La fin des AVK dans la FA non valvulaire?

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Liens d'intéret

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Lecture fees:	Bayer, BMS-Pfizer, Boston Scientific, Boehringer Ingelheim, Medtronic, Sanofi aventis
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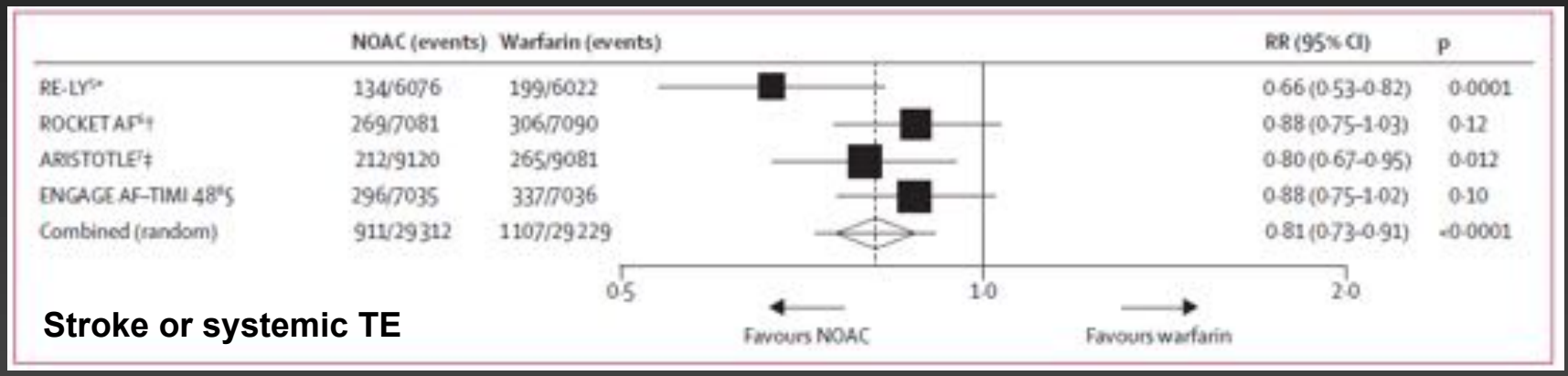
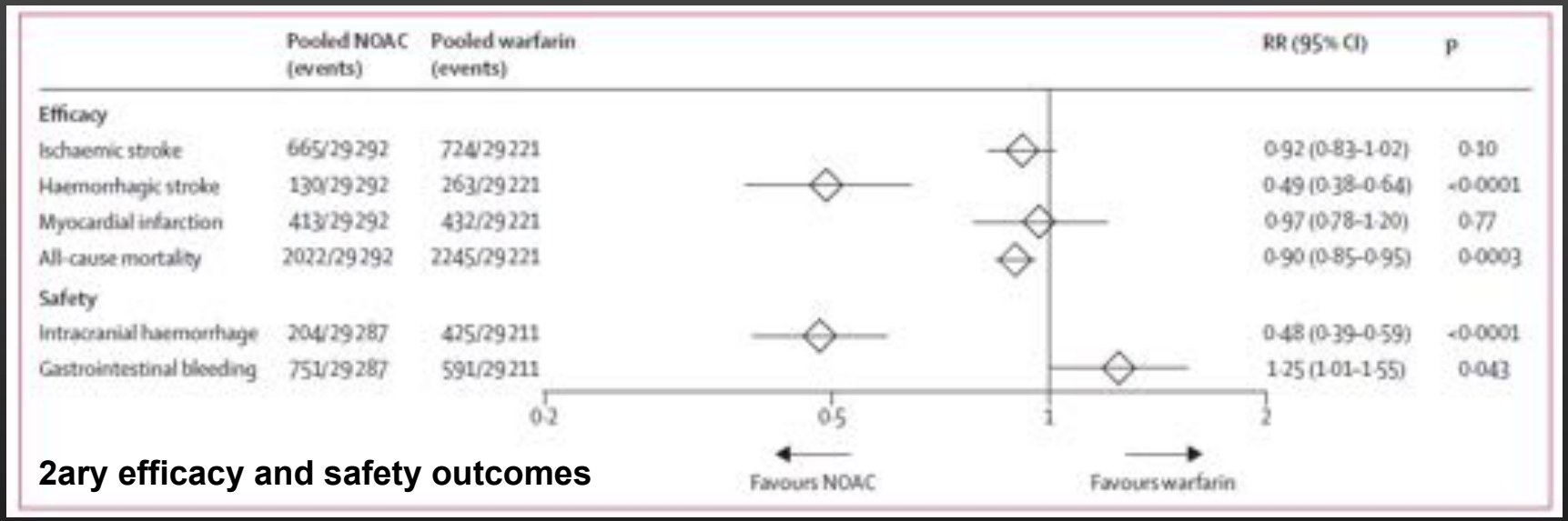
New oral anticoagulants and warfarin in patients with atrial fibrillation



Stroke or systemic TE



2ary efficacy and safety outcomes

Ruff CT et al, *Lancet 2013*

Limitations of VKA therapy

- Unpredictable response
- Narrow therapeutic window (INR range 2-3)
- Routine coagulation monitoring
- Slow onset/offset of action

VKA therapy has several limitations that make it difficult to use in practice

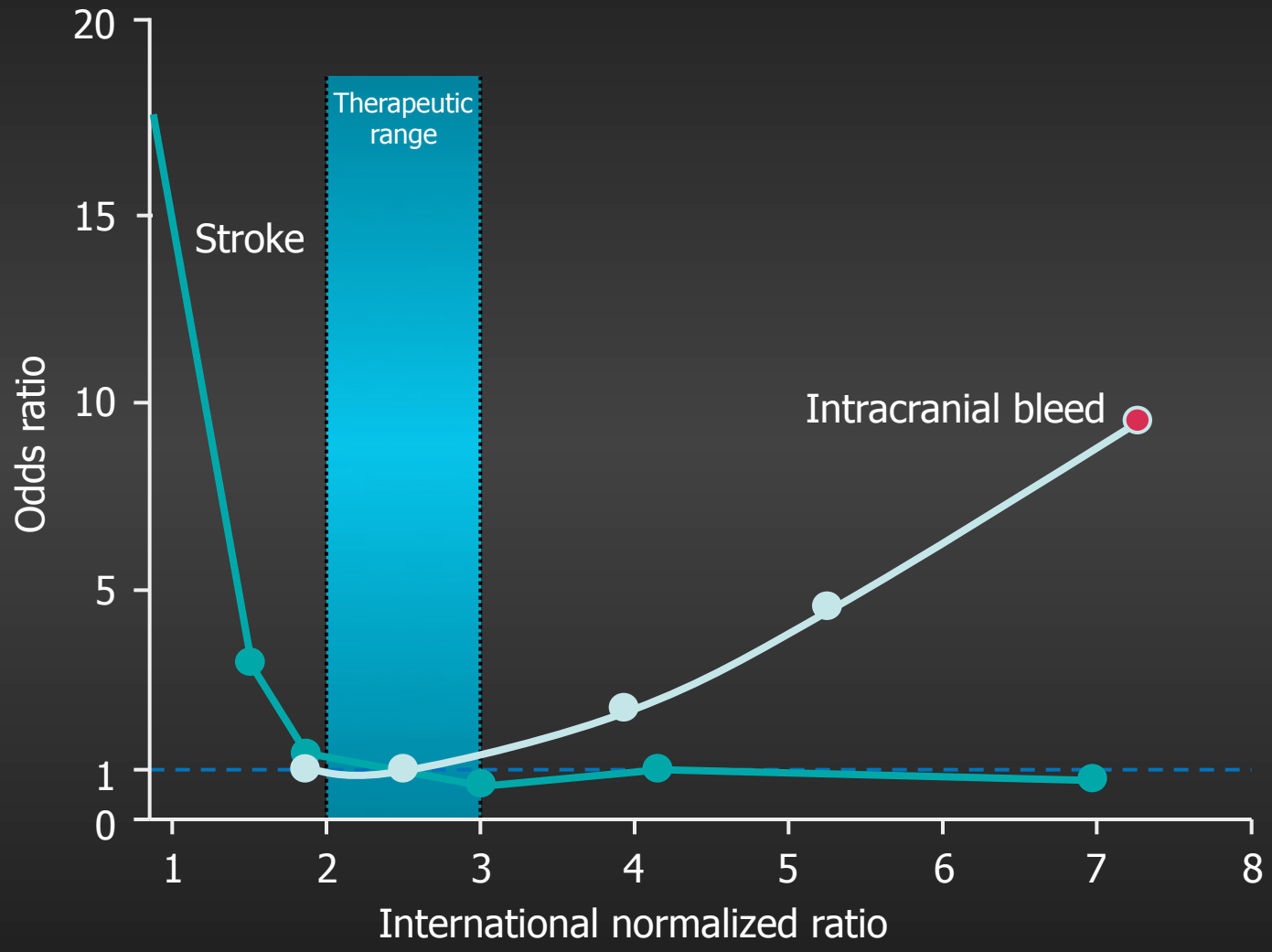
- Frequent dose adjustments
- Numerous food-drug interactions
- Numerous drug-drug interactions
- Warfarin resistance

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

VKAs require regular anticoagulation monitoring

- Careful monitoring of patients being treated with VKAs is critical due to the:
  - Narrow therapeutic window
  - Unpredictable relationship between VKA dose and the anticoagulant response
  - Influence of the quantity of vitamin K in the diet that can change over time

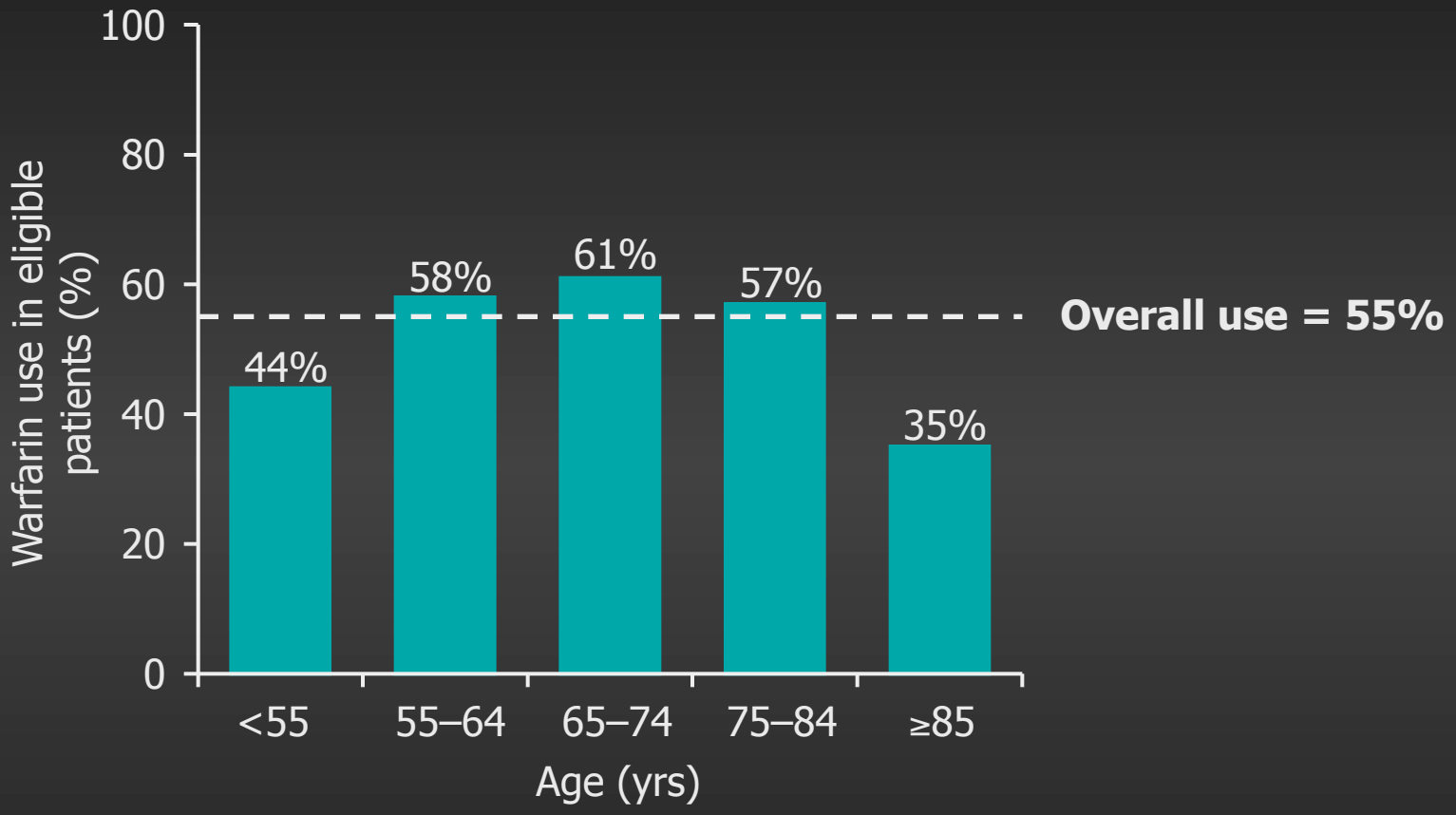
VKAs have a narrow therapeutic window



VKAs = vitamin K antagonists

ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354 & Eur Heart J 2006;27:1979–2030

Warfarin: used in only half of eligible patients with AF



- Under-use of warfarin is greatest in elderly patients who are at the highest risk of stroke

VKA = vitamin K antagonist

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

Drug and food interactions associated with an increased potency of VKAs

Drug/food	Examples
Analgesics	Acetaminophen, propoyphene, salicylates
Anti-arrhythmics	Amiodarone, propafenone, quinidine
Antibiotics	Ciprofloxacin, erythromycin, metronidazole
Antifungals	Fluconazole, itraconazole, miconazole
Beta-blockers	Propranolol
H_2-receptor antagonists/PPIs	Cimetidine, omeprazole
Lipid-lowering agents	Lovastatin, atorvastatin
Herbal products/dietary supplements	Vitamin E, garlic, devil's claw
Miscellaneous	Alcohol (if concomitant liver disease)

PPIs = proton pump inhibitors; VKAs = vitamin K antagonists

Holbrook AM et al. Arch Intern Med 2005;165:1095–106;
du Breuil AL & Umland EM. Am Fam Physician 2007;75:1031–42

Drug and food interactions associated with a reduced potency of VKAs

Drug/food	Examples
Antibiotics	Dicloxacillin, nafcillin, rifampicin
Antifungals	Griseofulvin
Immunosupressants	Azathioprine, cyclosporine
Lipid-lowering agents	Cholestyramine
Herbal products/dietary supplements	Coenzyme Q10, ginseng, St John's wort
Foods	Green tea, avocados (large amounts), food with high vitamin K content including broccoli and spinach
Miscellaneous	Carbamazepine, sucralfate, trazodone

VKAs = vitamin K antagonists

Holbrook AM et al. Arch Intern Med 2005;165:1095–106;
du Breuil AL & Umland EM. Am Fam Physician 2007;75:1031–42

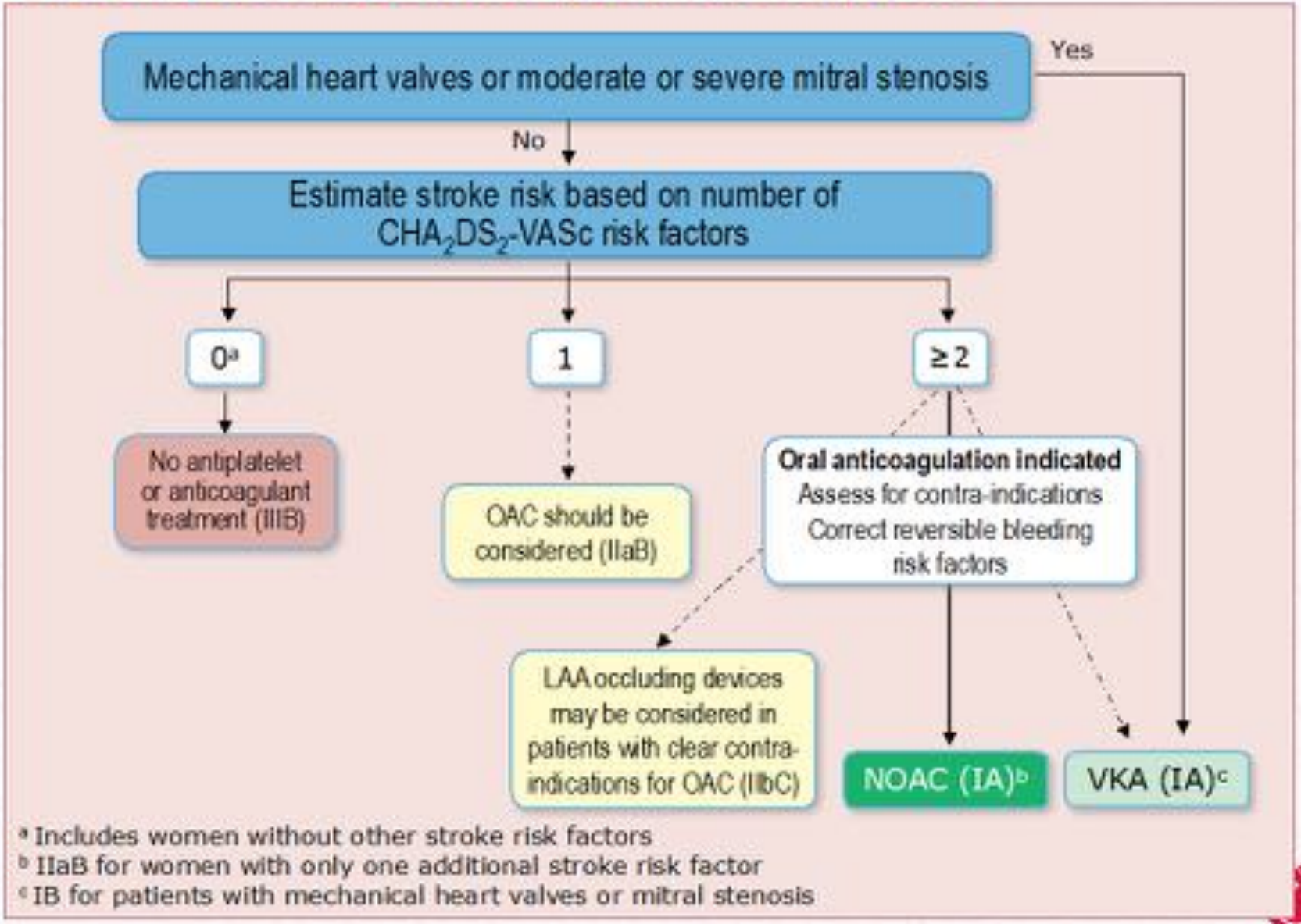
Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%	No PK data	+40%	Minor effect (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect	No data yet	No effect	No effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	+40%	No data yet	Minor effect (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%	No data yet	+77% (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180% (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR) (No dose reduction required by label)	Minor effect (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	No data yet	No effect	No effect
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90% (reduce NOAC dose by 50%)	+30-54%
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%	minus 54%	avoid if possible: minus 35%, but with compensatory increase of active metabolites	Up to minus 50%
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase	No data yet	Up to +153%
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%	+87-95% (reduce NOAC dose by 50%)	Up to +160%
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%	No effect	No effect	No effect
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%	minus 54%	minus 35%	Up to minus 50%
Other factors:					
Age ≥ 80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	
Weight ≤ 60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Red: contra-indicated/not recommended. **Orange**: reduce dose (from 150 to 110 mg BID for dabigatran; from 20 to 15 mg OD for rivaroxaban; from 5 to 2.5 mg BID for apixaban). **Yellow**: consider dose reduction if 2 or more 'yellow' factors are present. Hatching: no clinical or PK data available.
%: age had no significant effect after adjusting for weight and renal function.

2016 ESC guidelines for the management of AF

Stroke prevention in atrial fibrillation

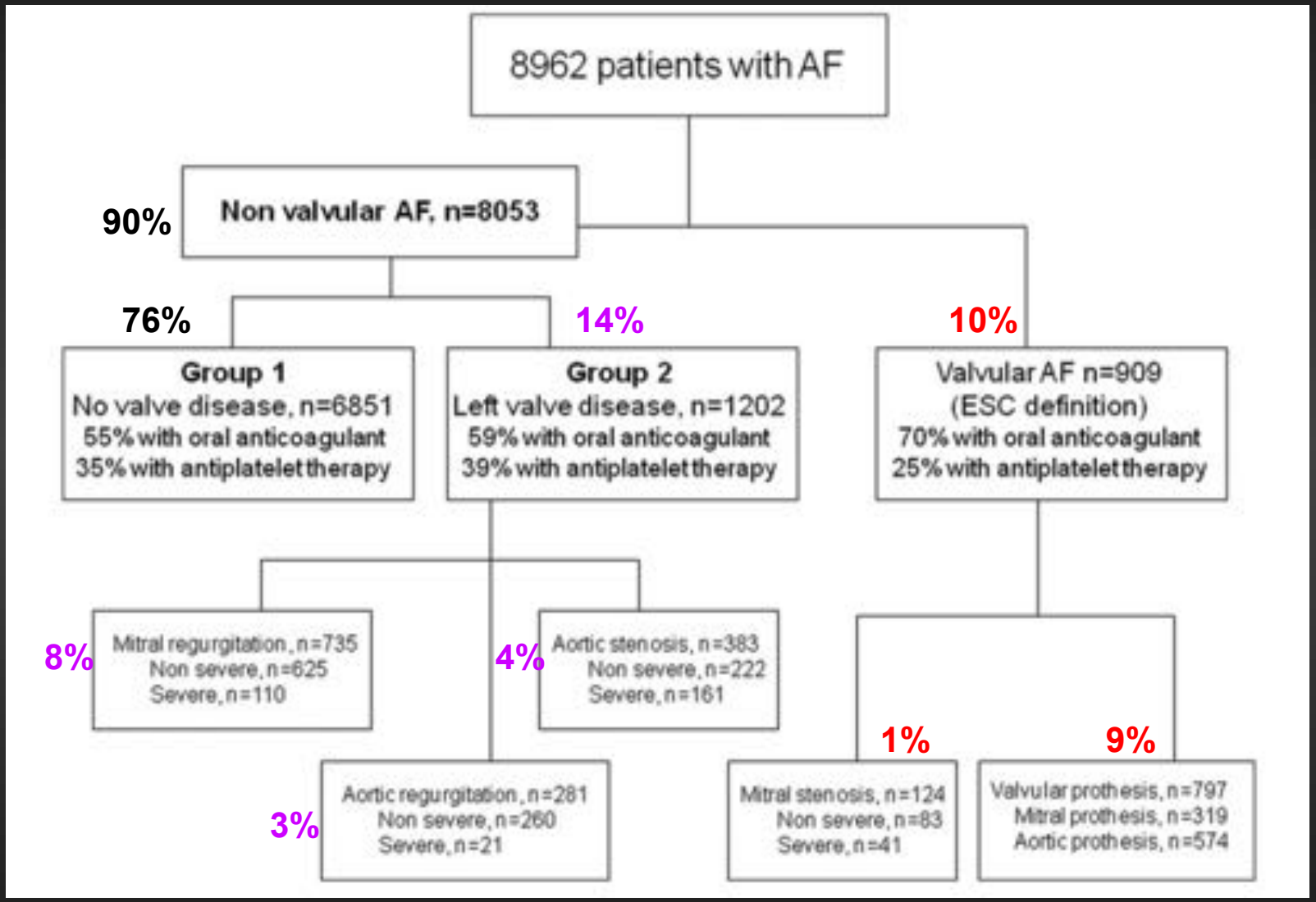


European Heart Journal - doi:10.1093/eurheartj/ehw210

How many AF patients eligible to NOACs ?

- « non valvular » AF
- At least 1 (or 2) risk factors
- eGFR > 30 ml/min

Valvular and non valvular AF in real-life



Philippart R. et al. *Eur Heart J* 2015

Renal Impairment and Stroke Risk in AF

Table 1 Characteristics of Patients With AF by Renal Impairment and eGFR

	Overall Study Population			Patients With Renal Impairment eGFR (ml/min/1.73 m²)		
	Normal Renal Function (n = 4,375)	Renal Impairment (n = 1,537)	p Value	30–59 (n = 1,196)	<30 (n = 341)	p Value
Age, yrs	68.2 ± 15.7	75.8 ± 10.9	<0.001	74.9 ± 10.8	79.3 ± 9.5	
Female	1,777 (40.6)	419 (27.3)	<0.001	234 (19.6)	185 (54.3)	<0.001
Type of AF						
Paroxysmal	2,635 (60.2)	760 (49.4)	<0.001	583 (48.7)	177 (51.9)	0.49
Permanent	1501 (34.3)	688 (44.8)		541 (45.2)	147 (43.1)	
Persistent	239 (5.5)	89 (5.8)		72 (6.0)	17 (5.0)	
CHA_2DS_2-VASc						
Low (score = 0)	475 (10.9)	38 (2.5)	<0.001	37 (3.1)	1 (0.3)	<0.001
Intermediate (score = 1)	682 (15.6)	91 (5.9)		86 (7.2)	5 (1.5)	
High (score ≥2)	3,218 (73.6)	1408 (91.6)		1073 (89.7)	335 (98.2)	

1196 (20.2%)
eGFR 30-59 ml/min/1.73m²

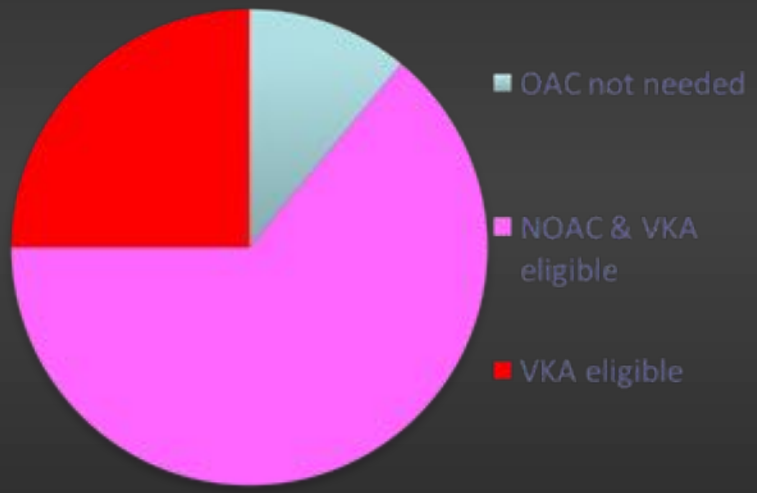
341 (5.8%)
eGFR <30 ml/min/1.73m²

Banerjee A. et al. *J Am Coll Cardiol* 2013

Do VKA still have a role in the management of AF?

How many AF patients eligible to NOACs ?

- « non valvular » AF : 90%
- At least 1 (or 2) risk factors : 80-90 %
- eGFR > 30 ml/min : 91%



Thus :

- NOAC eligible = 64% of all AF
- VKA eligible = 85-90% of all AF
  (10% valvular AF + 75-80% NVAF)
- <u>At least 25% of AF patients should receive VKA</u>

Fauchier L, Personal and unpublished data *2016*

Concerns about the Novel OACs

- Lack of monitoring – uncertainty with regard to dosing/ adherence
- No simple spot checks – “need-to-know” occasions
- Short half-life – concern with regard to missed doses
- Availability of antidote – how to manage major bleeding
- Drug–drug interactions – under- and over-dosing
- Clinical development not complete – e.g. peri-ablation
- Contraindications – valvular AF, P-gp modulators, low CrCl
- Need for regular renal function testing
- Relatively short experience – unknowns ahead?
- Expensive for the healthcare system and/or patients

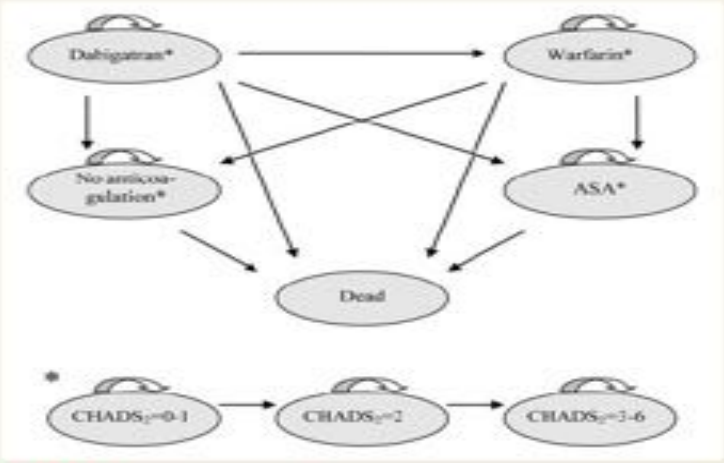
Uncertainty with NOACs dosing

- « One size cannot fit all ! »
- US Food and Drug Administration (FDA) :

SAVAYSA (edoxaban) tablets for oral use
Initial U.S. Approval: 2015

WARNING (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN
SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used

Cost-effectiveness of dabigatran



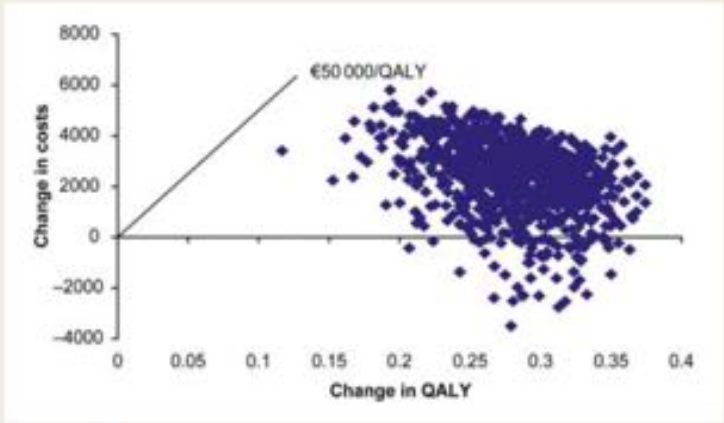


Figure 2 Cost-effectiveness plane illustrating probabilistic analysis with 1000 iterations of dabigatran compared with warfarin, costs in €.

Davidson T. et al, *Eur Heart J 2013*

Table 5 One-way sensitivity analyses of cost-effectiveness for dabigatran compared with warfarin, costs in €

Alternative scenarios	Cost per QALY gained
Base case	7742
Comparison with well-controlled warfarin patients	12 449
Comparison with poorly controlled warfarin patients	Dominant
Only $CHADS_2 = 0–1$	20 929
Only $CHADS_2 = 2$	8216
Only $CHADS_2 = 3–6$	2652
No transitions between treatments after second year	10 287
QALY loss from warfarin and ASA included	5540
Willingness to pay to replace warfarin included	Dominant
Costs of added life years included	27 514
Discount rate (costs and QALYs): 0%	6085
Discount rate (costs and QALYs): 5%	9077

« Dabigatran is a cost-effective treatment in Sweden »

Outcomes in RELY in relation to cTTR

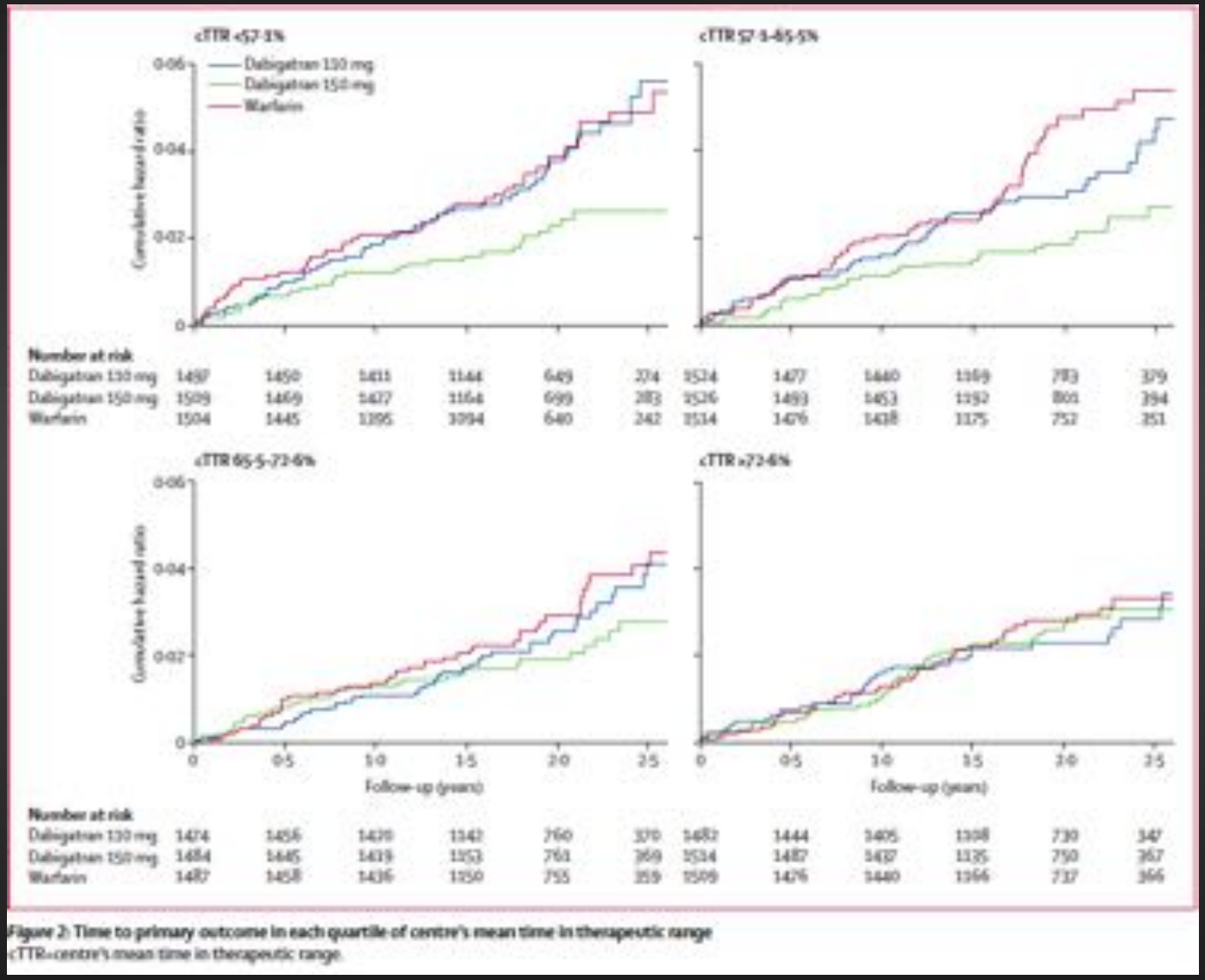


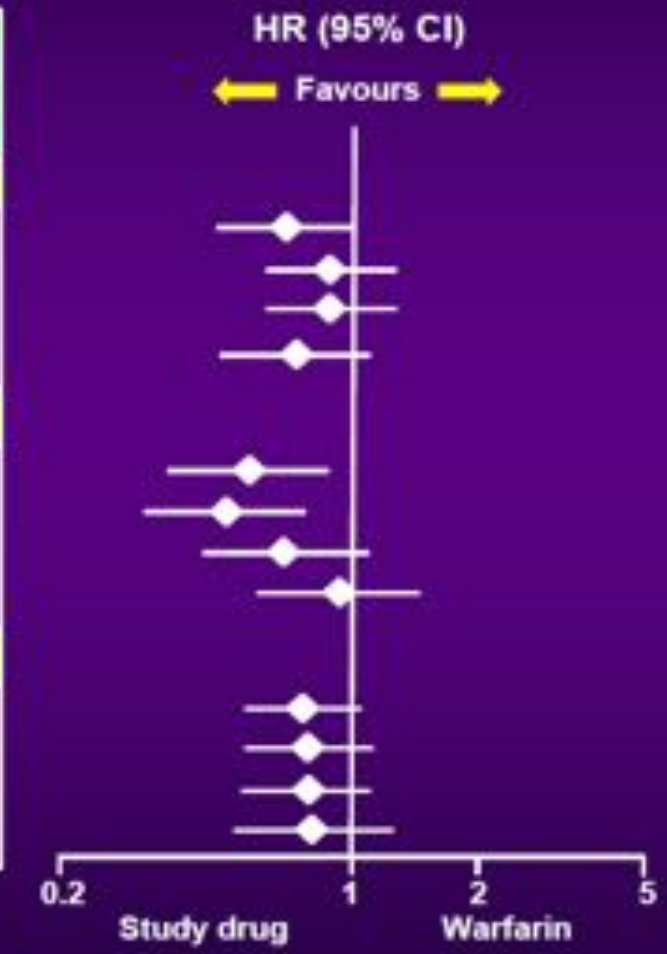
Figure 2: Time to primary outcome in each quartile of centre's mean time in therapeutic range
cTTR=centre's mean time in therapeutic range.

Wallentin L. et al, *Lancet 2010*

Novel OAC Trials in SPAF

Primary Efficacy Endpoint by TTR Quartiles

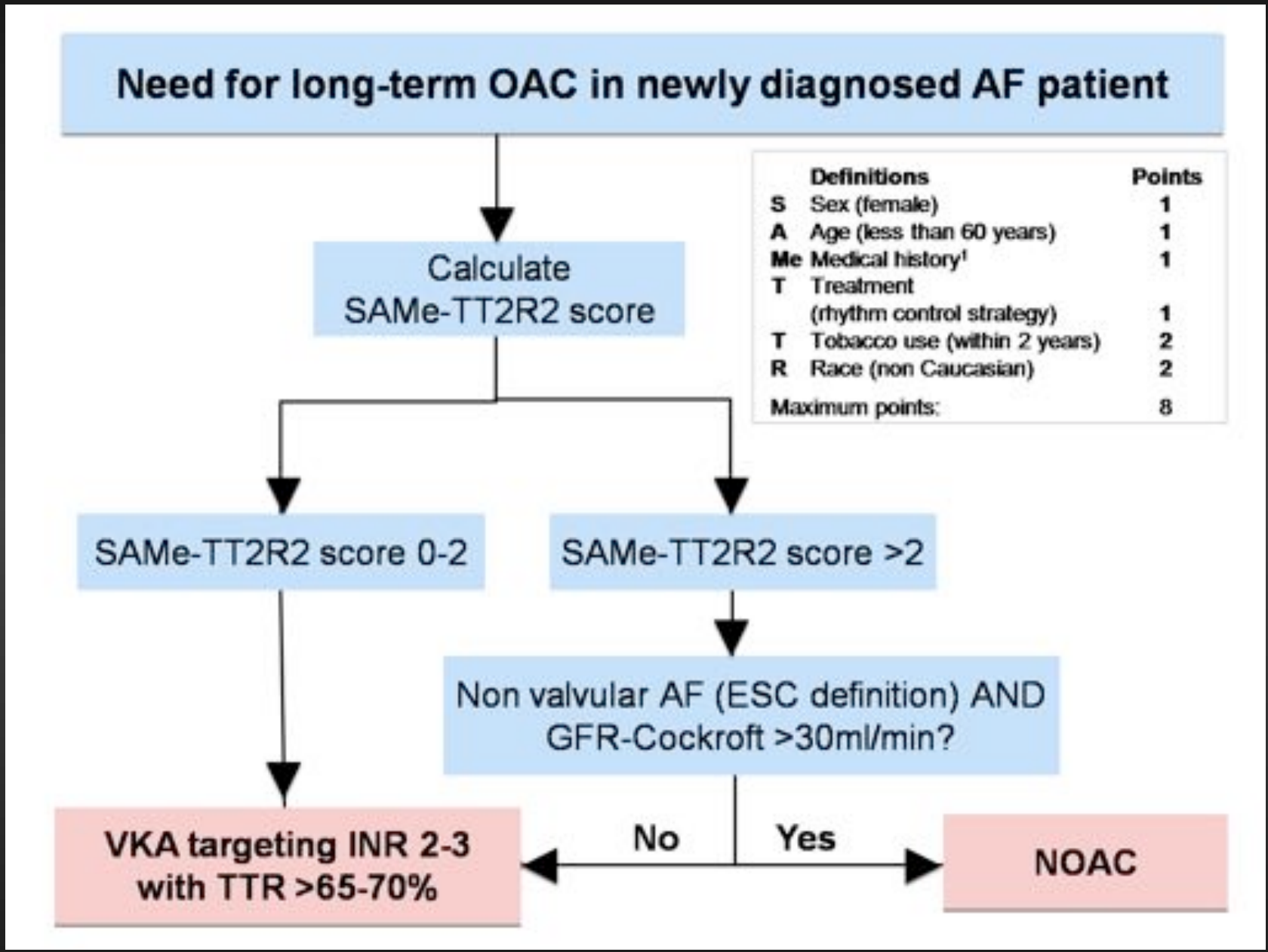
	Treatment group n/N (rate)	Warfarin n/N (rate)	*P* value (interaction)
ROCKET AF			
0.00–50.6%	45/1735 (1.77)	62/1689 (2.53)	0.736
50.7–58.5%	53/1746 (1.94)	63/1807 (2.18)	
58.6–65.7%	54/1734 (1.90)	62/1758 (2.14)	
65.7–100.0%	37/1676 (1.33)	55/1826 (1.80)	
RE-LY (Dabigatran 150 mg)			
<57.1%	32/1509 (1.1)	54/1504 (1.92)	0.20
57.1–65.5%	32/1526 (1.04)	62/1514 (2.06)	
65.5–72.6%	31/1484 (1.04)	45/1487 (1.51)	
>72.6%	38/1514 (1.27)	40/1509 (1.34)	
ARISTOTLE			
<58.0%	70/2266 (1.75)	88/2252 (2.28)	0.29
58.0–65.7%	54/2251 (1.30)	68/2278 (1.61)	
65.7–72.2%	51/2256 (1.21)	65/2266 (1.55)	
>72.2%	36/2266 (0.83)	44/2251 (1.02)	



TTR, time in therapeutic range

Rate = number of events per 100 patient-years; n = patients with events; N = number of patients in each subgroup

1. Patel et al, N Engl J Med 2011;365(10):883–91; 2. Wallentin et al, Lancet 2010;376(9745):975–83; 3. Wallentin et al, Presented at ESC Congress, August 27–31 2011; Paris, France



Fauchier L, Poli D, Olshansky B. *Thrombosis Haemostasis 2015*

SAMe-TT2R2 score and clinical events

TABLE 2 | Labile INR, Stroke/TE, Clinically Relevant Bleeding, and Mortality by Category of SAMe-TT_2R_2 Score

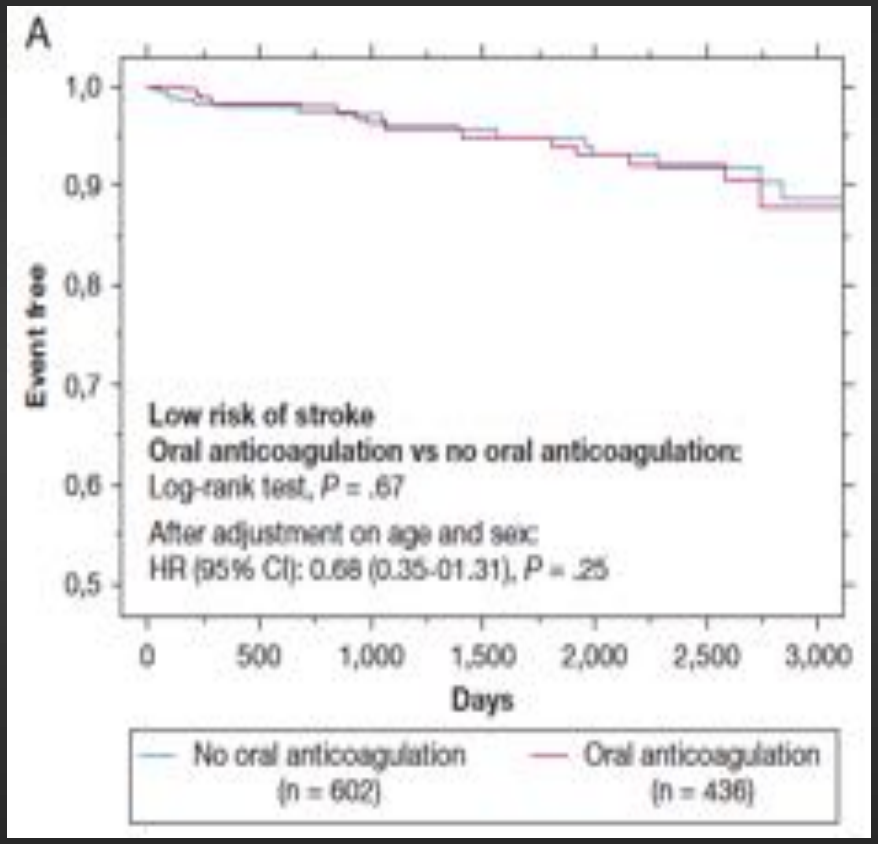
Variable	Whole Cohort	SAMe-TT_2R_2 Score			P Value
		0-1 (Low)	2 (Borderline)	>2 (High)	
No. patients		4,504 (55)	2,252 (28)	1,364 (17)	—
Labile INR	172 (2.1)	77 (1.7)	52 (2.3)	43 (3.2)	.004
		Ref	1.36 (0.95-1.94)	1.87 (1.28-2.73)	—
Stroke/TE during follow-up	652 (8.0)	325 (7.2)	211 (9.4)	116 (8.5)	.007
		Ref	1.33 (1.11-1.59)	1.20 (0.96-1.49)	—
Severe bleeding	724 (8.9)	375 (8.3)	175 (7.8)	174 (12.8)	<.0001
		Ref	0.93 (0.77-1.12)	1.61 (1.33-1.95)	—
Major BARC bleeding	250 (3.1)	120 (2.7)	57 (2.5)	73 (5.4)	<.0001
		Ref	0.95 (0.69-1.31)	2.07 (1.53-2.78)	—
Death	1,010 (12.4)	533 (11.8)	267 (11.9)	210 (15.4)	.002
		Ref	1.00 (0.86-1.17)	1.36 (1.14-1.61)	—

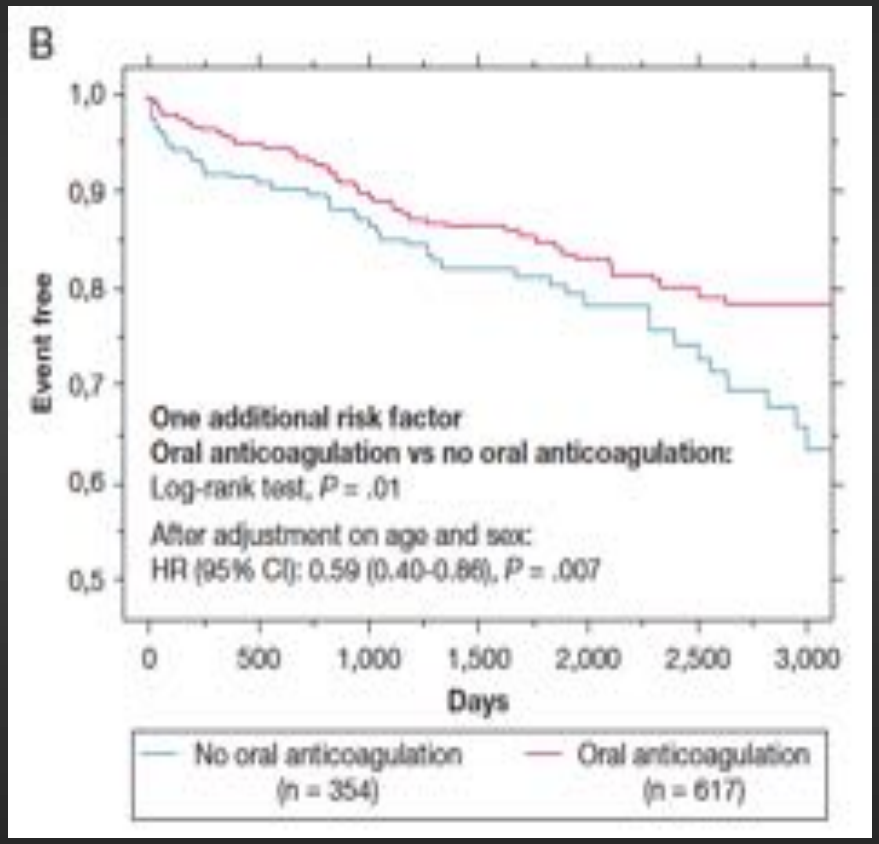
Data are presented as No. (%) or hazard ratio (95% CI). BARC = Bleeding Academic Research Consortium; INR = international normalized ratio; Ref = reference; SAMe-TT_2R_2 = sex female, age <60 y, medical history (more than two comorbidities), treatment (interacting drugs, eg, amiodarone for rhythm control), tobacco use (doubled), race (doubled); TE = thromboembolism.

- Among patients taking VKAs, the SAMe-TT2R2 score was predictive of labile INR, stroke/TE, severe bleeding and death.
- This was not the case for patients not taking VKAs.

Lip GYH, Haguenoer K, Saint-Etienne S, Fauchier L. *Chest 2014*

AF and One Additional Stroke Risk Factor
Death, stroke or syst. thromboembolism





Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, Babuty D, Lip GYH. *Chest 2015*

Event rates for different outcomes for non-anticoagulated AF patients with less than 2 Non-Gender Related stroke risk factors

Fauchier ... Lip. Stroke 2016 DOI: 10.1161/STROKEAHA.116.013253

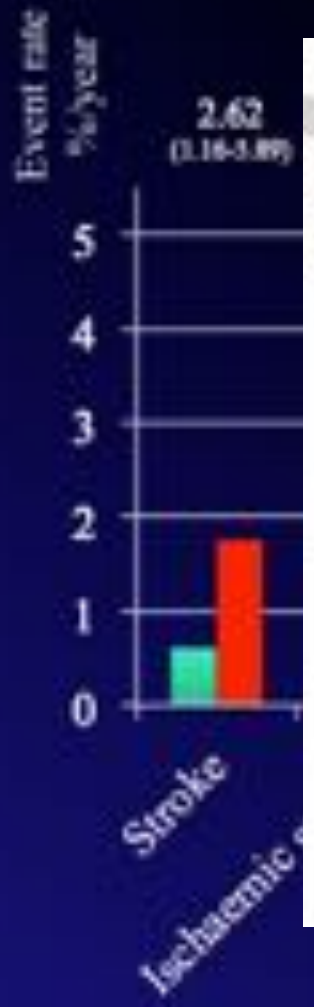


Table 4. Net Clinical Benefit Analysis of Stroke Prevention Strategy for Atrial Fibrillation Patients With 1 NGR Stroke Risk Factor (CHA_2DS_2-VASc 1 in Males and 2 in Females) in Group B and Group D

Stroke Prevention Strategy	Net Clinical Benefit, %/y (95% CI) According to Singer et al[12]	Net Clinical Benefit, %/y (95%CI) According to Connolly et al[13]
Compared with no antithrombotic therapy		
Antiplatelet drugs (and no VKA)	−0.13 (−1.06 to −0.02)	−0.72 (−1.50 to −0.34)
VKA	0.30 (0.15 to 0.61)	1.42 (1.01 to 1.99)
Compared with antiplatelet drugs (and no VKA)		
VKA	0.43 (0.24 to 0.78)	2.14 (1.62 to 2.82)

Conclusions

- Les AOD sont equivalents ou supérieurs à la Warfarine pour réduire le risque d'AVC, de saignement intra-cranien ou de décès.
- Les recommandations suggèrent donc de traiter lorsque cela est possible les patients à risque par AOD plutôt que par AVK.
- Les AVK restent indispensables en cas de FA avec prothèse valvulaire mécanique ou RM, DFG < 30 ml/min, et plus largement pour des raisons médico-économiques.

Conclusions

- Novel OACs are equivalent to or better than warfarin in terms of reducing stroke, SE, mortality, and intracranial haemorrhage
- Guidelines may prefer treatment with novel OACs over dose-adjusted VKA therapy for AF patients at thromboembolic risk
- VKA are still needed for valvular AF, patients with GFR < 30 ml/min and from an health economic perspective