Anticoagulación oral en Atención Primaria

ACOD

Extremadura, marzo 2017

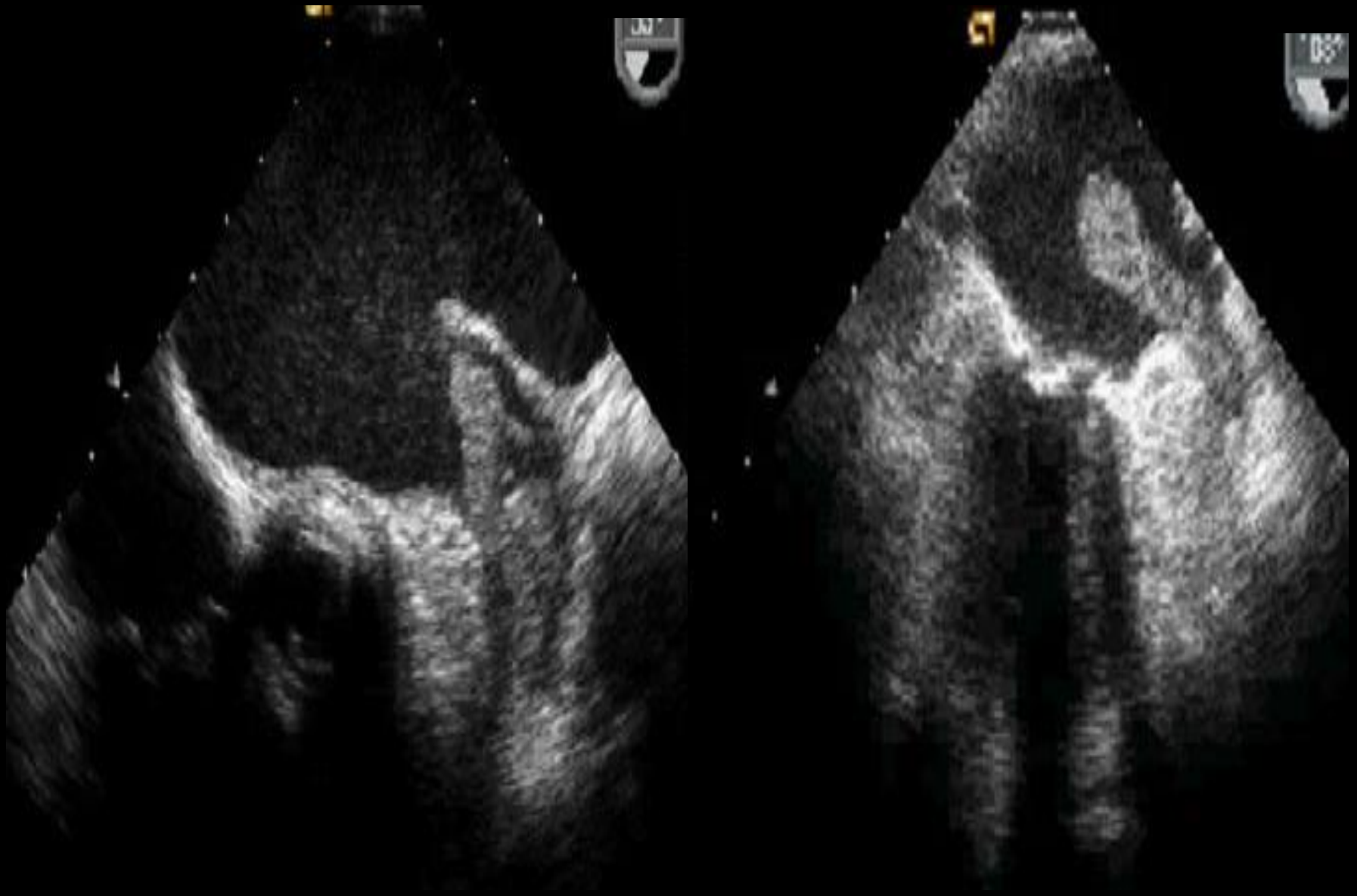
Domingo Marzal Martín

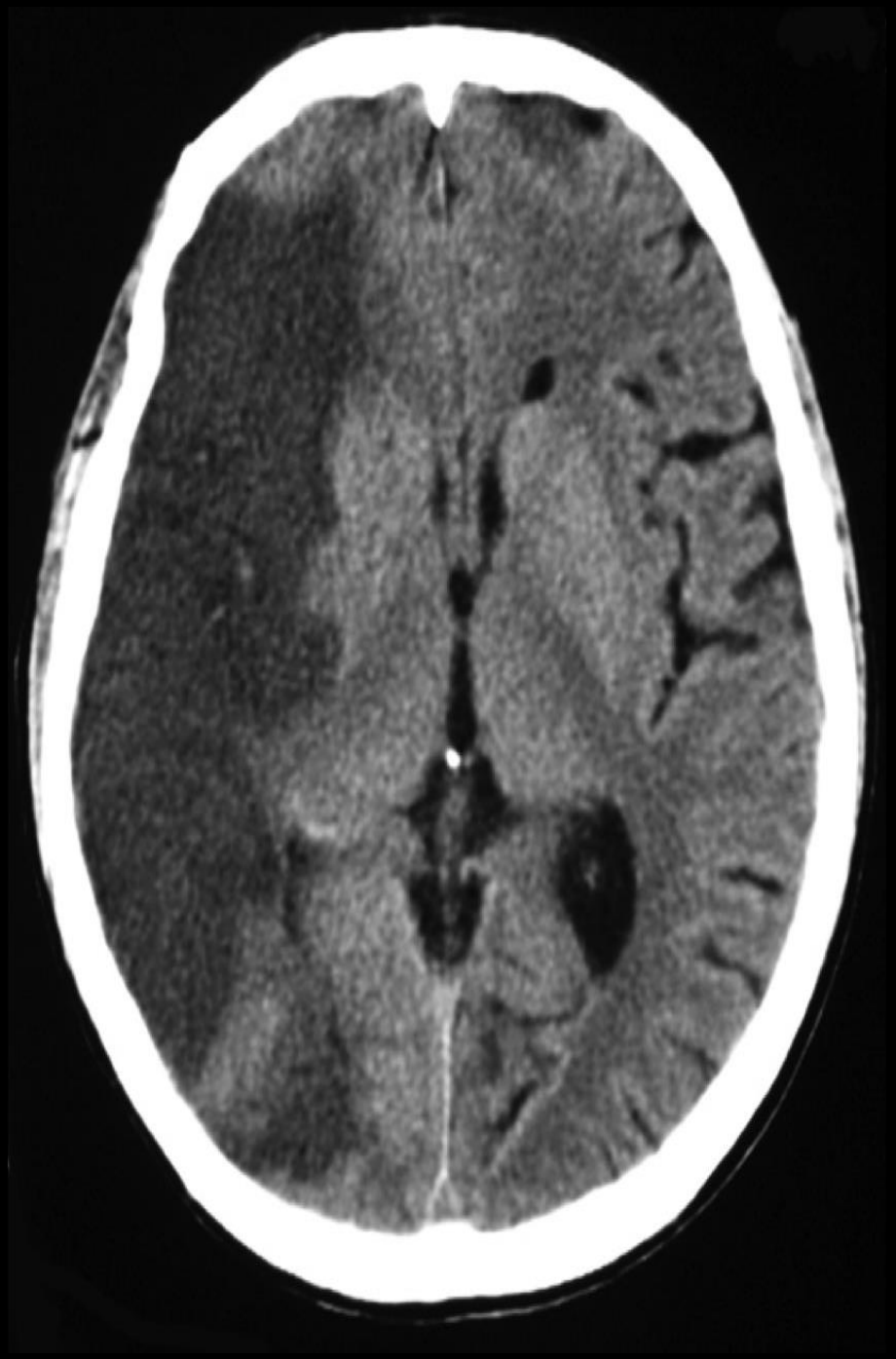
SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

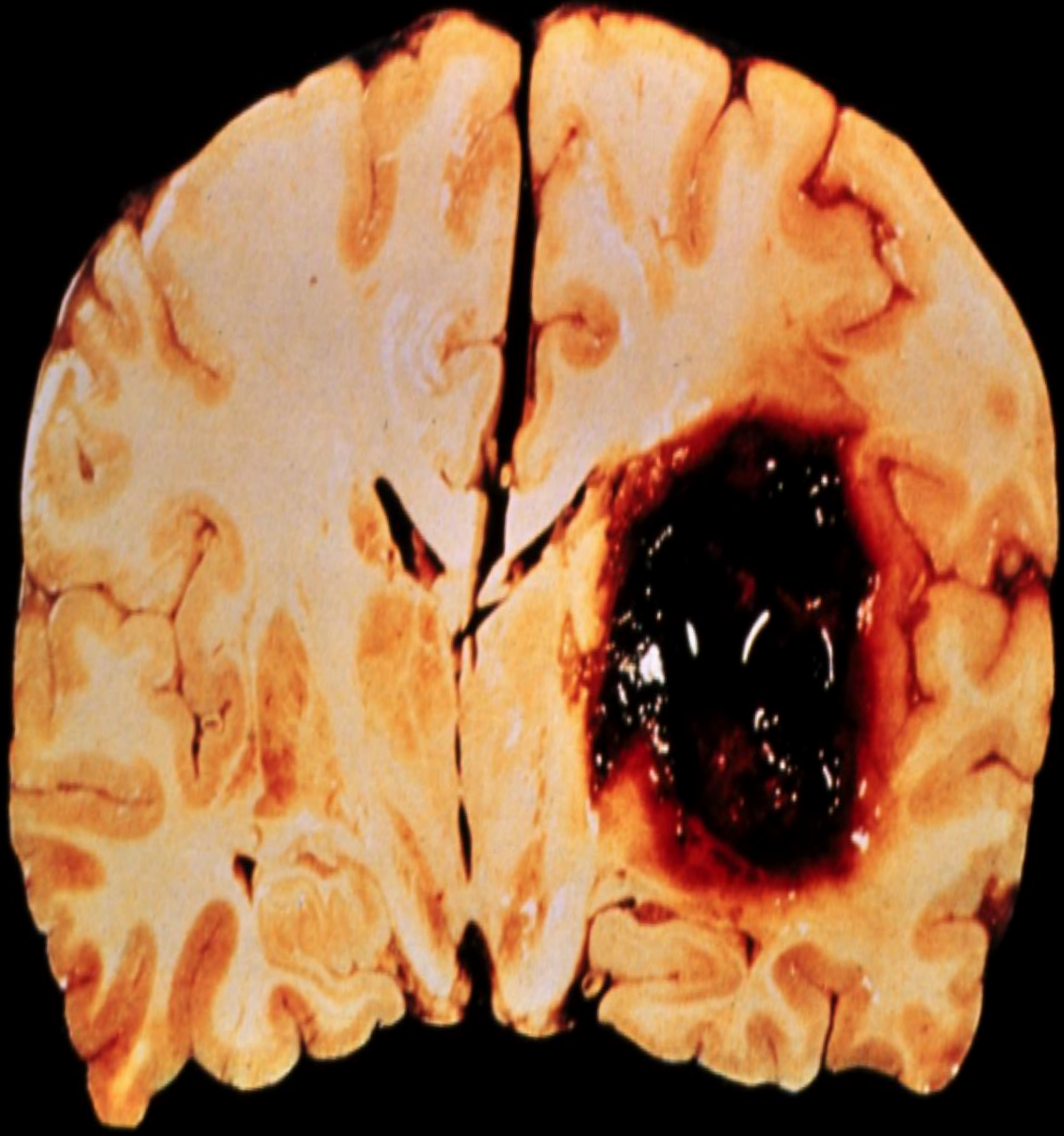
Servicio de Cardiología

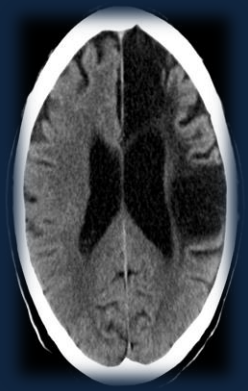
SES

Complejo Hospitalario de Mérida

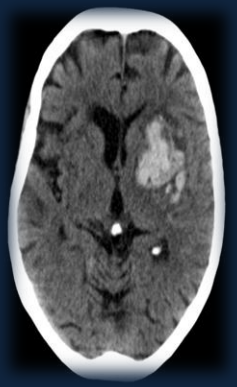


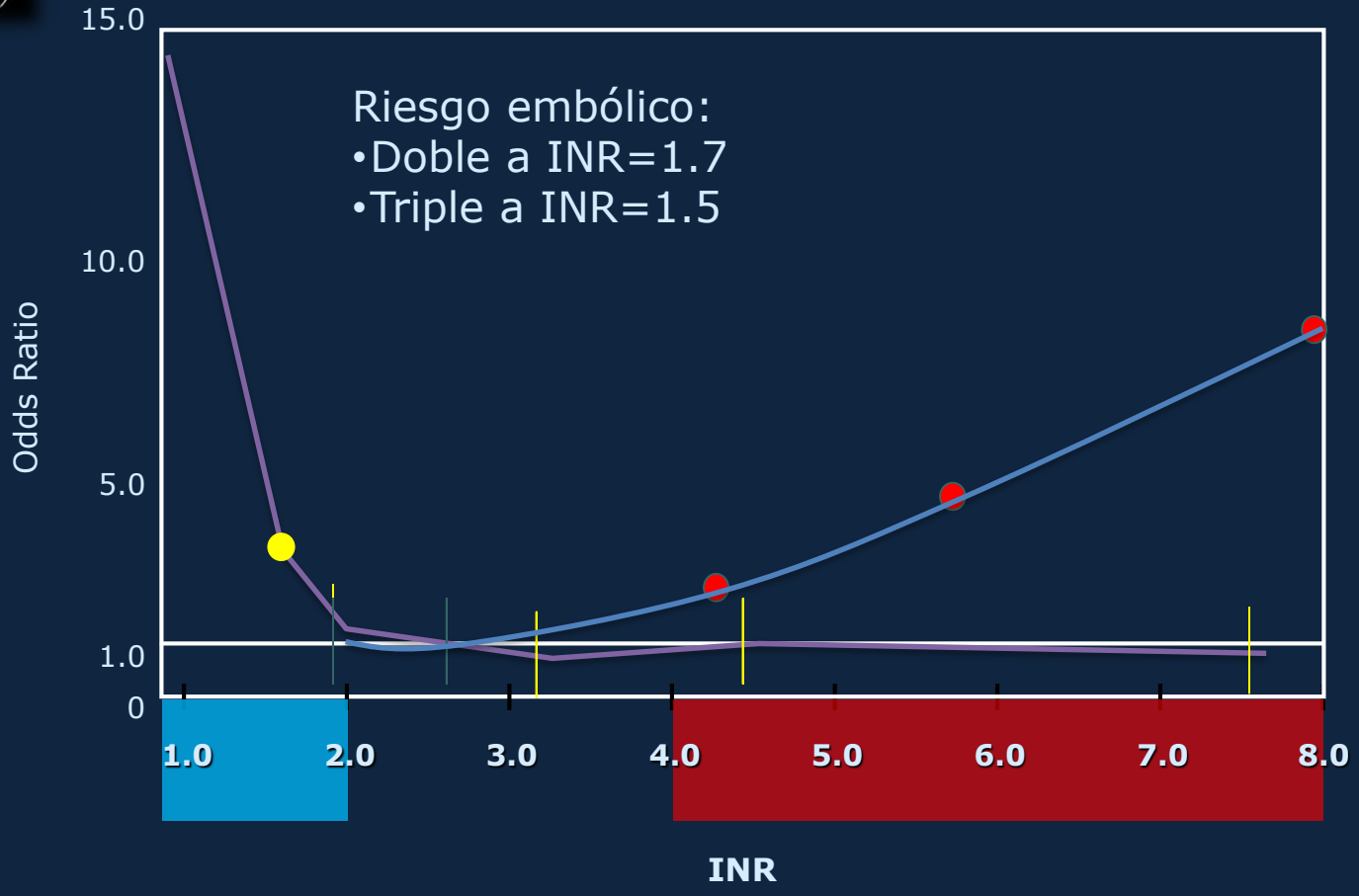






Margen terapéutico dicumarínicos

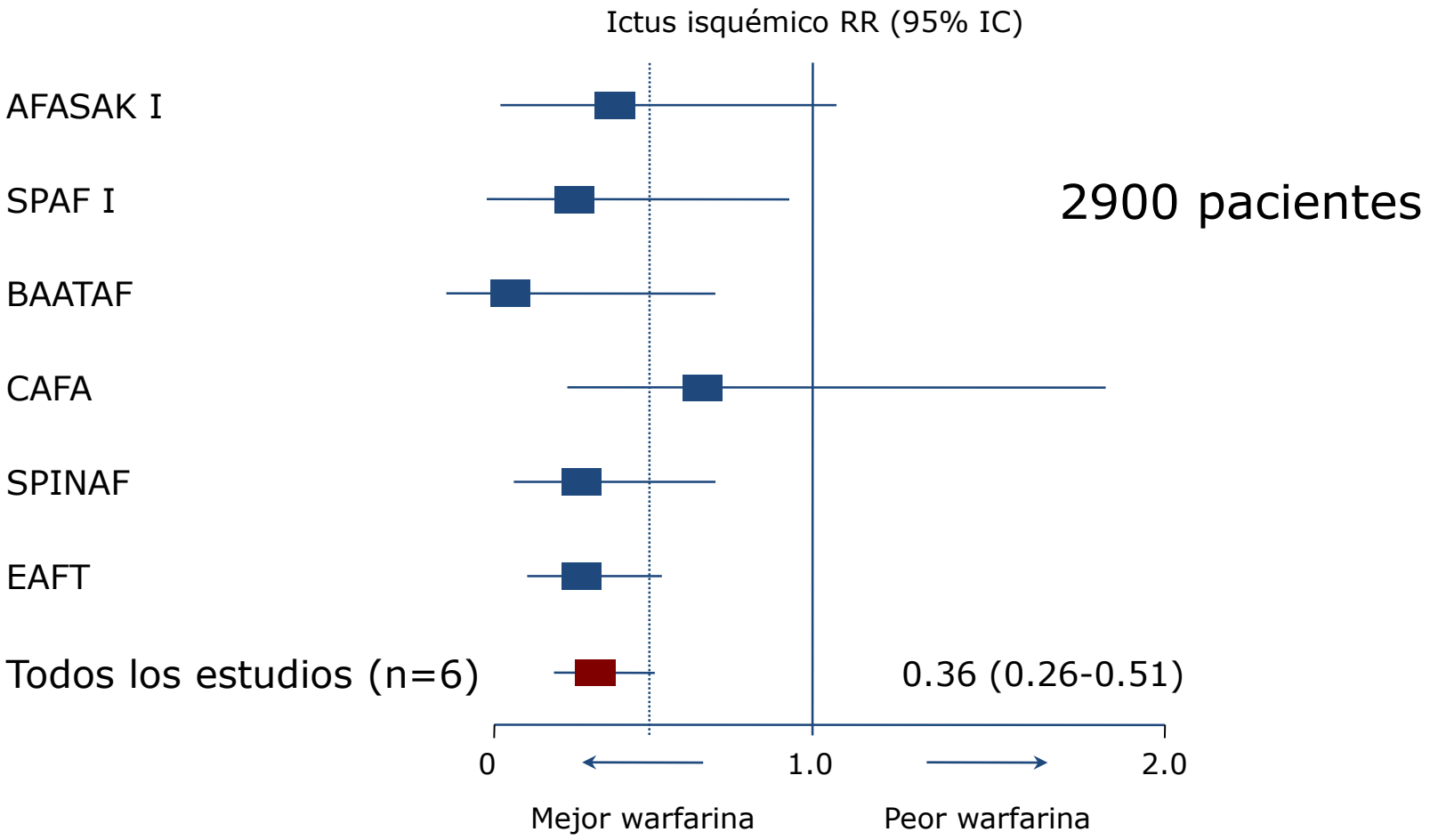




ACV isquémico
Hemorragia intracraneal

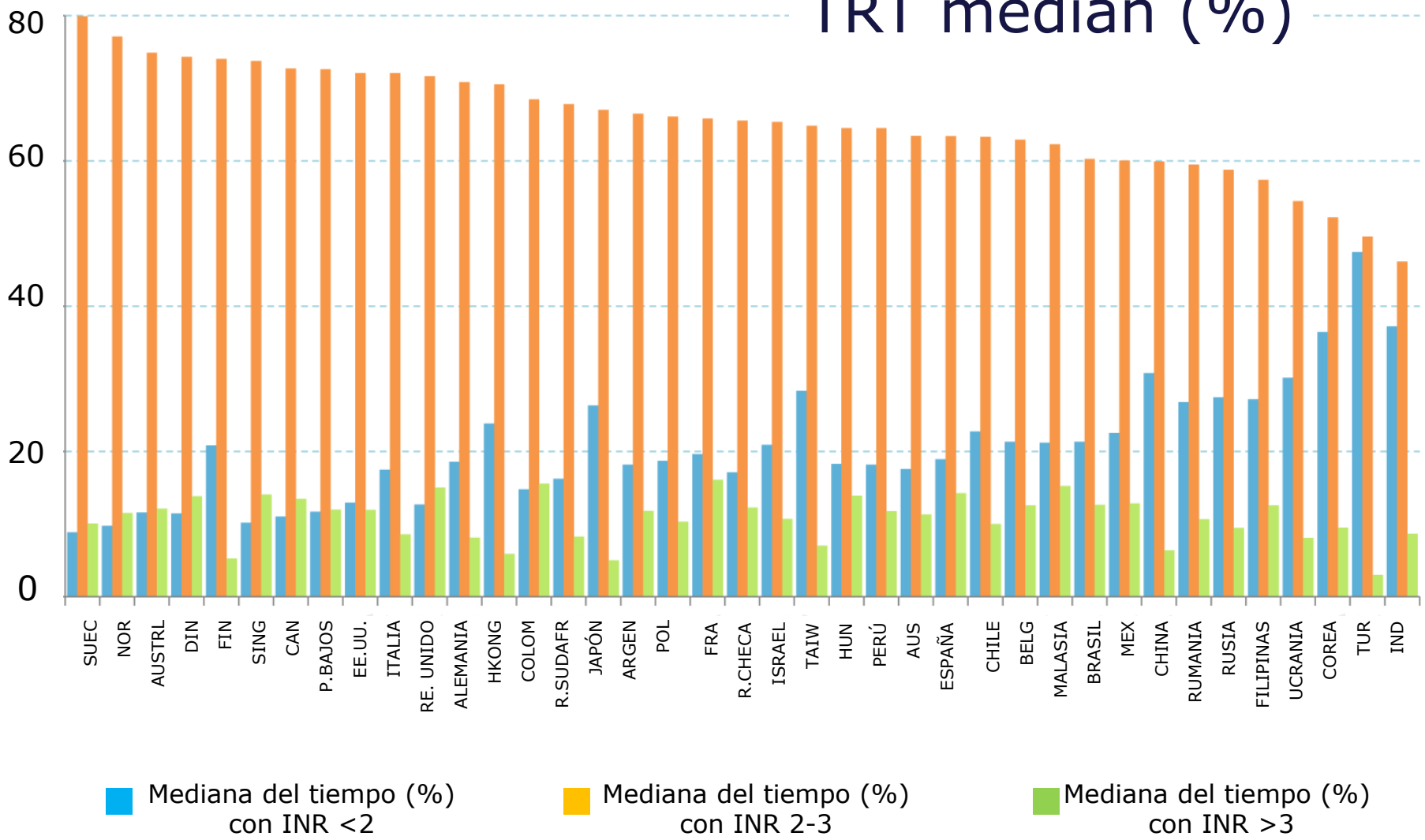
Hylek EM, et al. N Eng J Med. 1996;335:540-6
Hylek EM, et al. Ann Intern Med. 1994;120:897-902

Evidencia científica ACO clásicos

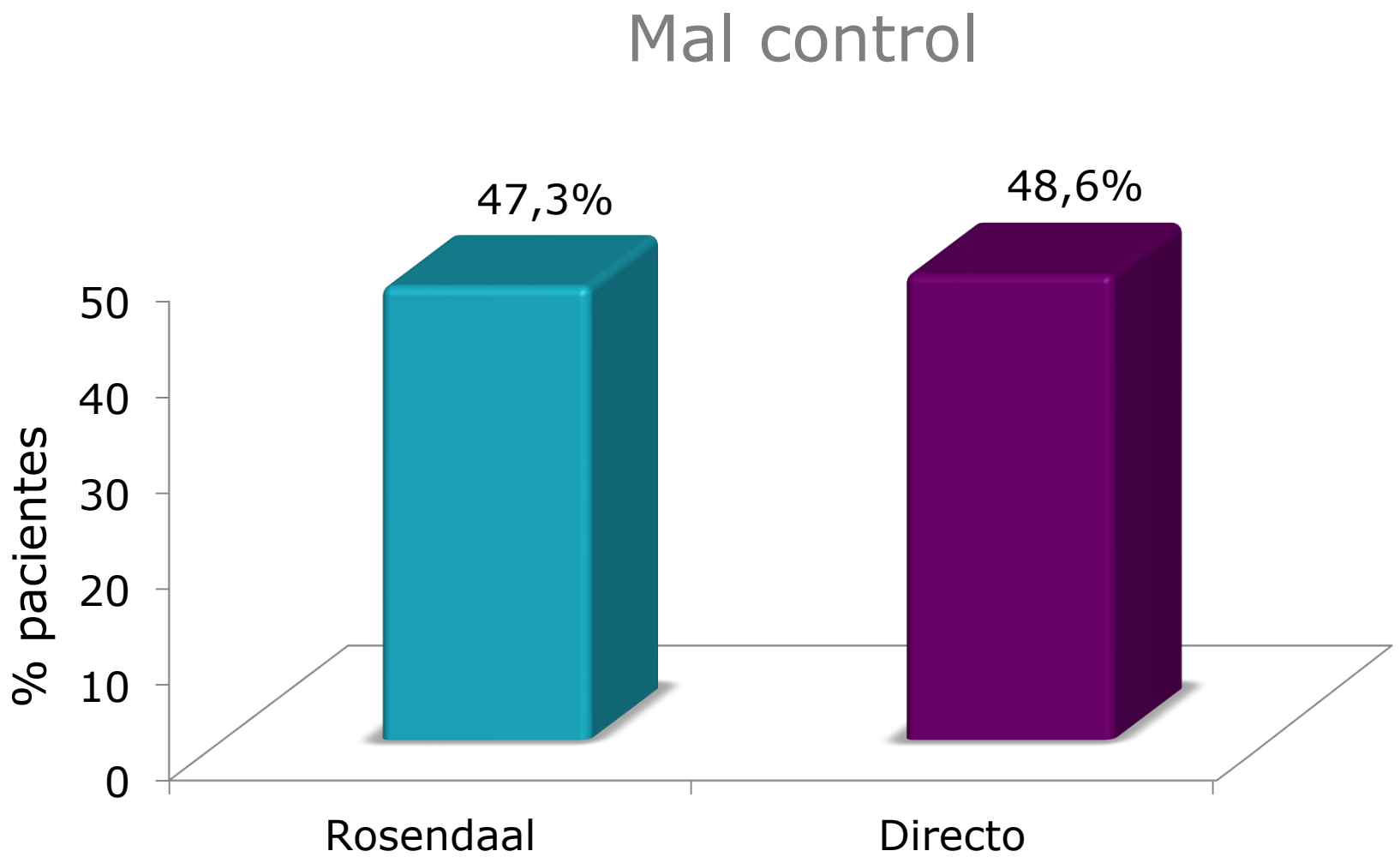


Hart RG, et al. Ann Intern Med 2007;146:857-67

TRT median (%)

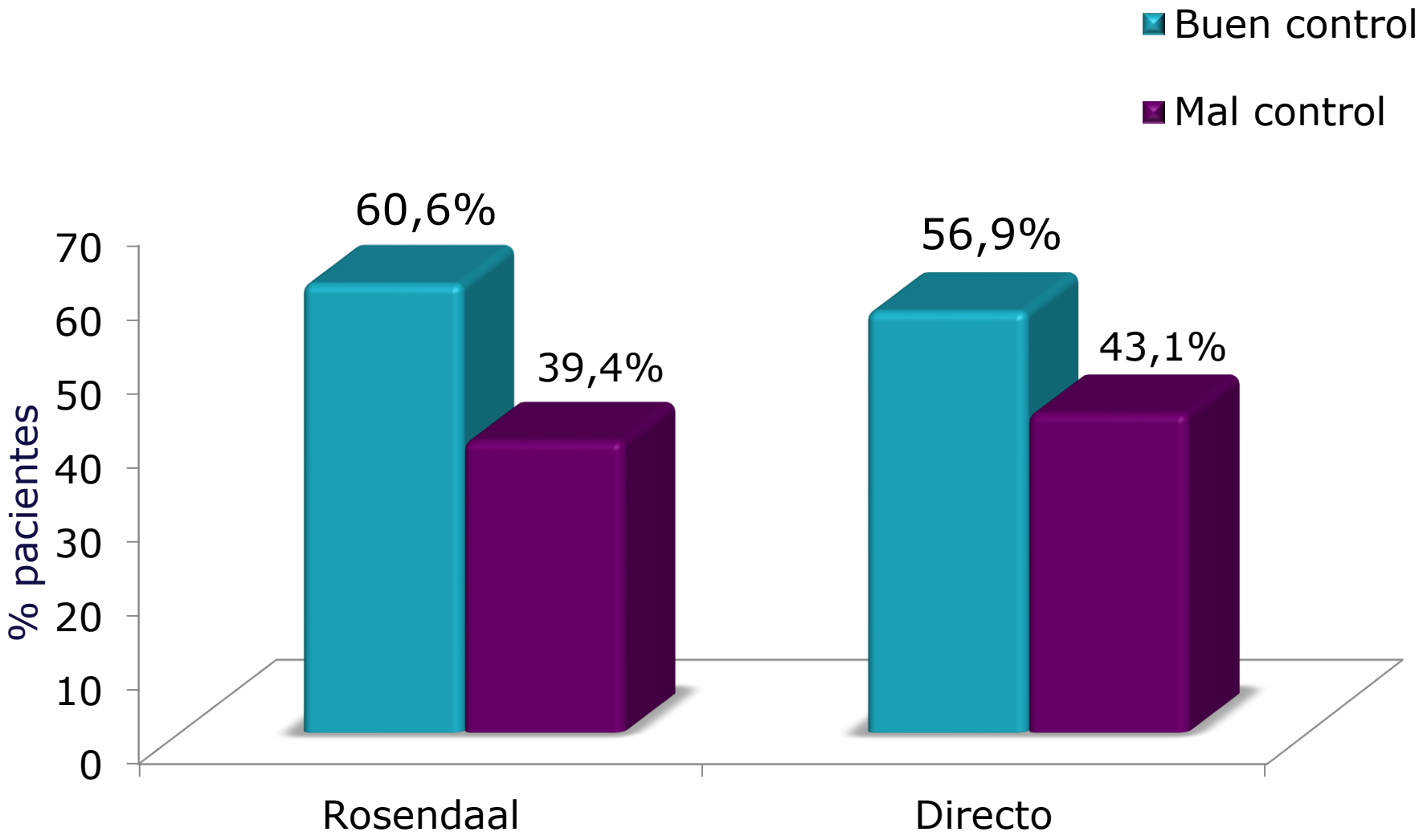

80
60
40
20
0
SUEC
NOR
AUSTRL
DIN
FIN
SING
CAN
P.BAJOS
EE.UU.
ITALIA
RE. UNIDO
ALEMANIA
HKONG
COLOM
R.SUDAFR
JAPÓN
ARGEN
POL
FRA
R.CHECA
ISRAEL
TAIW
HUN
PERÚ
AUS
ESPAÑA
CHILE
BELG
MALASIA
BRASIL
MEX
CHINA
RUMANIA
RUSIA
FILIPINAS
UCRANIA
COREA
TUR
IND
Mediana del tiempo (%) con INR <2
Mediana del tiempo (%) con INR 2-3
Mediana del tiempo (%) con INR >3

Estudio CALIFA



Anguita M, et al. Rev Esp Cardiol. 2015 68:761-8

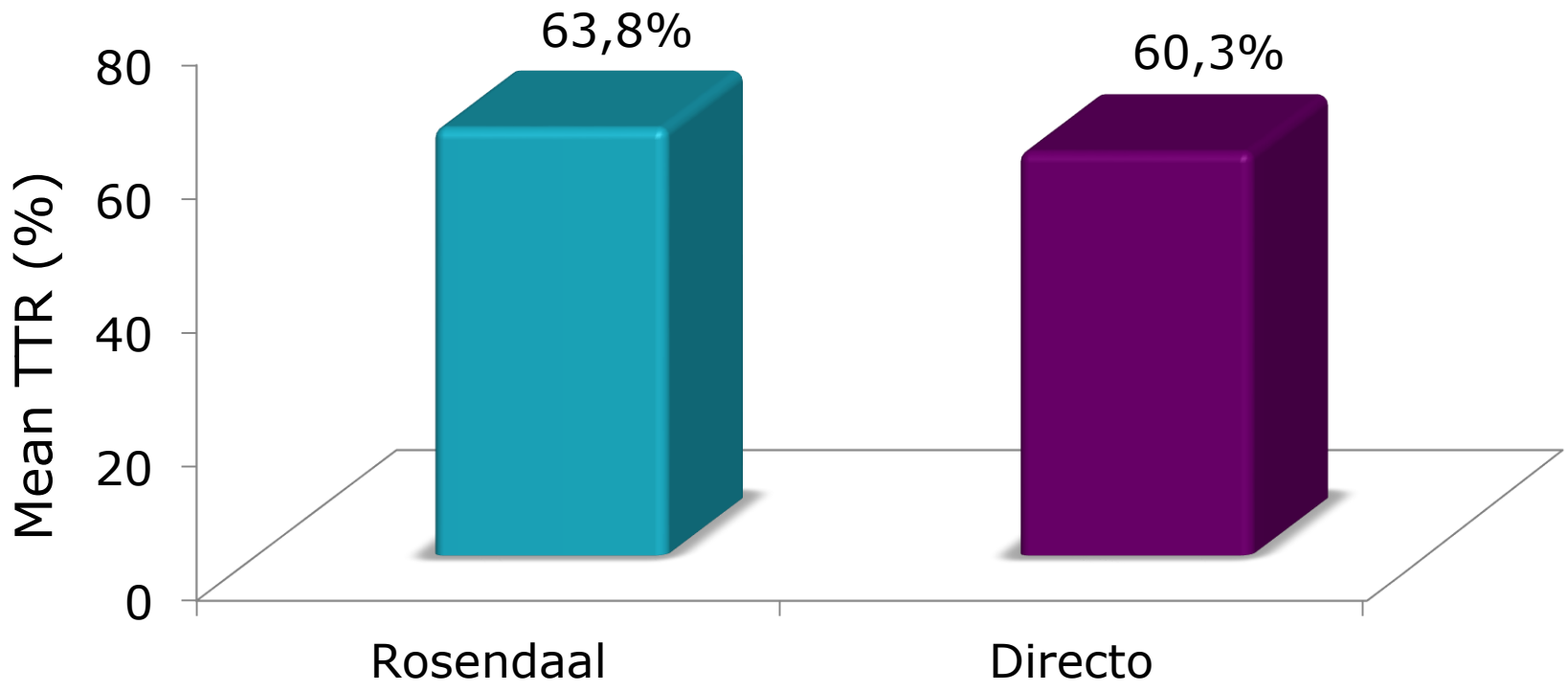
Estudio PAULA



Barrios V, et al. Rev Esp Cardiol. 2015 68:740-2

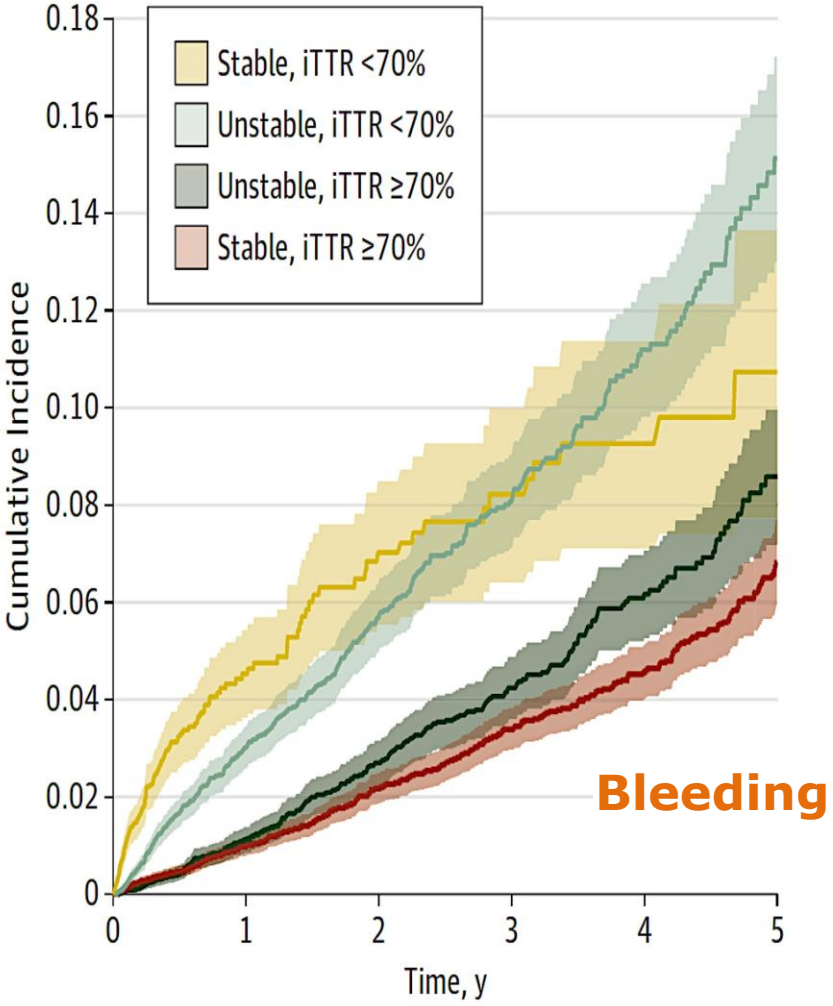
Estudio FANTASIIA

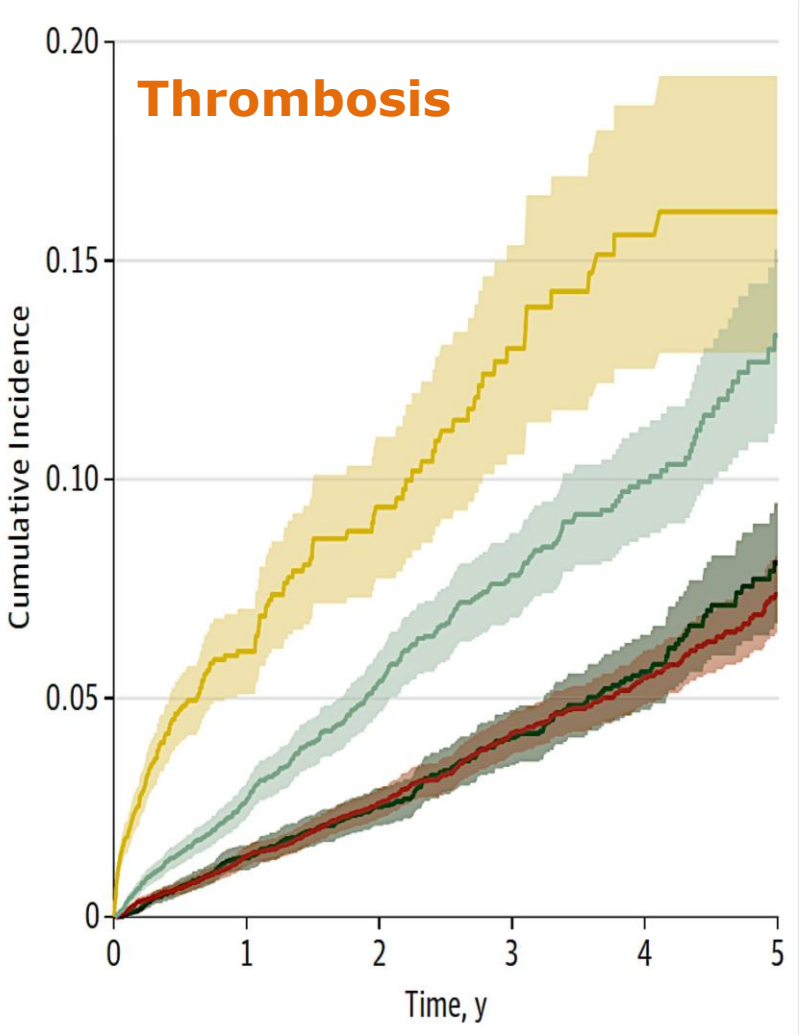
Prevalence of poor anticoagulation control 54%



Bertomeu-Martínez V, et al. Clin. Cardiol. 2015;38:357-64

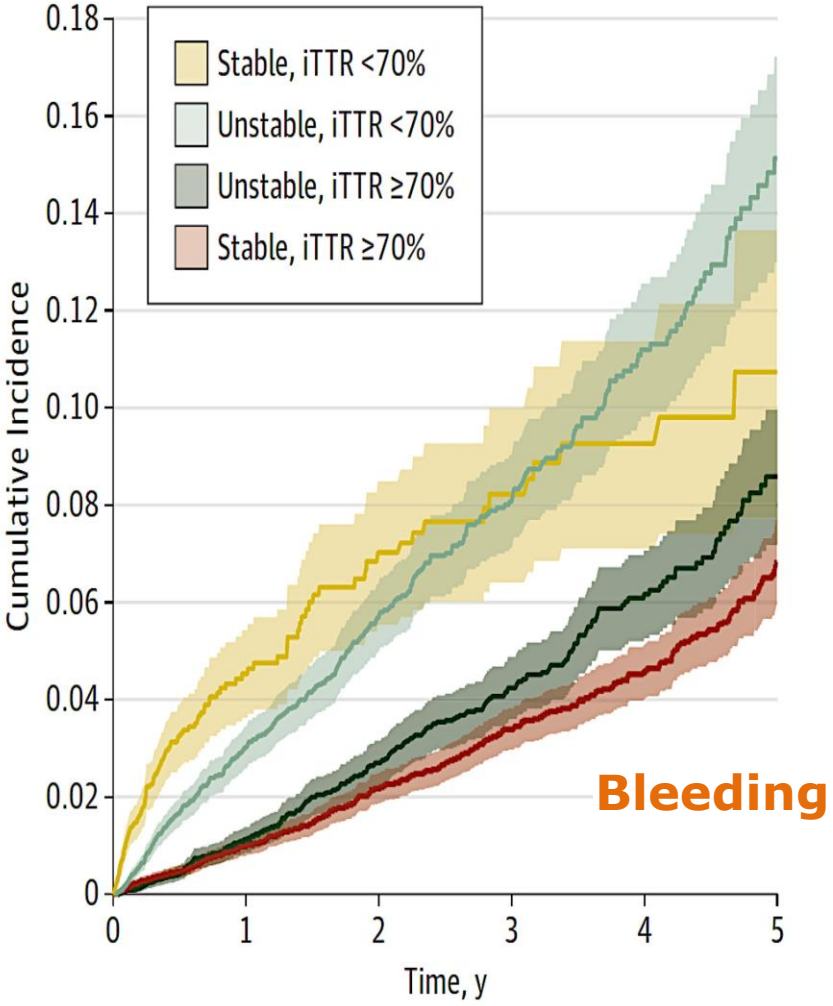
Outcomes in a Warfarin-Treated Population With Atrial Fibrillation

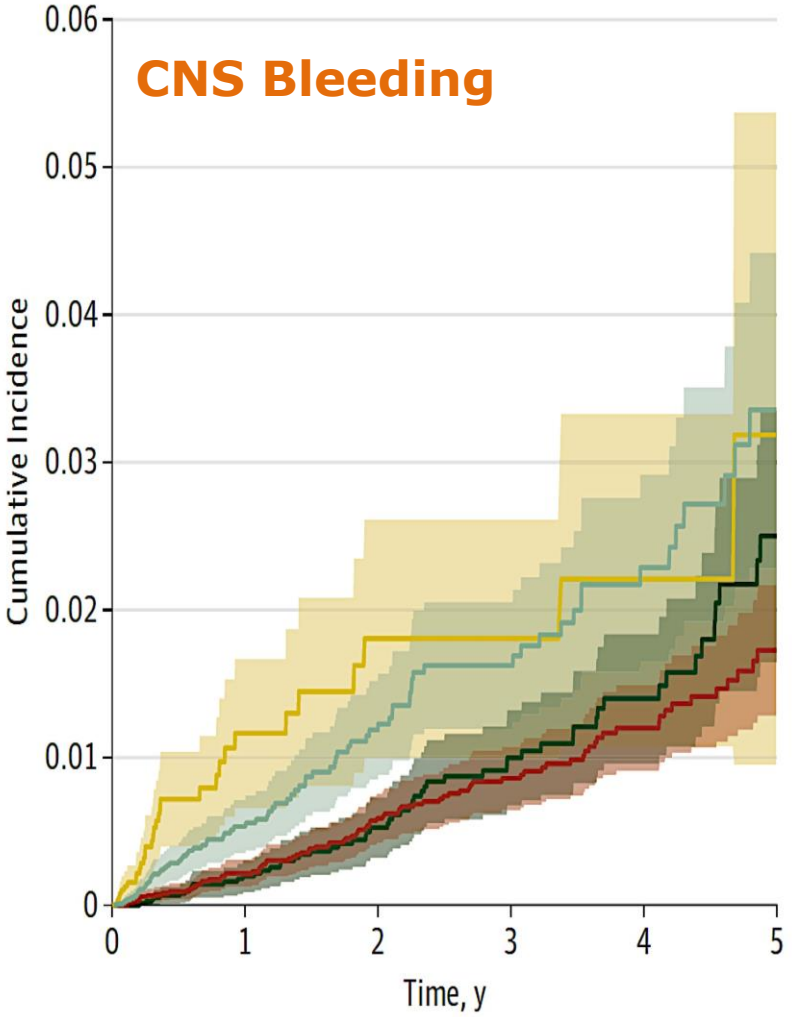




Björck F, et al. JAMA Cardiol. 2016;1:172-80

Outcomes in a Warfarin-Treated Population With Atrial Fibrillation





Björck F, et al. JAMA Cardiol. 2016;1:172-80

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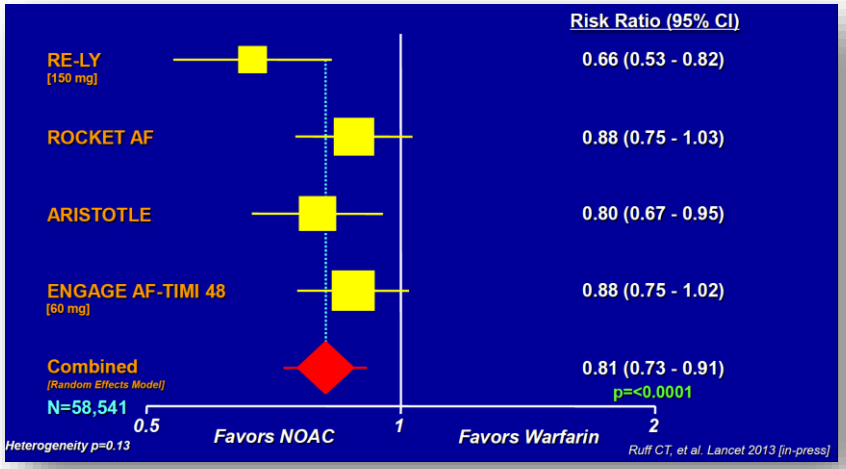
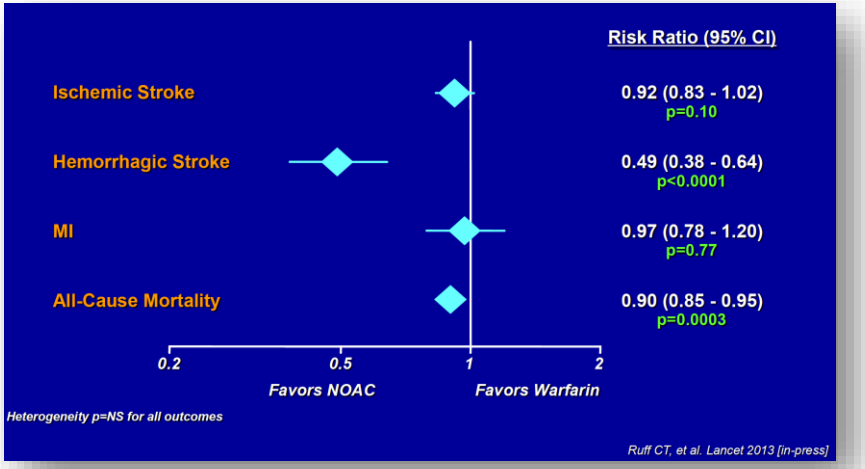
Efficacy and safety of NOAC vs warfarin in AF: meta-analysis

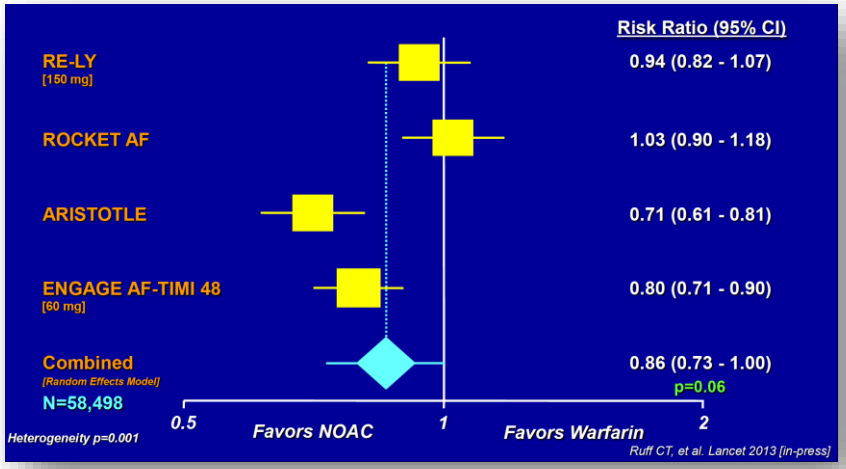
stroke or SEE



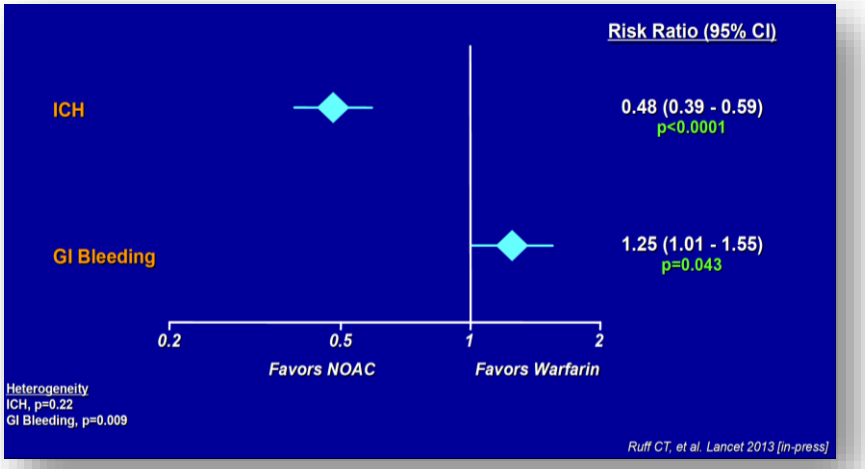
secondary efficacy outcomes



major bleedings

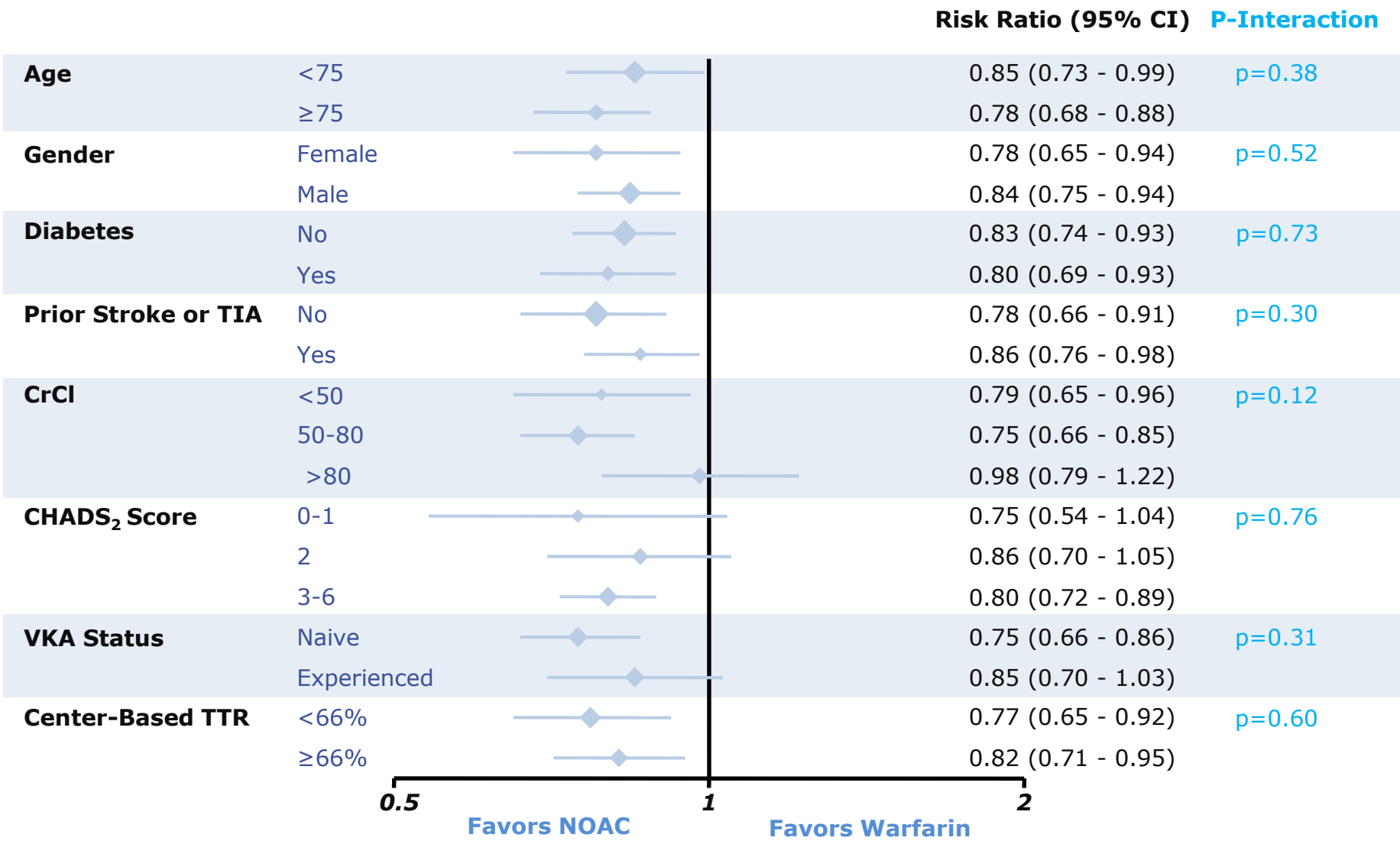


secondary safety outcomes



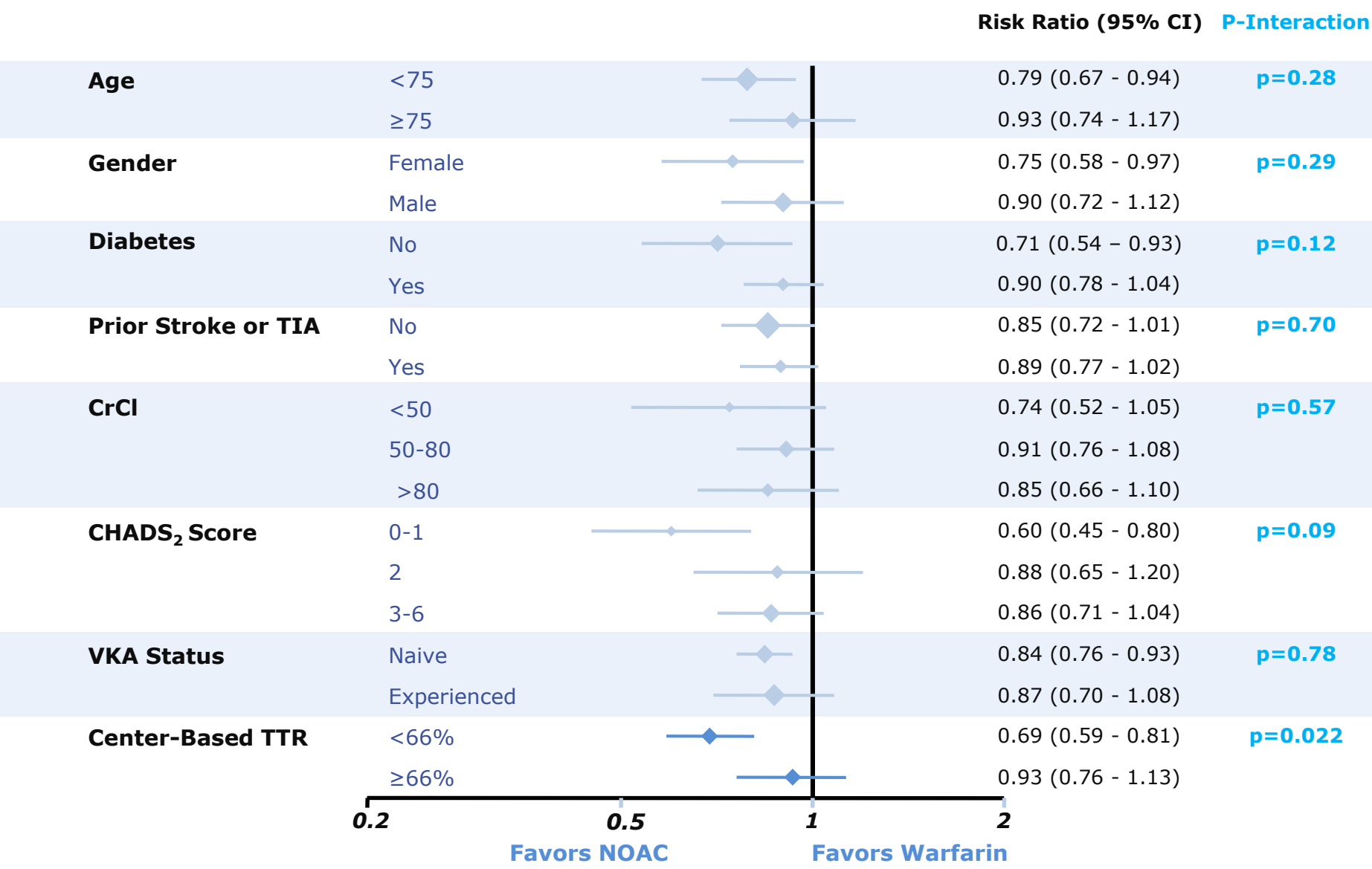
Ruff CT, et al. Lancet 2014;383:955-62

Subgroups: stroke or SEE



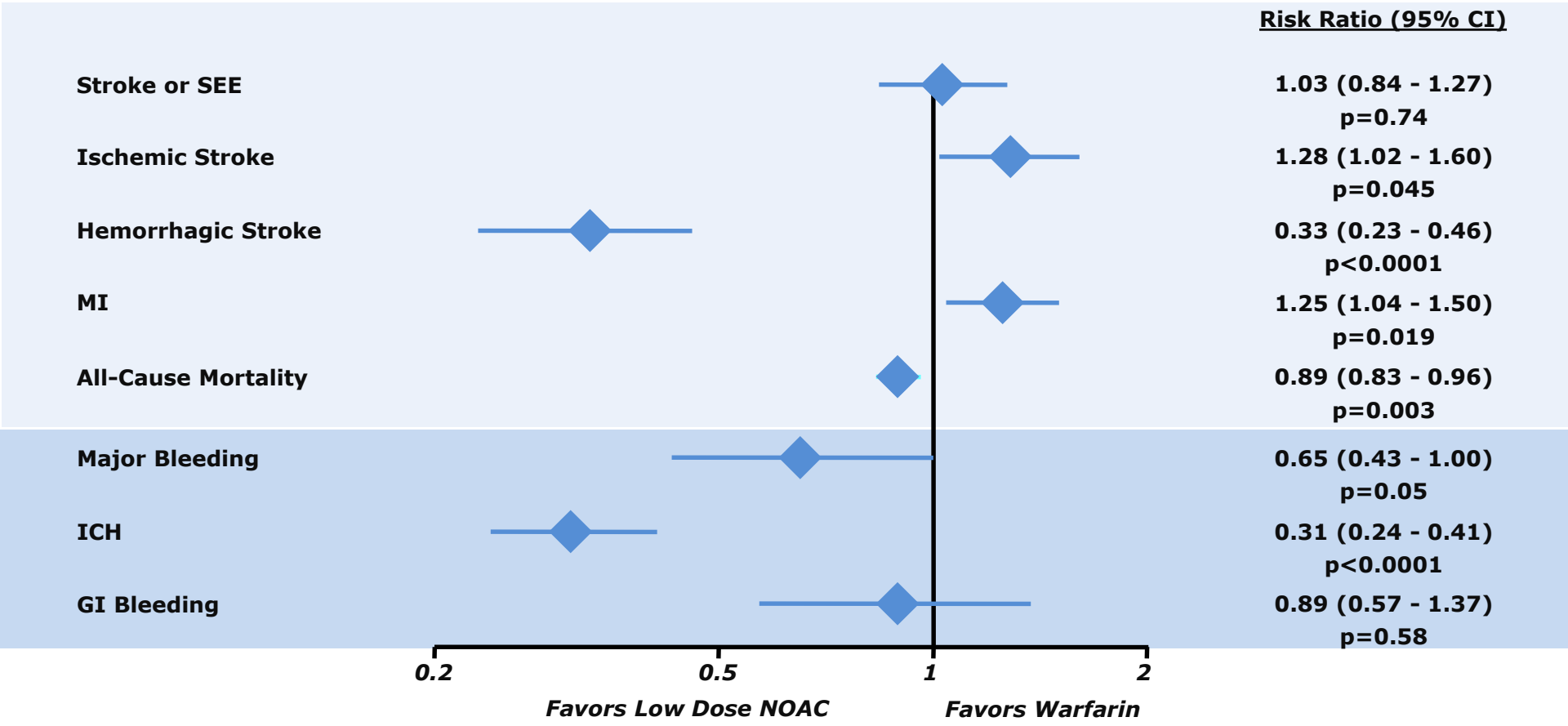
Ruff CT, et al. Lancet 2014;383:955-62

Subgroups: major bleeding



Ruff CT, et al. Lancet 2014;383:955-62

Low dose regimens
efficacy & safety outcomes



Heterogeneity
P=NS for outcomes except:
Major Bleeding, p=<0.001
GI Bleeding, p=0.01

Ruff CT, et al. Lancet 2014;383:955-62

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

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	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

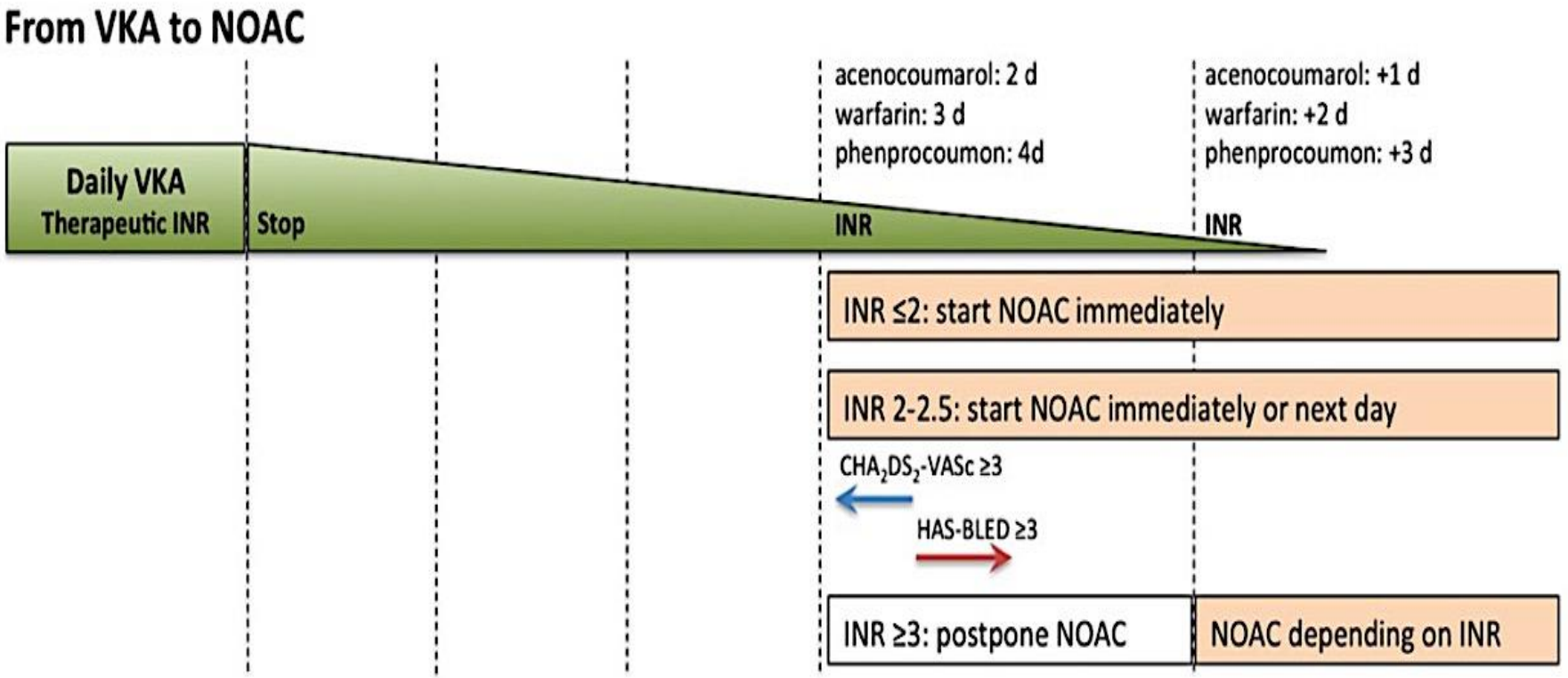
Heidbuchel H, et al. Europace. 2015;17:1467-507

Valvular indications and contra-indications for NOAC therapy in atrial fibrillation patients

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate-to-severe mitral stenosis (usually of rheumatic origin)		✓
Mild-to-moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)[10]	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

Heidbuchel H, et al. Eur Heart J. 2016 [Epub ahead of print]

Switching between VKA and NOACs and vice versa



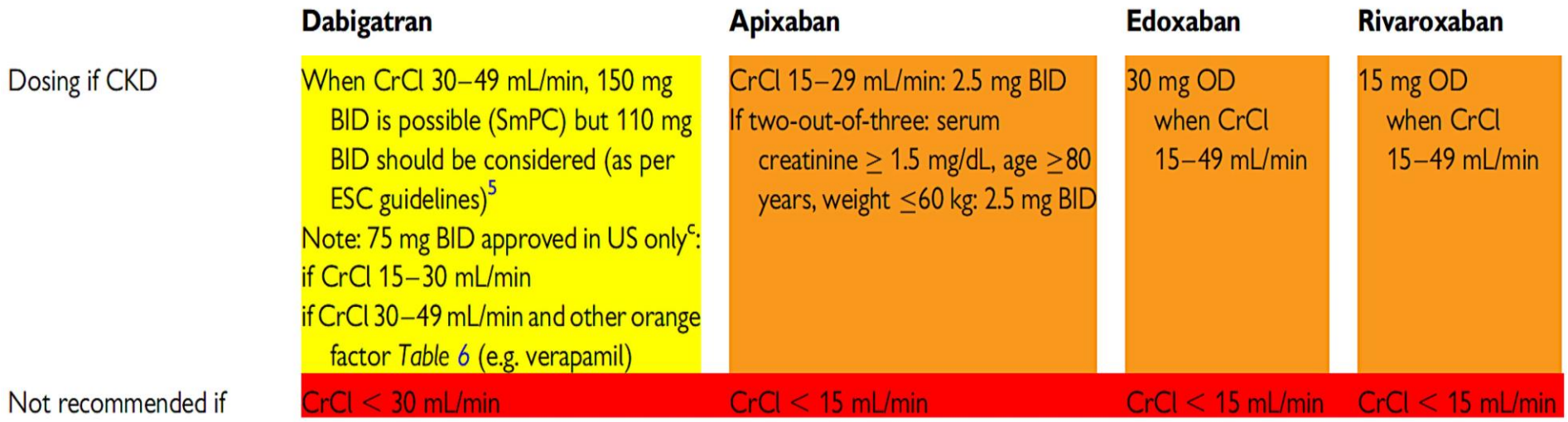
Heidbuchel H, et al. Eur Heart J. 2016 [Epub ahead of print]

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

EUROPEAN SOCIETY OF CARDIOLOGY

Pharmacokinetic characteristics of NOACs

	Dabigatran	Rivaroxaban[a]	Apixaban	Edoxaban
Renal elimination	80%	33%	27%	50% [a]33% excreted unchanged



Heidbuchel H, et al. Europace. 2015;17:1467-507

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%	No PK data[a]	+40%	Minor effect[a] (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)

Interactions clinical factors

NOAC dose adaptation

Heidbuchel H, et al. Eur Heart J. 2016 [Epub ahead of print]

Interactions clinical factors

NOAC dose adaptation

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
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%

Heidbuchel H, et al. Eur Heart J. 2016 [Epub ahead of print]

Interactions clinical factors

NOAC dose adaptation

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
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

Heidbuchel H, et al. Eur Heart J. 2016 [Epub ahead of print]

Interactions clinical factors

NOAC dose adaptation

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Others					
Carbamazepine[b]; Phenobarbital[b]; Phenytoin[b]; St John's wort[b]	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		b	d	
Age ≥75 years	Increased plasma level			d	
Weight ≤ 60 kg	Increased plasma level		b		
Renal function	Increased plasma level	See specific dose instructions according to renal function			
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			

Heidbuchel H, et al. Eur Heart J. 2016 [Epub ahead of print]

Visado ACO

CHA_2DS_2VASc

$SAMe\text{-}TT_2R_2$ >2

CVE

Reducción TRT a 6 meses

SAMe-TT_2R_2

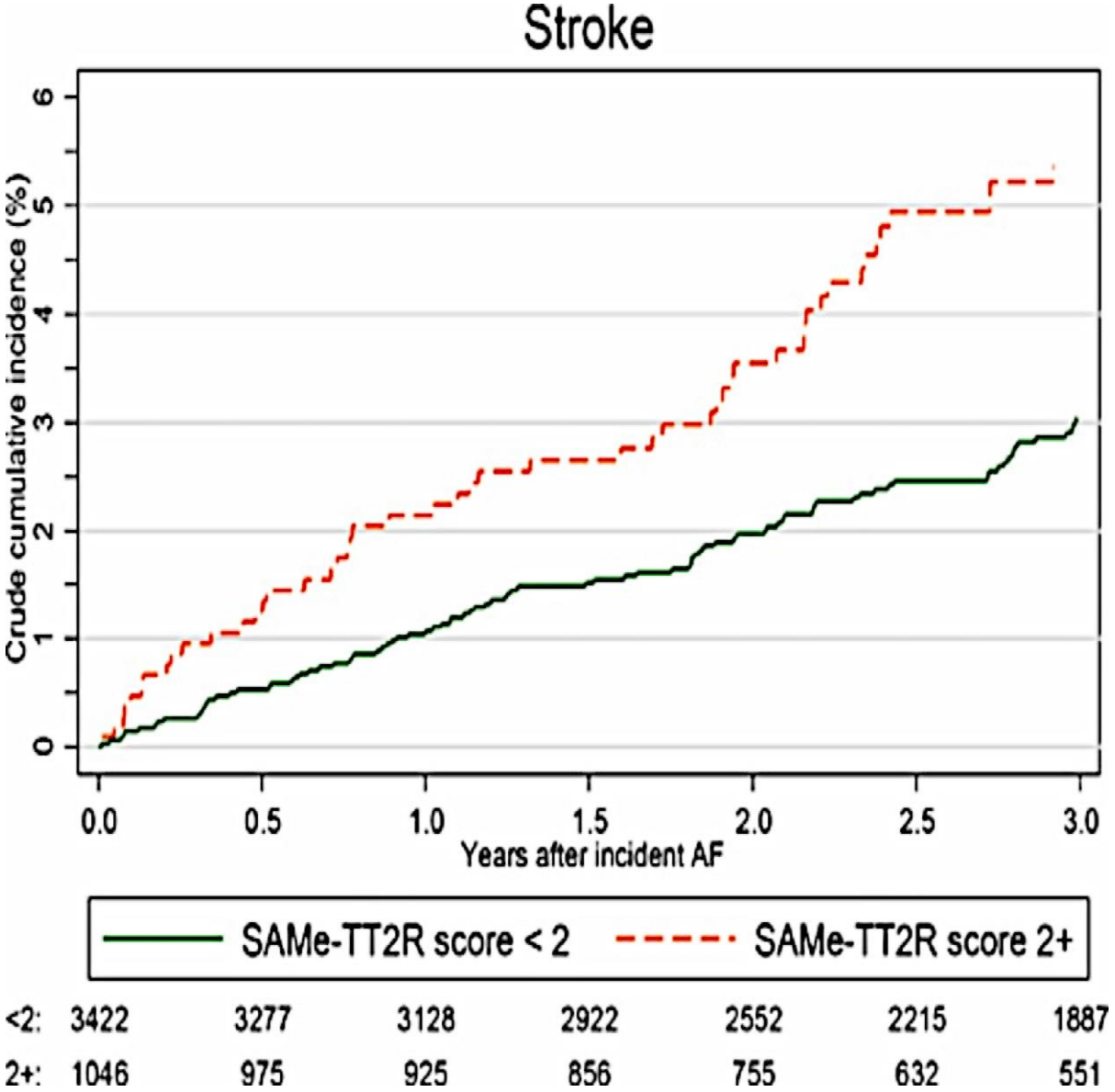
Factors Affecting Quality of Anticoagulation Control Among Patients With Atrial Fibrillation on Warfarin

The SAMe-TT_2R_2 Score

score SAMe-TT_2R_2	
Variable	Points
Sex (female)	1
Age (<60 years)	1
Medical history	1
Treatment (interacting drugs)	1
Tobacco use	2
Race (nonwhite)	2

Apostolakis S, et al. Chest 2013;144:1555-63

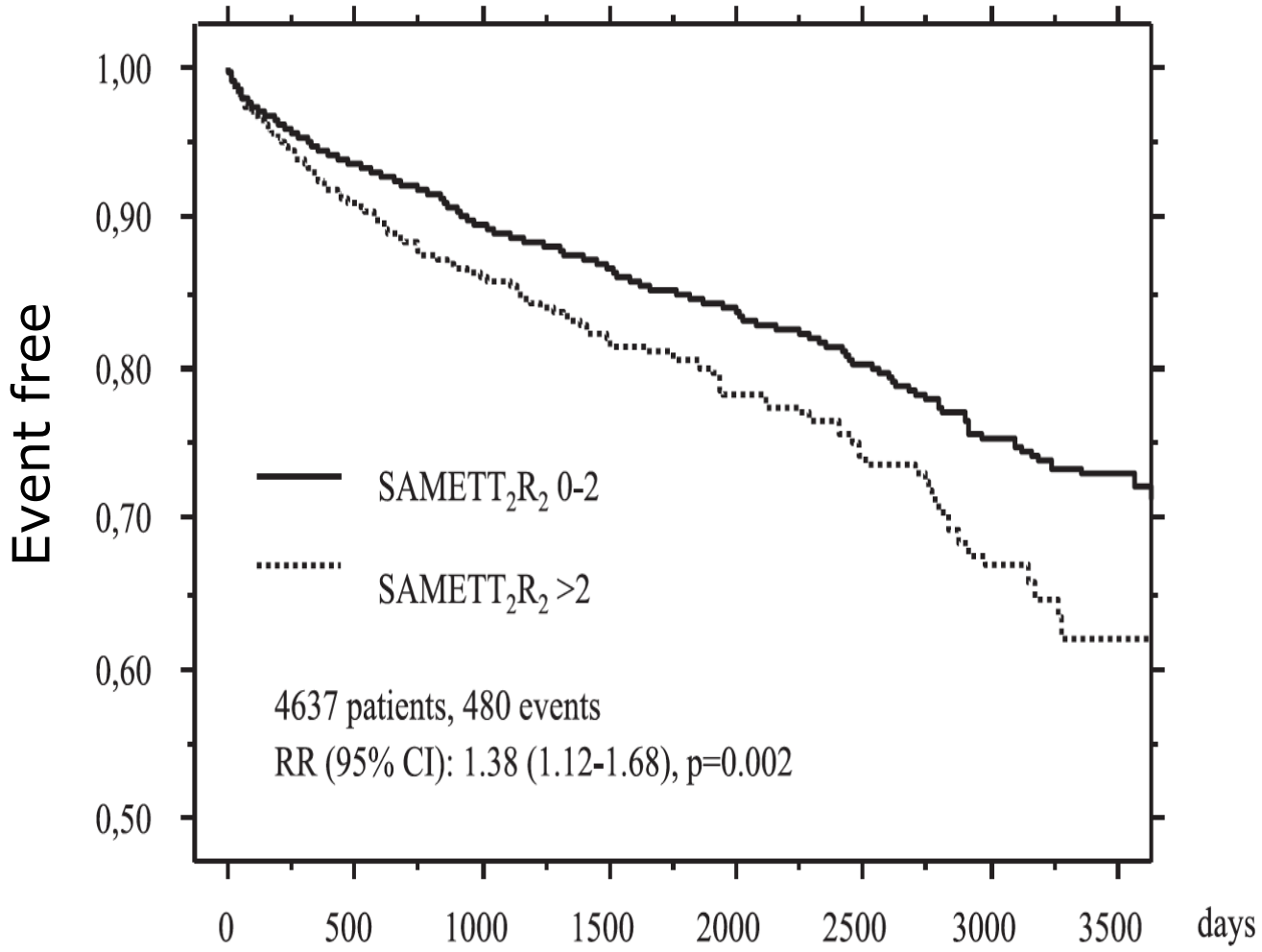
SAMe-TT_2R_2 scores predict stroke risk after VKA for AF



Martínez C, et al. Circulation. 2014;130: A19565

Relationship of the SAMe-TT_2R_2 Score to Poor-Quality Anticoagulation, Stroke, Clinically Relevant Bleeding, and Mortality in Patients With Atrial Fibrillation

Severe bleeding AF with VKA



Lip G, et al. Chest 2014;146:719-26

Relationship of the SAMe-TT_2R_2 Score to Poor-Quality Anticoagulation, Stroke, Clinically Relevant Bleeding, and Mortality in Patients With Atrial Fibrillation

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)		.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)		.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)		<.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)		<.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)		.002
		Ref	1.00 (0.86-1.17)	1.36 (1.14-1.61)	...

Lip G, et al. Chest 2014;146:719-26