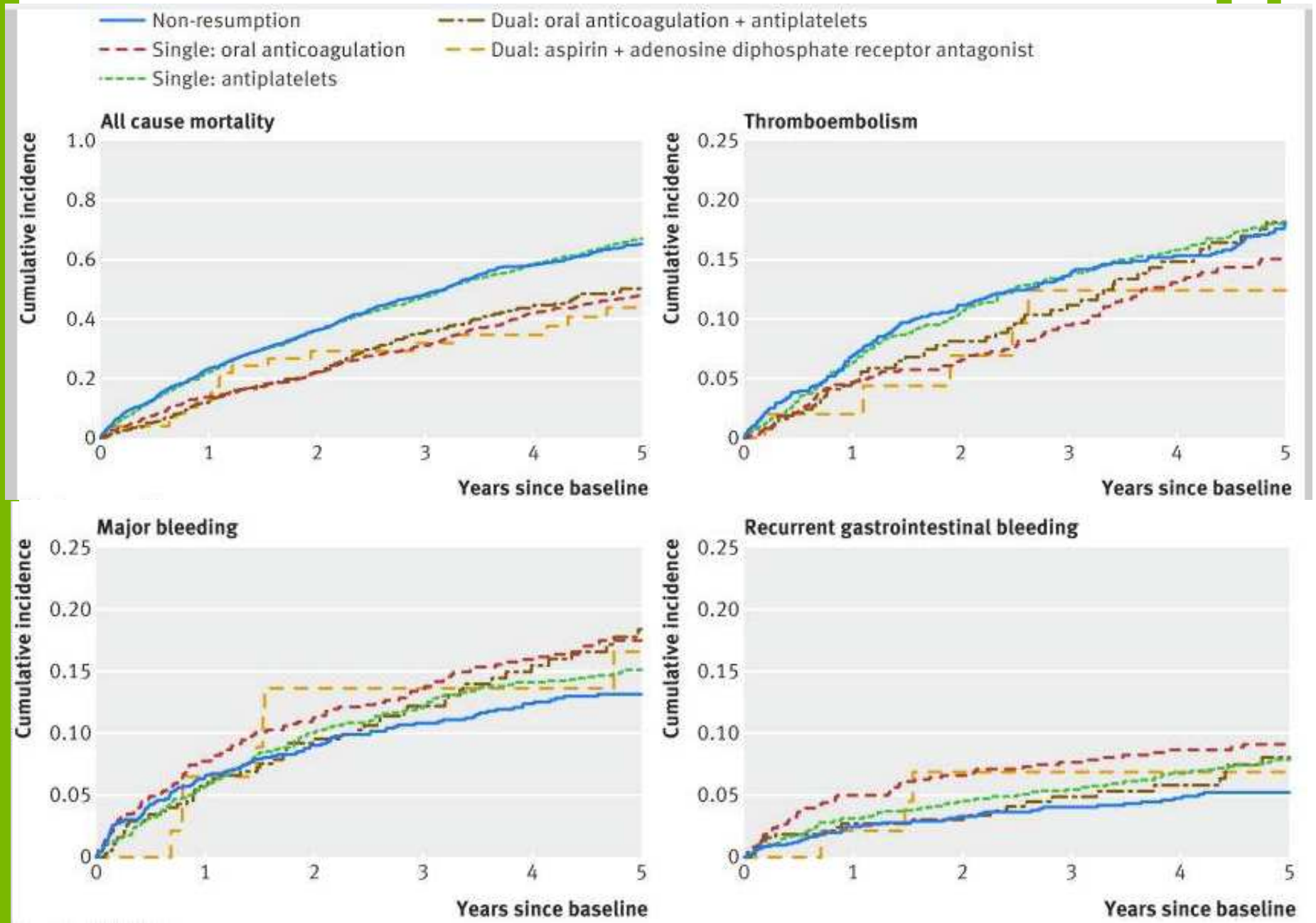
Oral anticoagulants				
VKA	INR-adjusted dose (AF, VTE, mechanical heart valve)	With age, lower doses required to achieve target INR		Closer monitoring in the elderly
Dabigatran[b]	110-mg b.i.d. (not for VTE; 110-mg not available in the USA) and 150-mg b.i.d. (nonvalvular AF, VTE)	In AF, 110-mg b.i.d. should be considered for age 75–79 years (IIa B);[66] 110-mg b.i.d. is EMA-approved for AF patients ≥80 years	Avoid if CrCl <30 mL/min. 75-mg b.i.d. FDA-approved if CrCl 30 mL/min with concomitant dronedarone or systemic ketoconazole.	For age ≥75 years, rates of major extracranial bleeds with 110-mg b.i.d. not significantly lower (with 150-mg b.i.d. numerically higher) vs. warfarin[66]
Rivaroxaban[b]	20-mg o.d. (for VTE, 15-mg b.i.d. in first 21 days) (nonvalvular AF, VTE)		15-mg if CrCl 15–49 mL/min. Avoid if CrCl <15 mL/min	No dose adjustment for age (I A)[67,68,w34,w35]
Apixaban[b]	5-mg b.i.d. (nonvalvular AF, VTE)	2.5-mg b.i.d. EMA/FDA-approved if 2 or more of: age ≥80 years, body weight ≤60 kg, serum Cr ≥1.5 mg/dL (I A)[8,9,w36]	2.5-mg b.i.d. if 2 or more of age ≥80 years, body weight ≤60 kg, serum Cr ≥1.5 mg/dL. Avoid if CrCl <15 mL/min	
Edoxaban[b,c]	60-mg o.d. (FDA-approved for nonvalvular AF and VTE)		30-mg o.d. if CrCl 15–50 mL/min (FDA-approved). FDA recommends avoidance if CrCl <15 or >95 mL/min	No dose adjustment for age (I A)[69,w38]

ESC guideline 2015 in elderly

After GI bleed



Staerk et al BMJ 2015

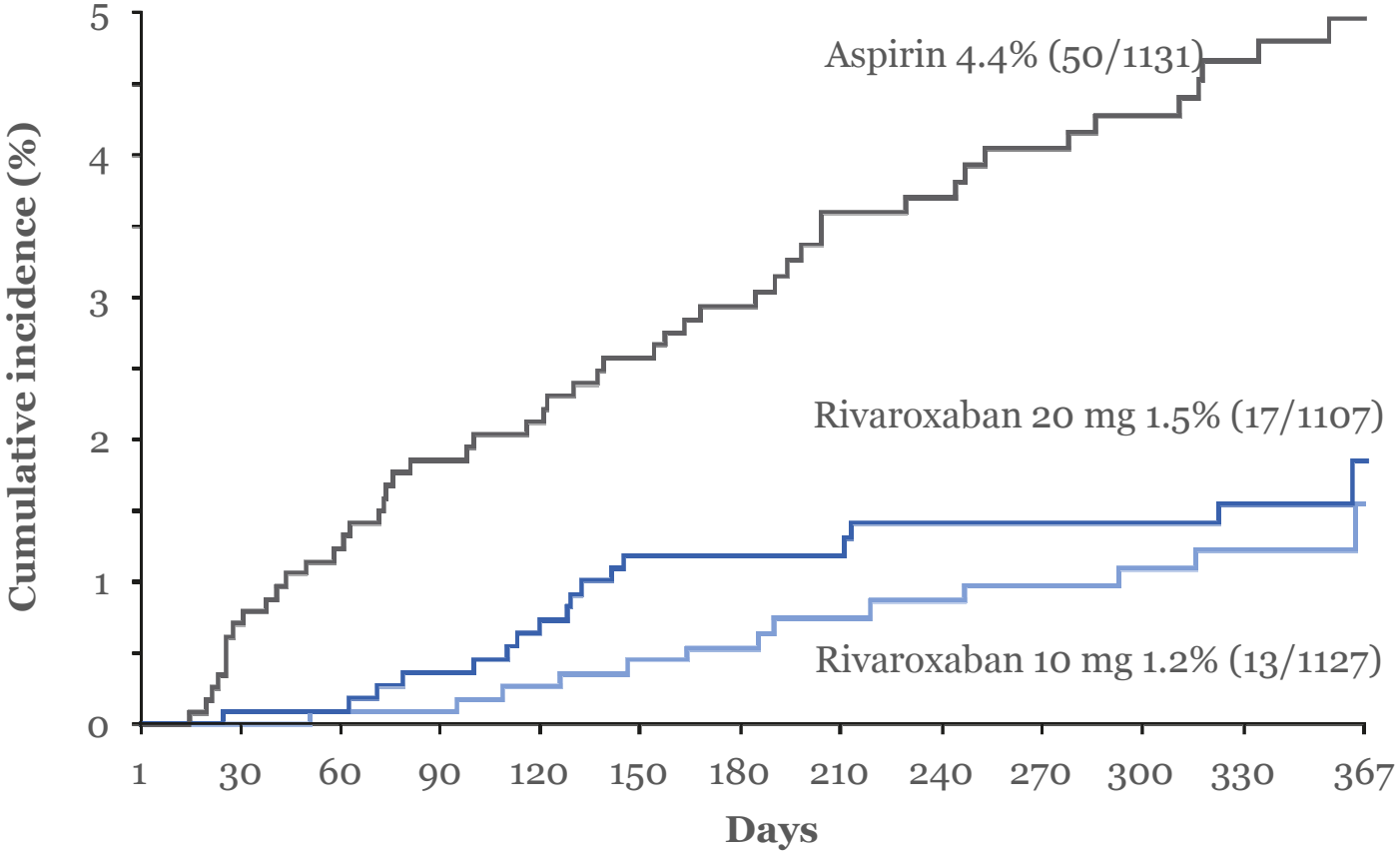

Non-resumption
Dual: oral anticoagulation + antiplatelets
Single: oral anticoagulation
Dual: aspirin + adenosine diphosphate receptor antagonist
Single: antiplatelets
All cause mortality
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
Years since baseline
Thromboembolism
Cumulative incidence
0.25
0.20
0.15
0.10
0.05
0
0
1
2
3
4
5
Years since baseline
Major bleeding
Cumulative incidence
0.25
0.20
0.15
0.10
0.05
0
0
1
2
3
4
5
Years since baseline
Recurrent gastrointestinal bleeding
Cumulative incidence
0.25
0.20
0.15
0.10
0.05
0
0
1
2
3
4
5
Years since baseline

Wat kosten de antistollingsmiddelen?

Bedrag in euro's	VKA*	LMWH	DOAC
Per dag	0.62	4.60	2.10**
Per jaar	225	1679	912

*Inclusief kosten trombosedienst
**Schatting, werkelijke kosten onbekend

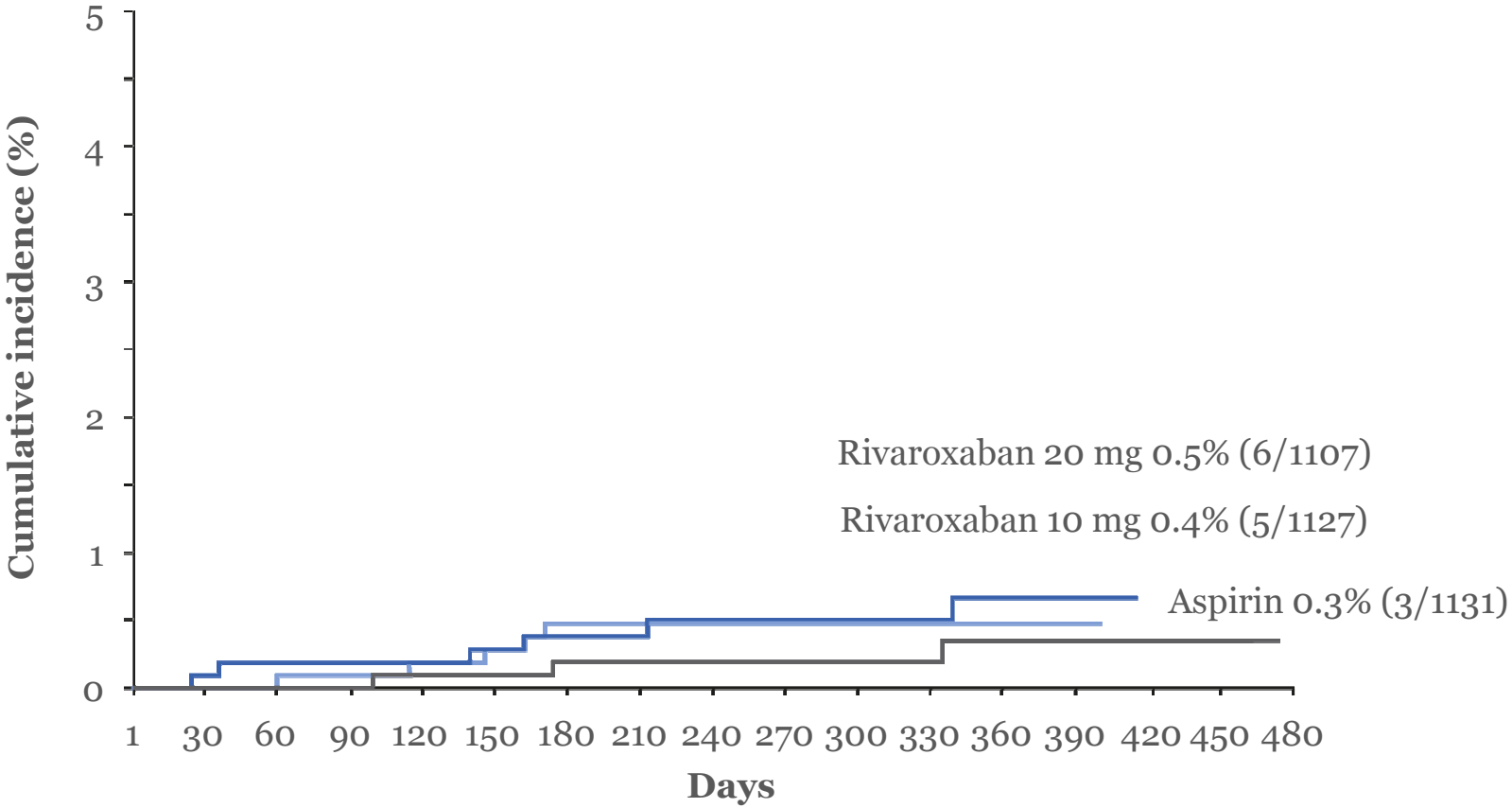
Dosis reductie NOACs na VTE



Number of patients at risk													
Rivaroxaban 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

VTE, venous thromboembolism; HR, hazard ratio

Bloedingen



Number of patients at risk																	
Rivaroxaban 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

Primary outcome: major bleeding onset during study treatment up to 2 days after stop of study treatment

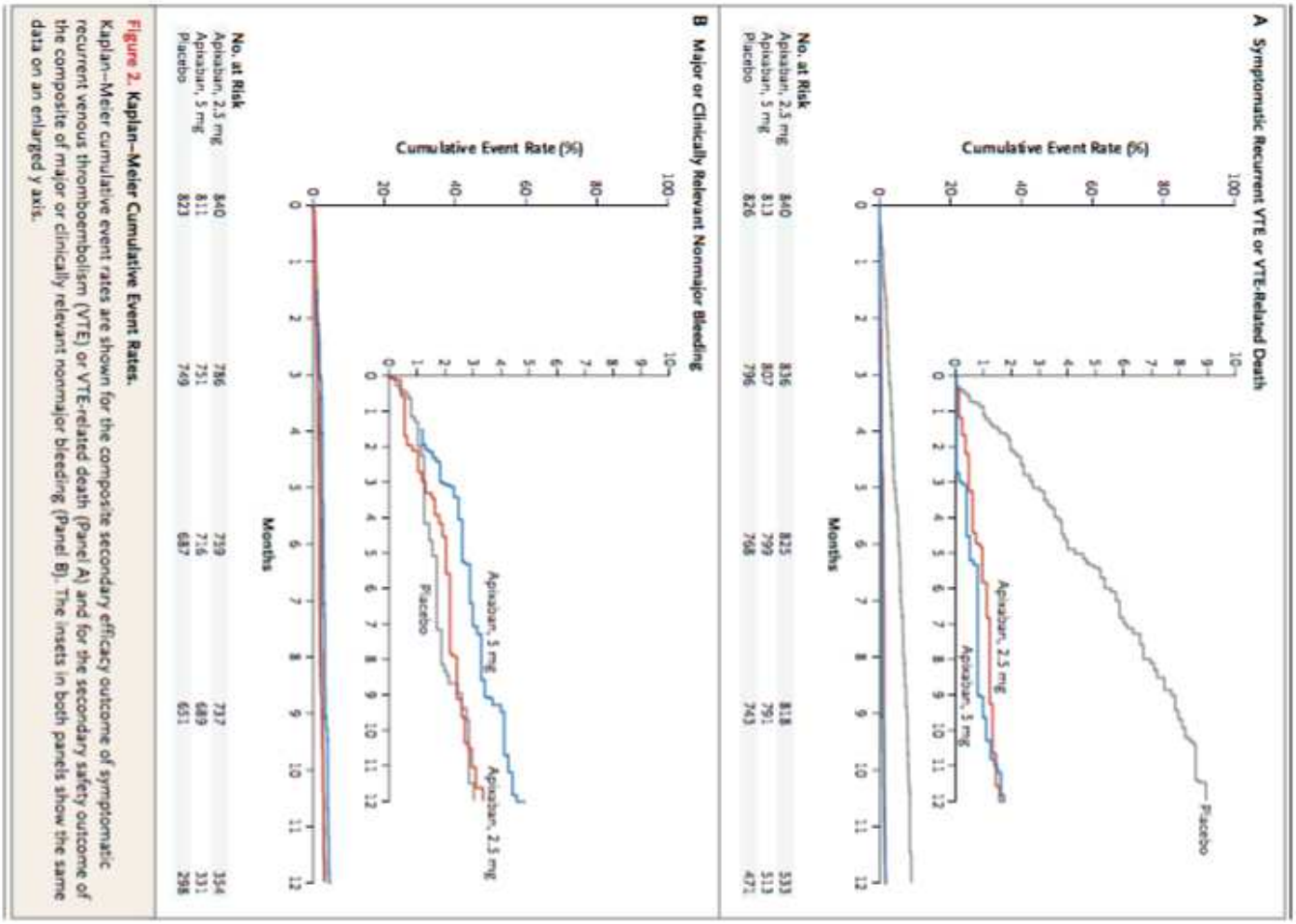


Figure 2. Kaplan–Meier Cumulative Event Rates.

Kaplan–Meier cumulative event rates are shown for the composite secondary efficacy outcome of symptomatic recurrent venous thromboembolism (VTE) or VTE-related death (Panel A) and for the secondary safety outcome of the composite of major or clinically relevant nonmajor bleeding (Panel B). The insets in both panels show the same data on an enlarged y axis.

Conclusie

- DOACs meest voorgeschreven orale antistolling
- Evidente voordelen in gebruikersgemak
- Zorg verschuift van de trombosedienst naar eerstelijn en apotheek: compliance!!!
- Duur van antistolling zal toenemen
- Er blijft een indicatie voor behandeling met VKA