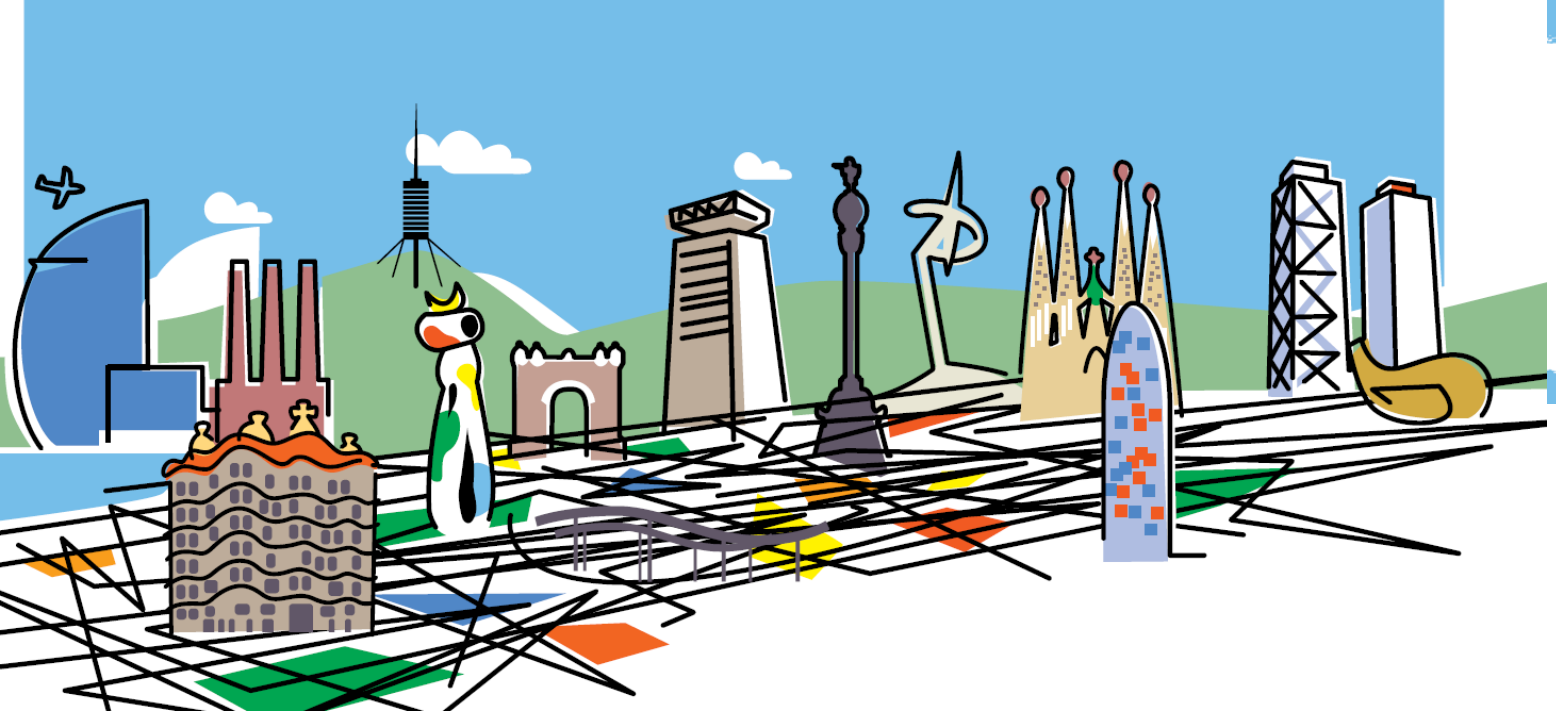


Congrés SOCIETAT CATALANOBALEAR MEDICINA INTERNA XVIII EDICIÓ

ANTICOAGULANTES ORALES DE ACCIÓN DIRECTA en la práctica clínica

FJ Muñoz

Hospital de Mollet

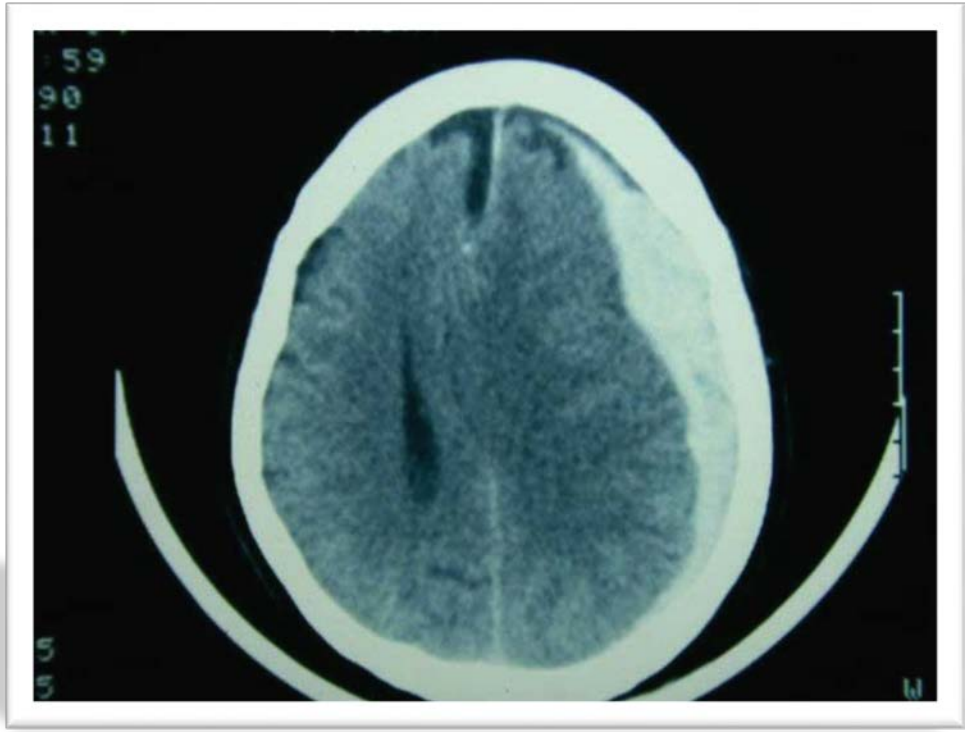
Caso clínico

- Varón de 67 años con antecedentes de HTA, Dislipemia, DM tipo2.
- Historia cardiológica: Cardiopatía isquémica con triple pontaje coronario en 1997. Actualmente en fase de cardiopatia dilatada con FE 23% y episodios de ICC con FE deprimida. Fibrilación auricular permanente.
- Enfermedad renal crónica estadío 3b con FGE de 40ml/min.
- 2015 sufrió una hemorragia intracraneal en forma de hematoma subdural tras TCE estando en tratamiento con acenocumarol, que requirió drenaje quirúrgico.
- CHA_2DS_2-VASc 4 y HAS-BLED 4.

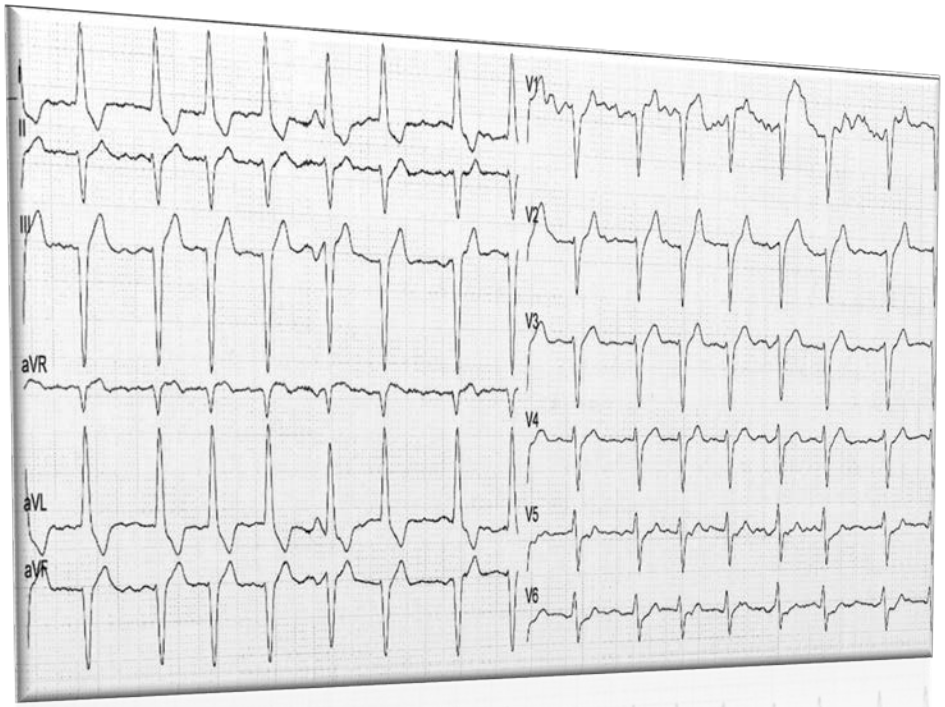
Preguntas

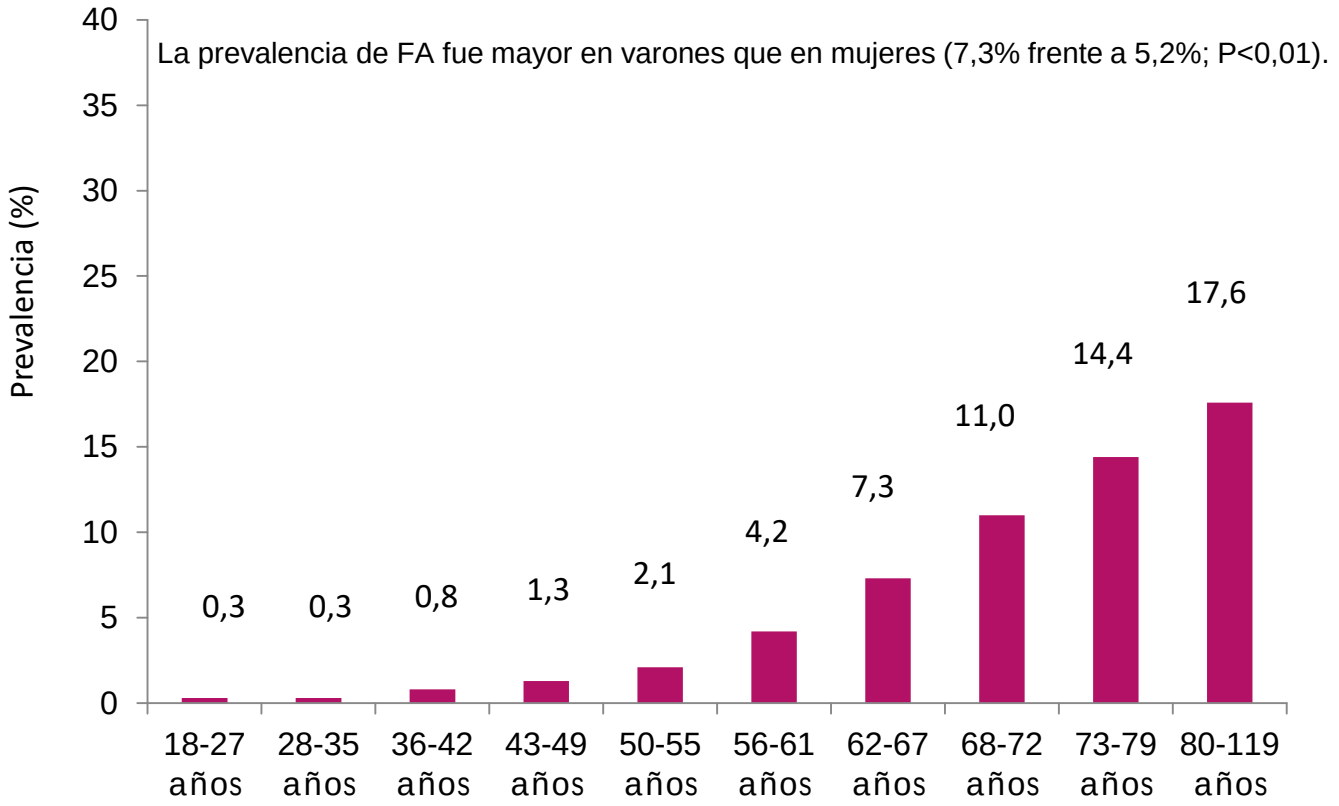
1. ¿Debemos administrar tratamiento anticoagulante a nuestro paciente?

2. ¿Cuál sería la mejor opción terapéutica?



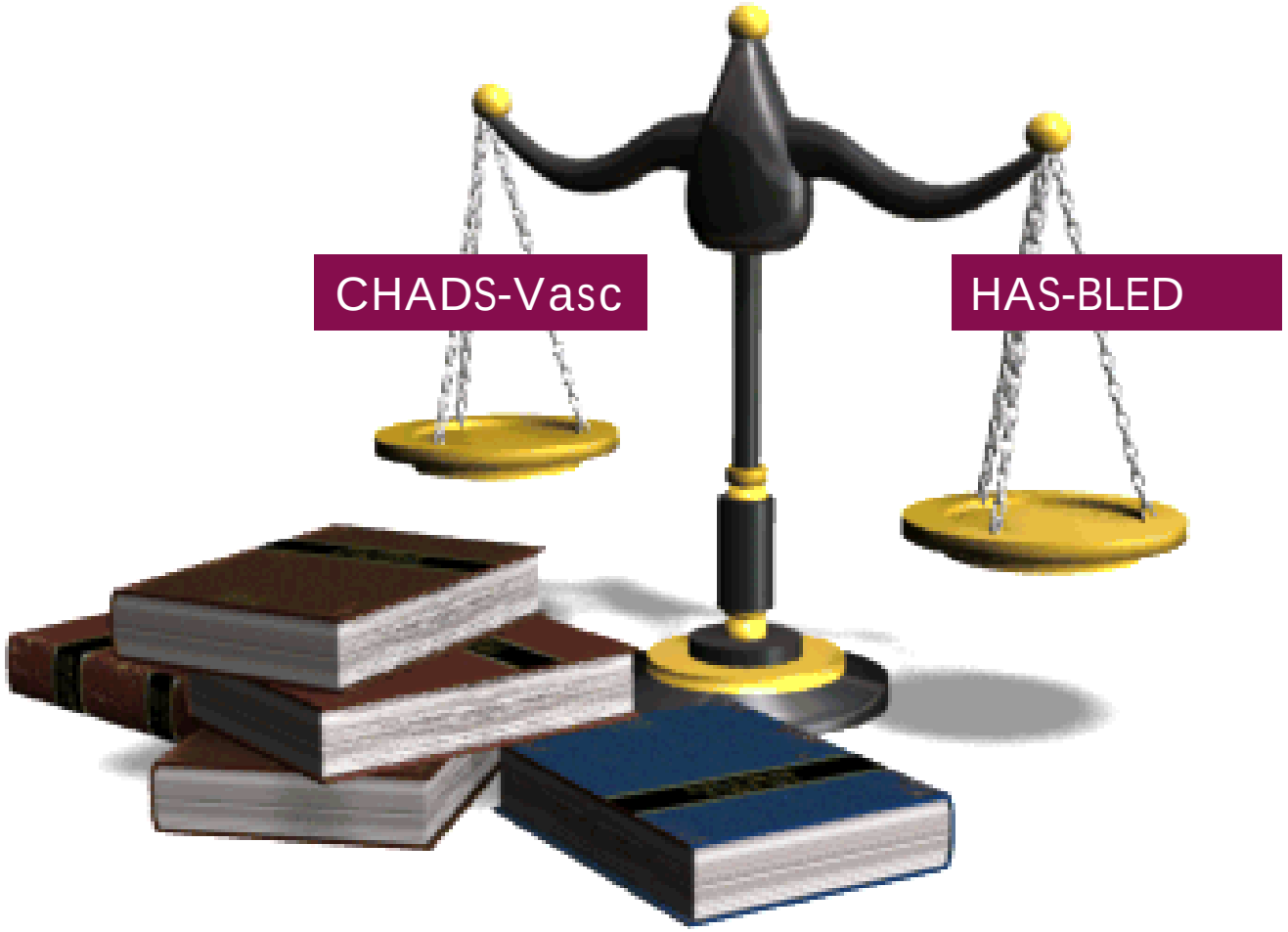
Prevalencia de FA en España de acuerdo con la edad. Estudio Val-FAAP





Barrios V. Rev Esp Cardiol 2012

¿Tenemos que anticoagular?



Escalas de riesgo

Table 11 Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism in the CHA_2DS_2-VASc score

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65–74 years	+1
Sex category (female)	+1

CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

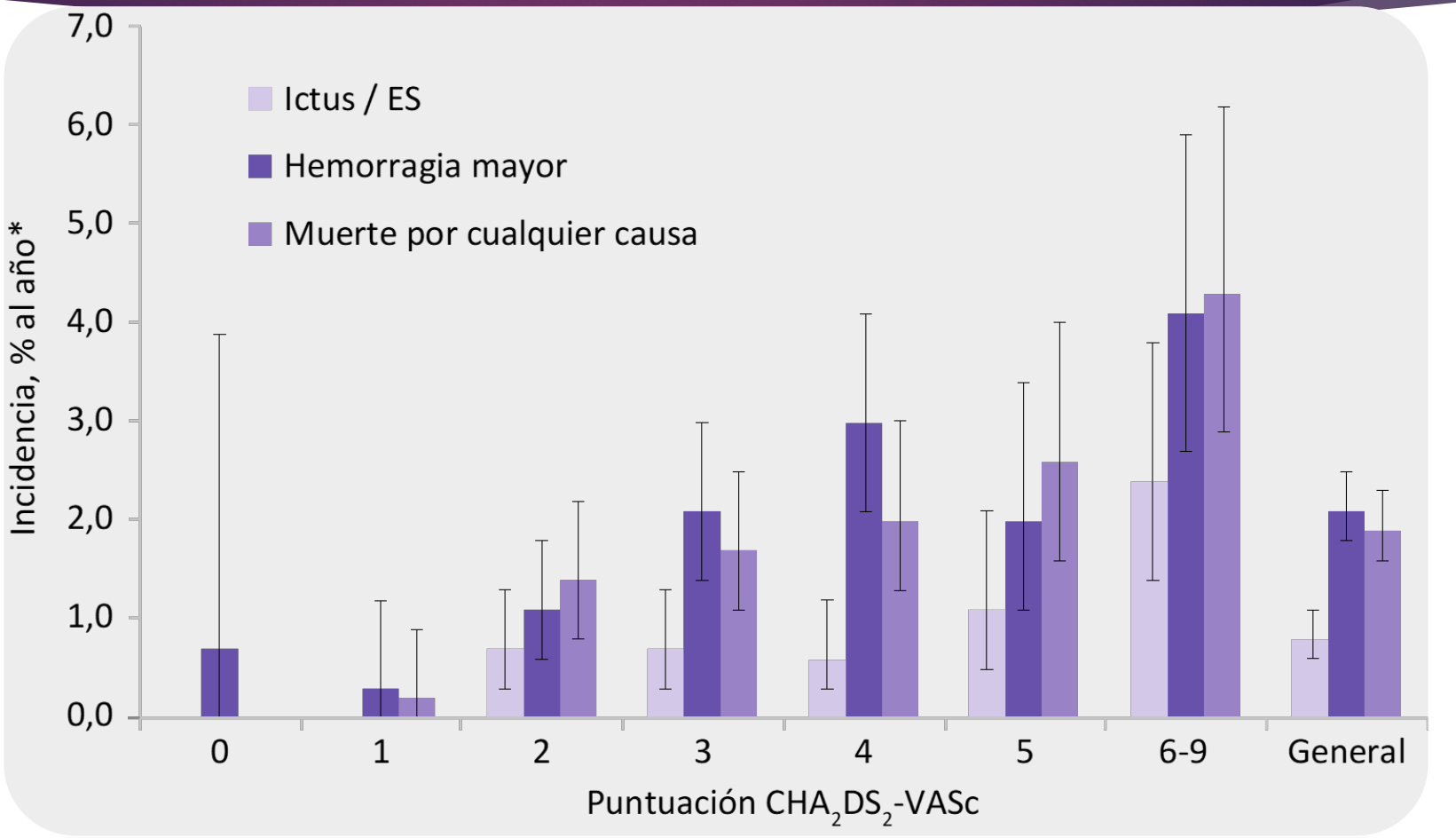
Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

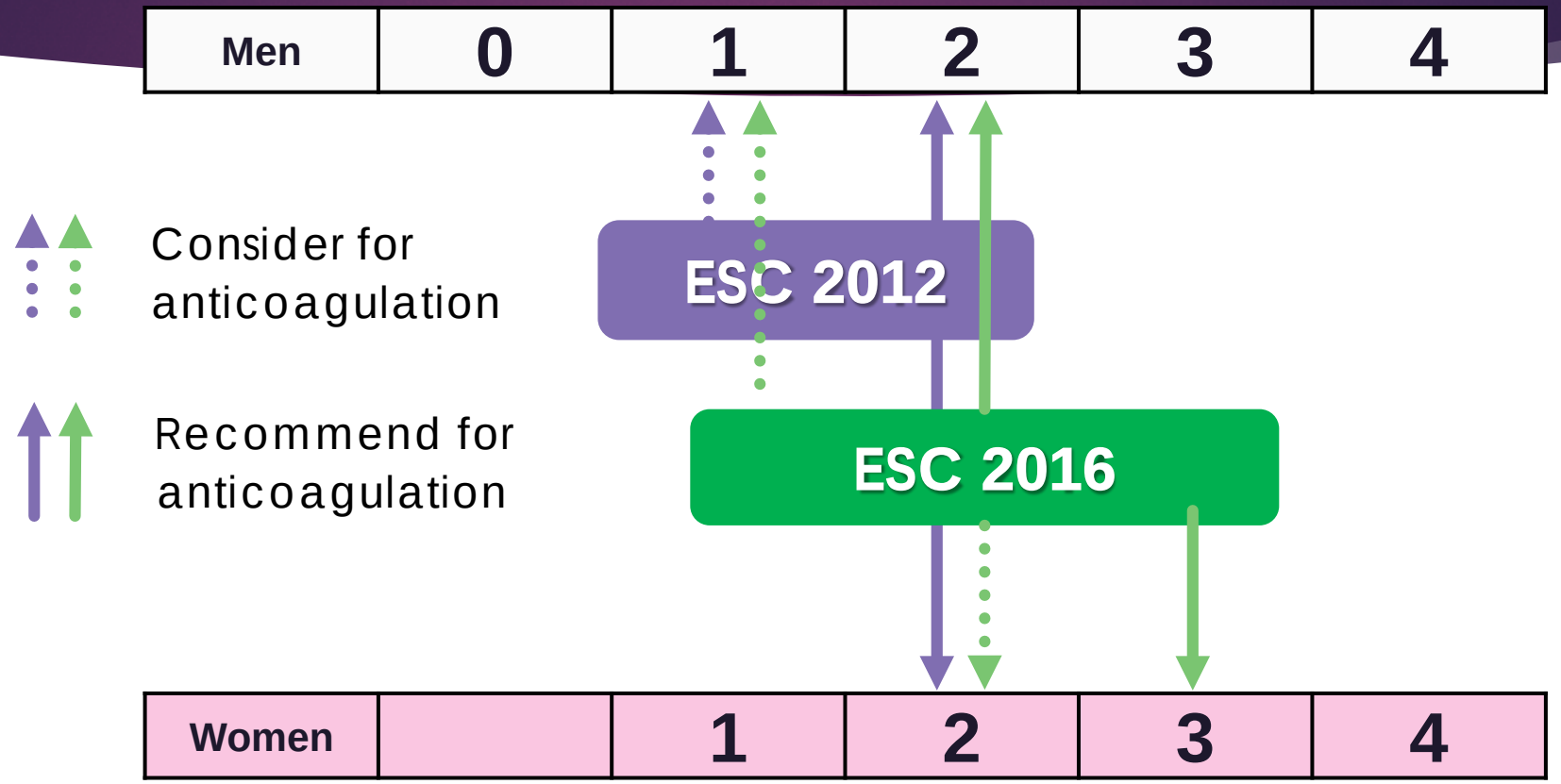
European Heart Journal (2010) **31**, 2369–2429
doi:10.1093/eurheartj/ehq278

EUROPEAN SOCIETY OF CARDIOLOGY®

Incidencia de ictus / ES, hemorragia mayor y muerte por cualquier causa, según CHA_2DS_2-VASc (XANTUS)

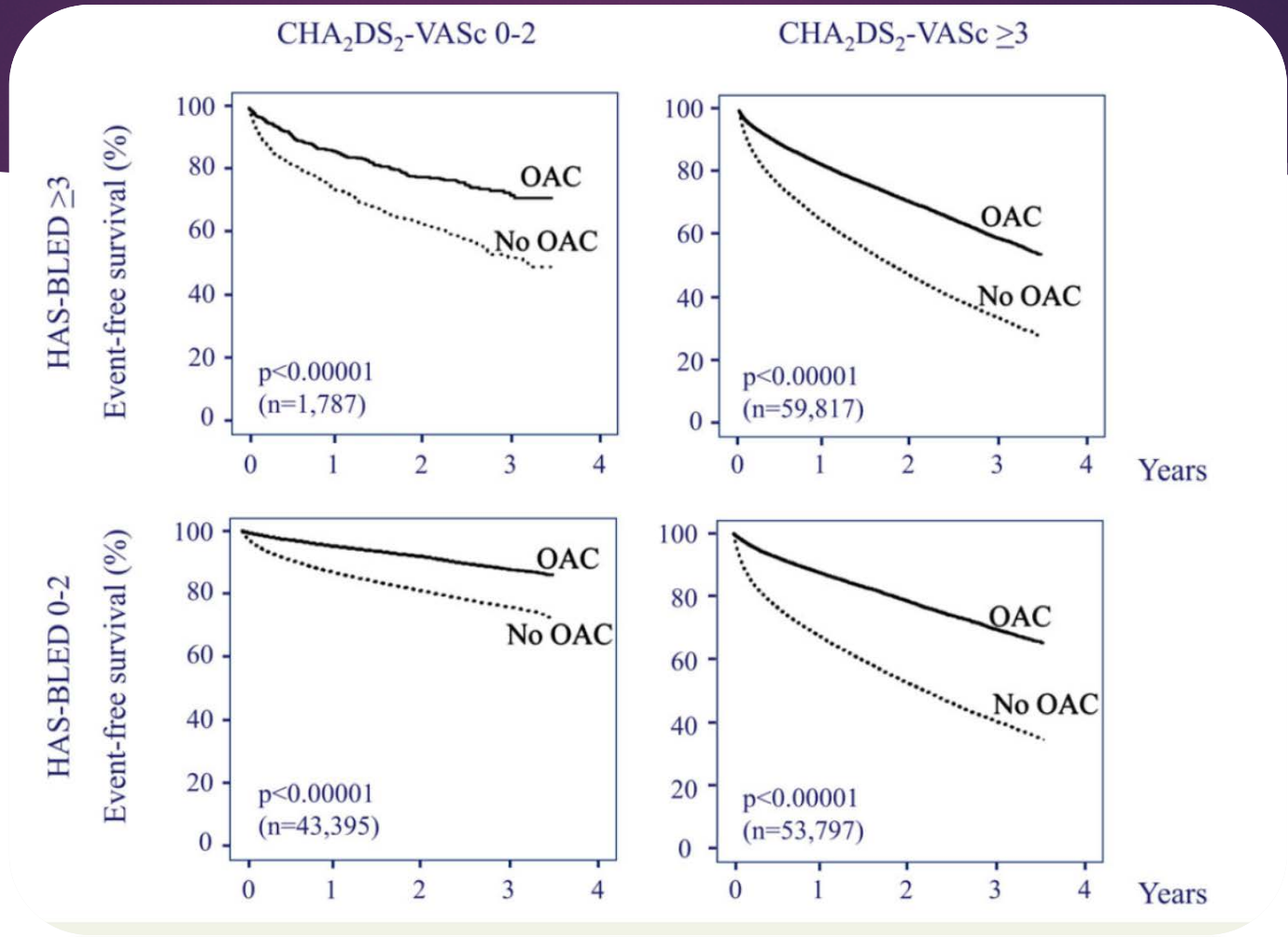


Indicación de anticoagulación



1. Camm AJ. *Eur Heart J.* 2012;33:2719-47.
2. Kirchhof P *et al*, *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw210

Beneficio clínico neto de la anticoagulación en FA

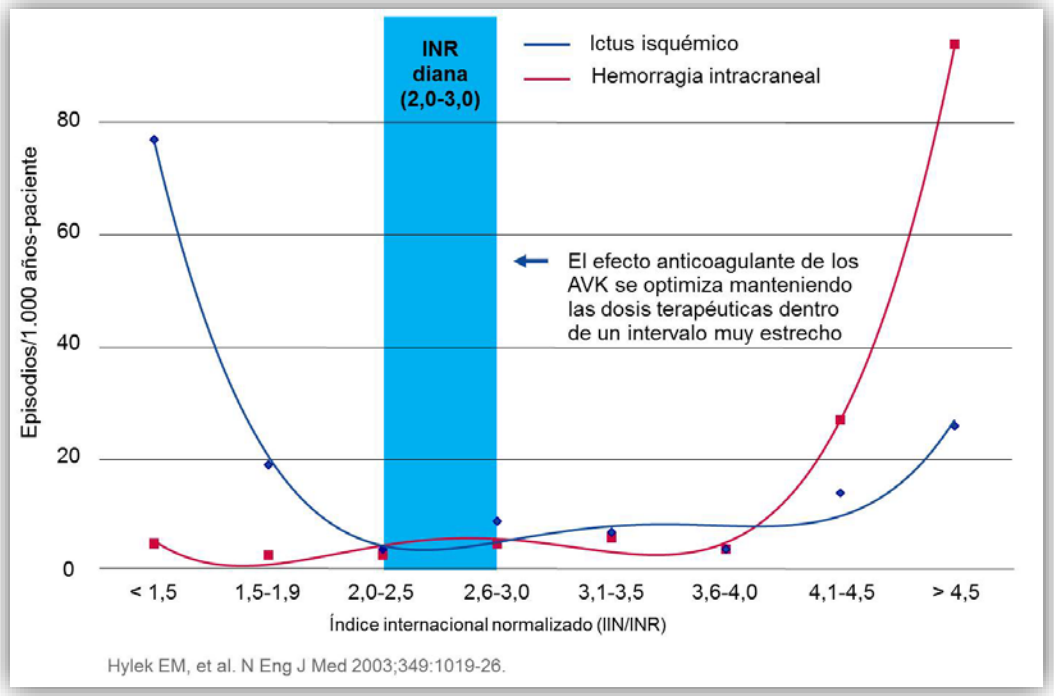


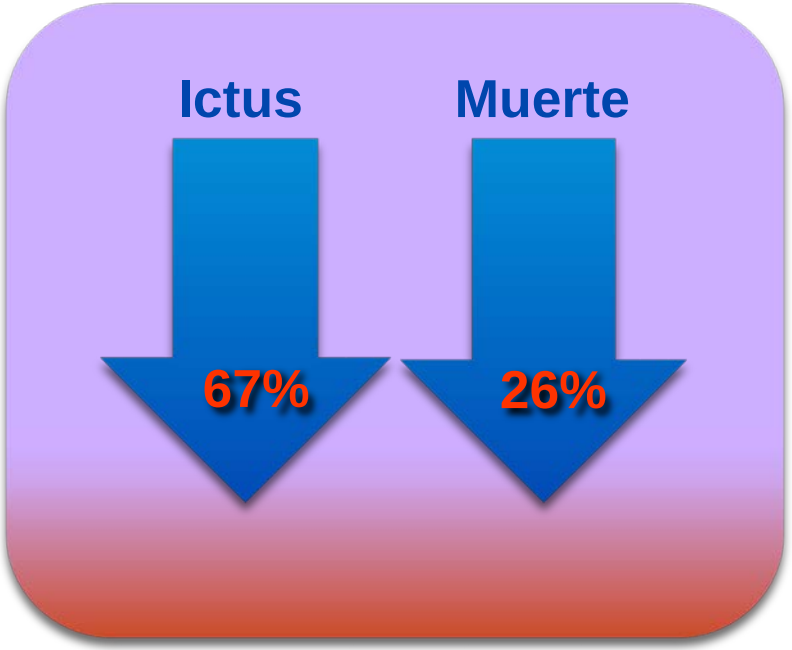
Supervivencia libre de eventos: muerte, ictus isquémico o hemorragia intracraneal

Friberg L. Circulation 2012

Tratamiento tradicional de la FA con AVK

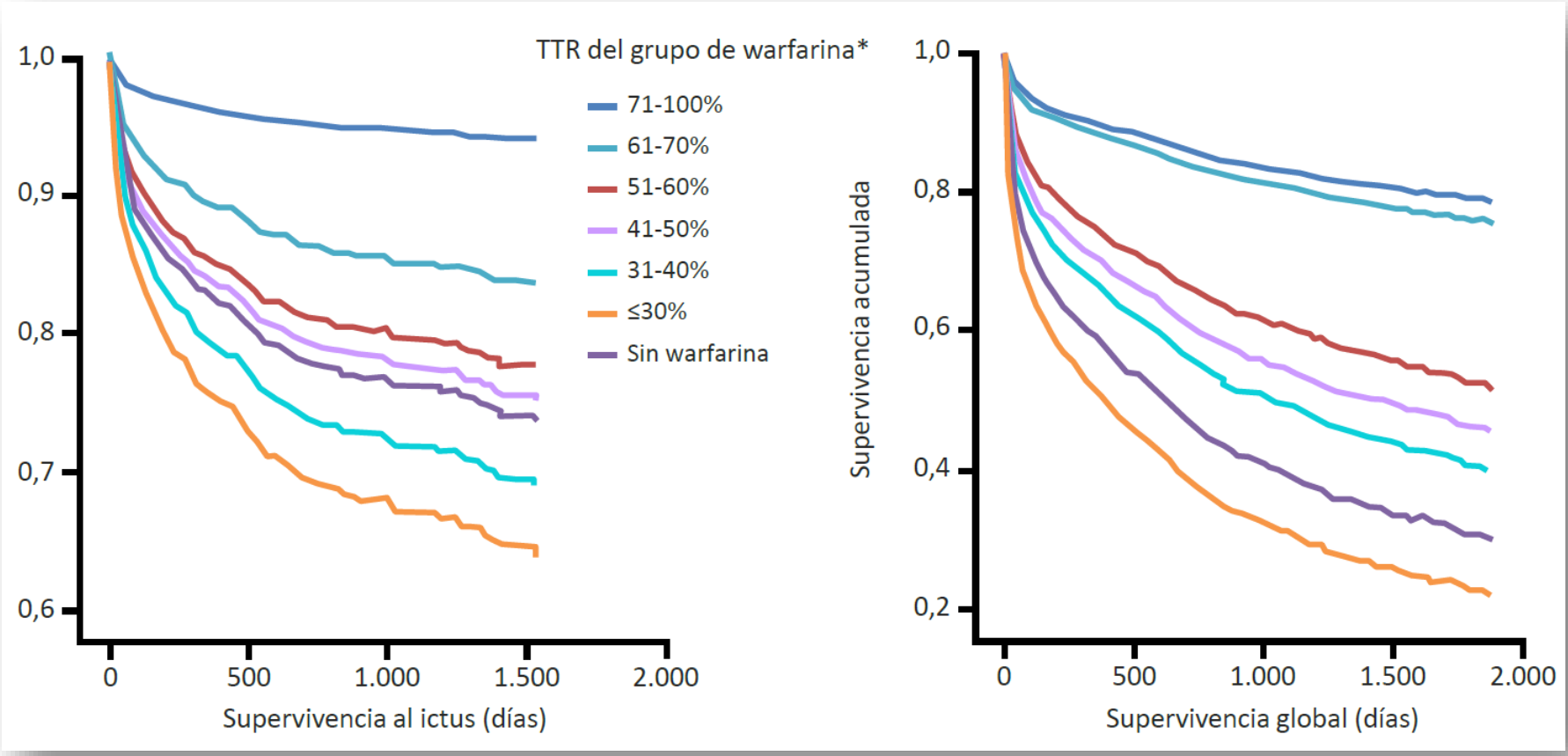
- 2/3 de los ictus por FA se pueden prevenir con un uso de AVK adecuado (INR 2-3)
- Un metaanálisis de 29 estudios en 28.044 pacientes demostró que una dosis ajustada de warfarina reduce el ictus isquémico y la mortalidad por todas la causas





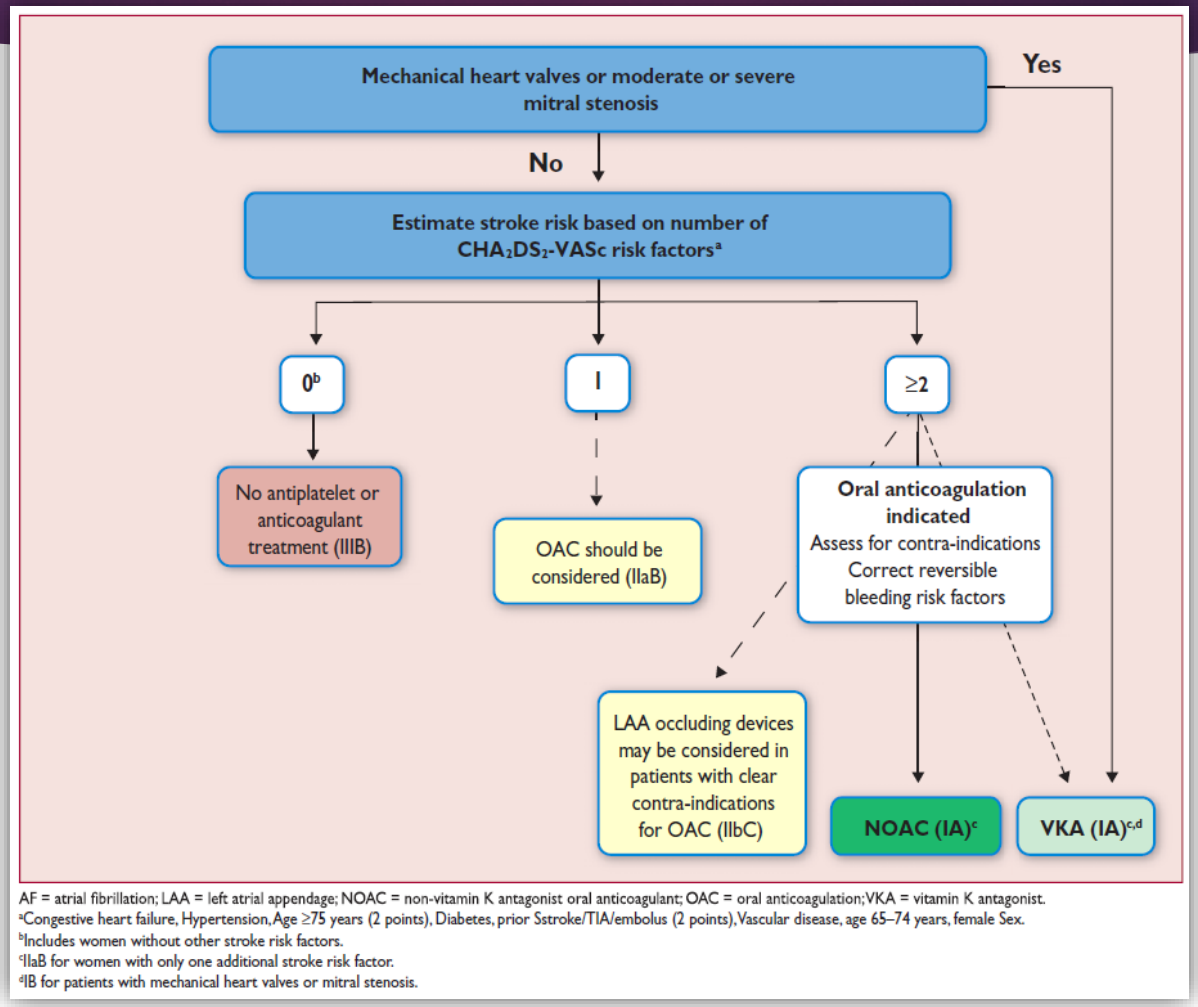
Hart RG. Ann Intern Med 2007

Riesgo de ictus y supervivencia según TRT



Morgan et al. Thromb Res. 2009;124:37-41.

Initiation of Stroke Prevention Therapy in AF



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 Sstroke/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.

Kirchhof P et al, Eur Heart J 2016

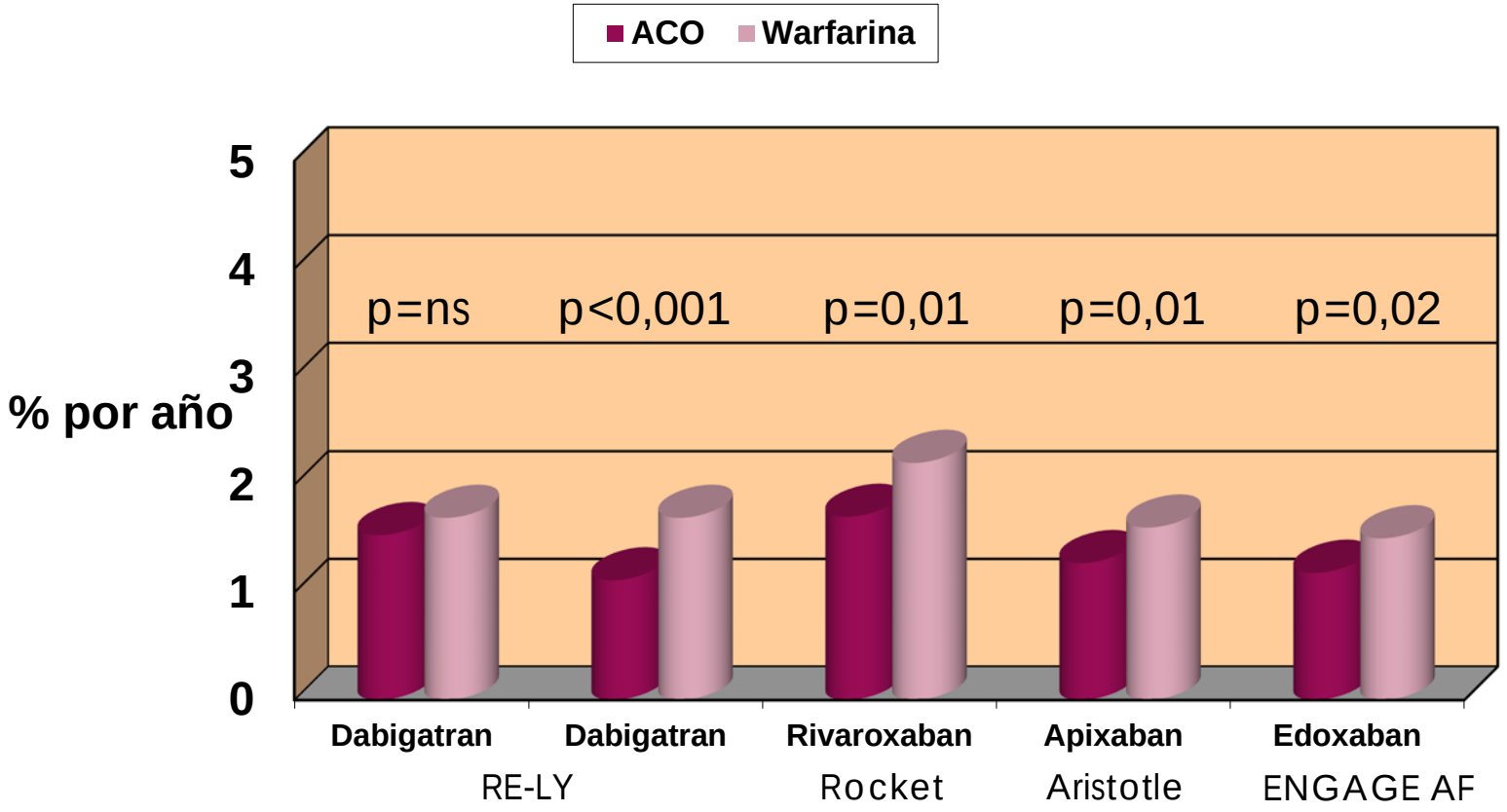
NOACs are the New Standard of Care for Stroke Prevention in Eligible Patients with AF*

Recommendations	Class	Level
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a **NOAC is recommended in preference to a Vitamin K antagonist**.	I	A
AF patients already on treatment with a vitamin K antagonist may be considered for **NOAC treatment if TTR is not well controlled** despite good adherence, **or if patient preference** without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A

*Those without mechanical heart valves or moderate or severe mitral stenosis

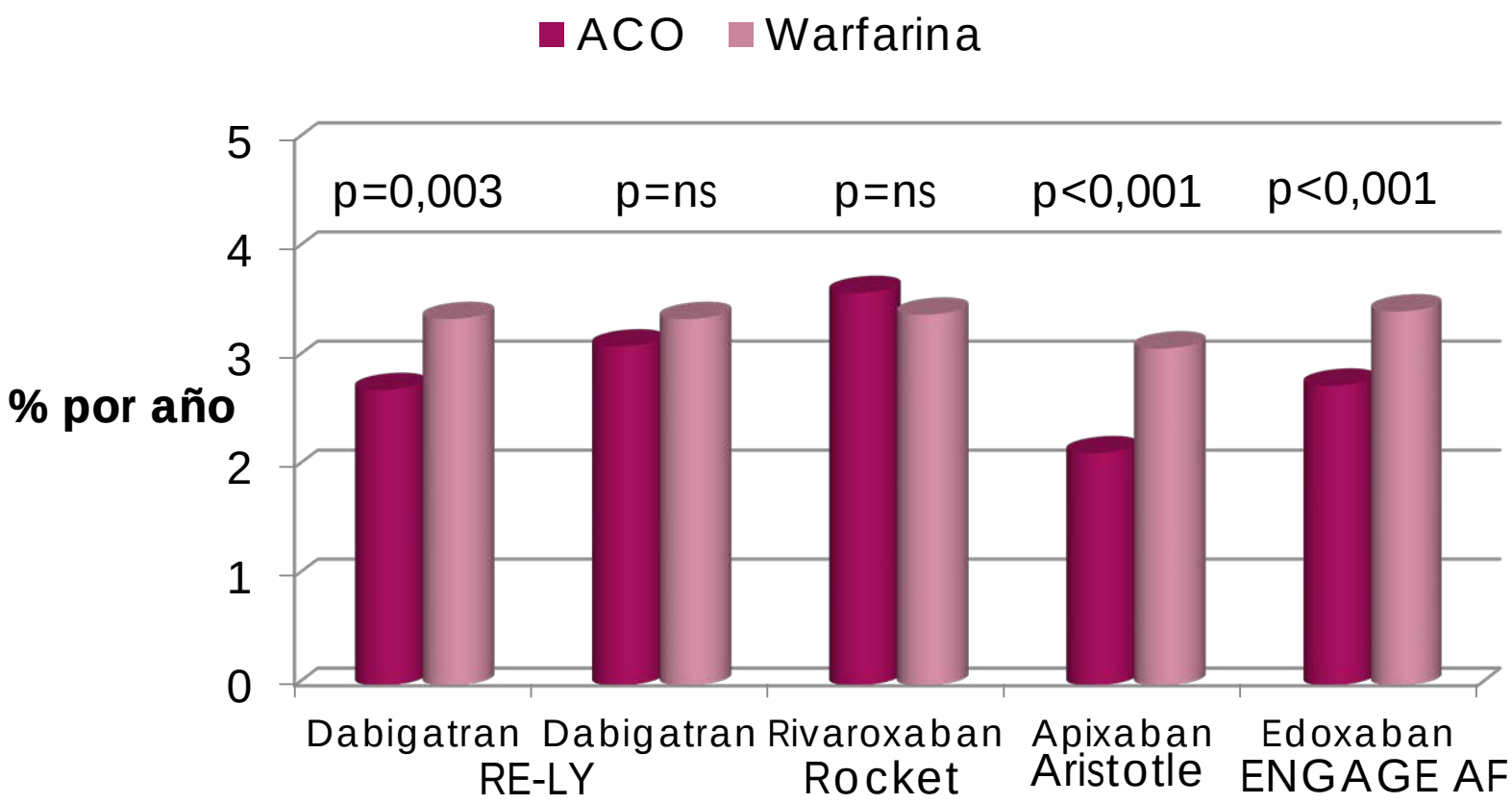
Kirchhof P et al, Eur Heart J 2016

Fibrilación auricular
Resultados de eficacia



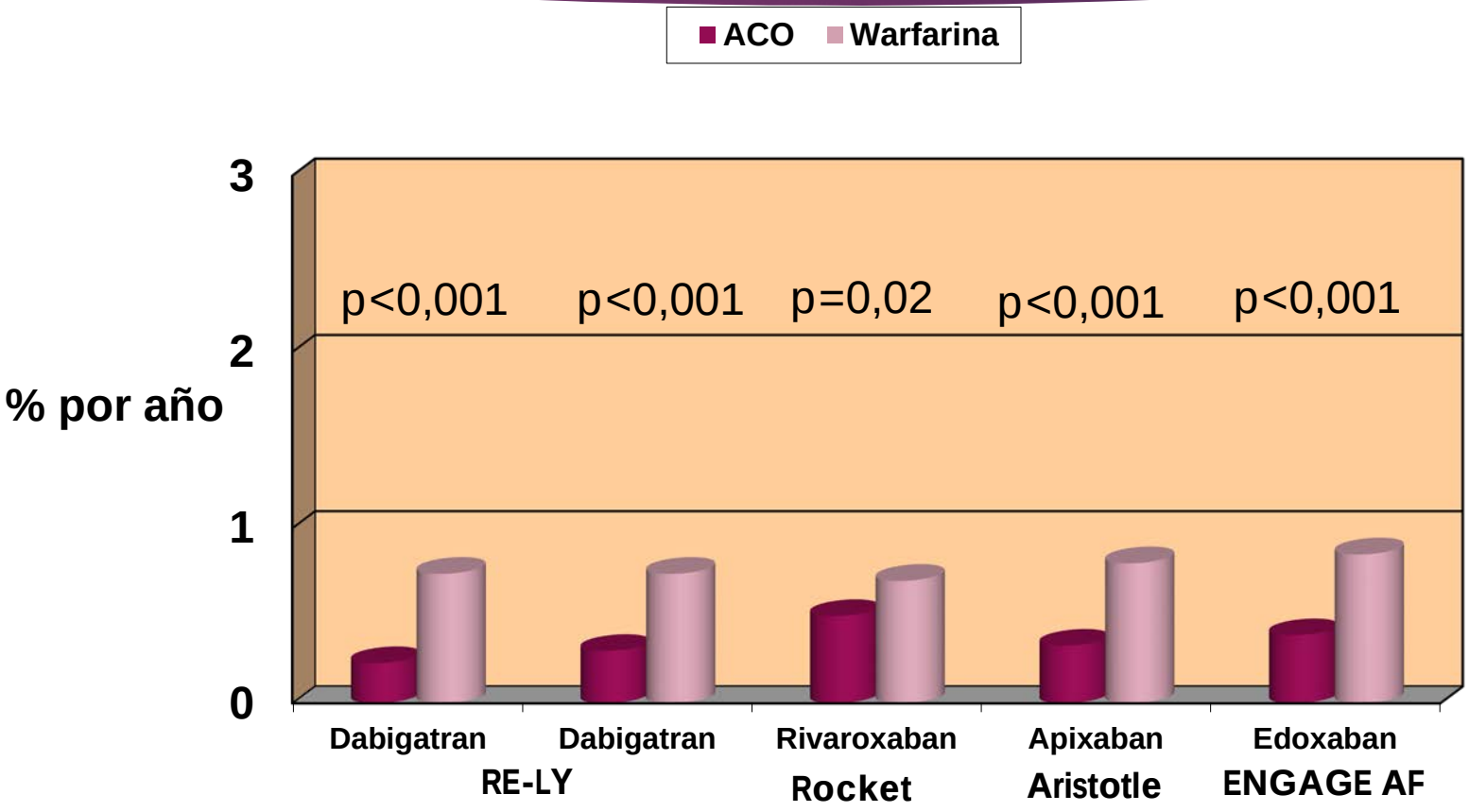
Objetivo primario: Ictus o embolismo sistémico

Resultados de seguridad



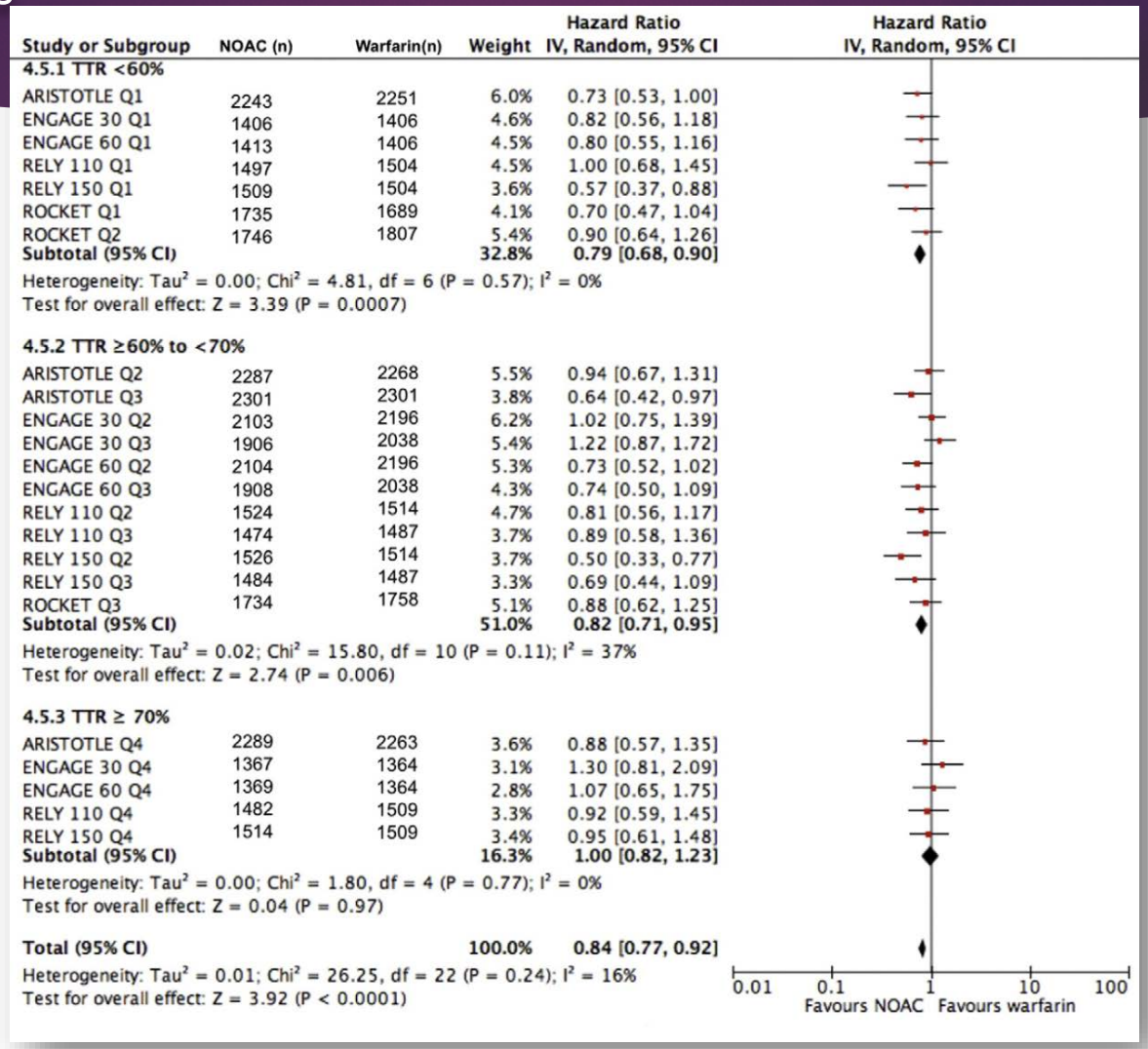
Objetivo: sangrado grave

Fibrilación auricular
Resultados de seguridad



Objetivo: hemorragia intracraneal

Non-vitamin K antagonist oral anticoagulants compared withwarfarin at different levels of INR control in atrial fibrillation: A meta-analysis of randomized trials

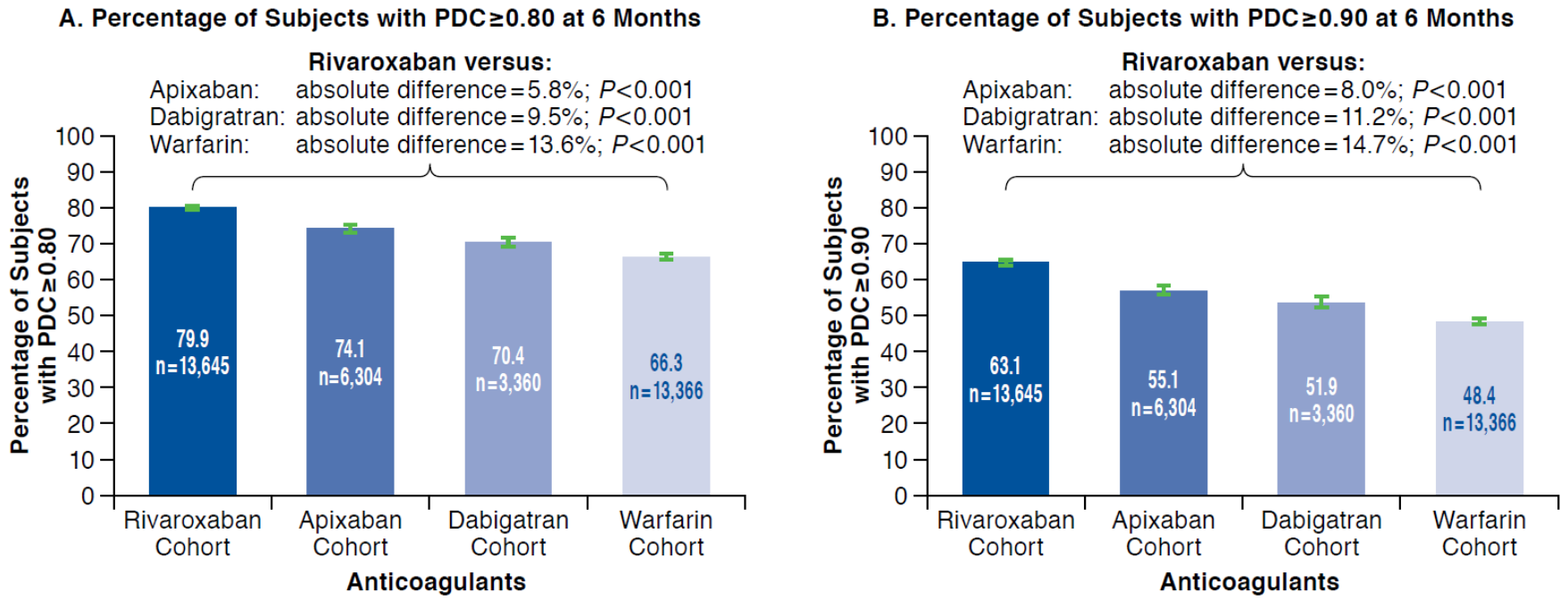


Ictus o embolismo sistémico

Carmo J. Intern J Cardiol 2017

Adherencia de los NACOS

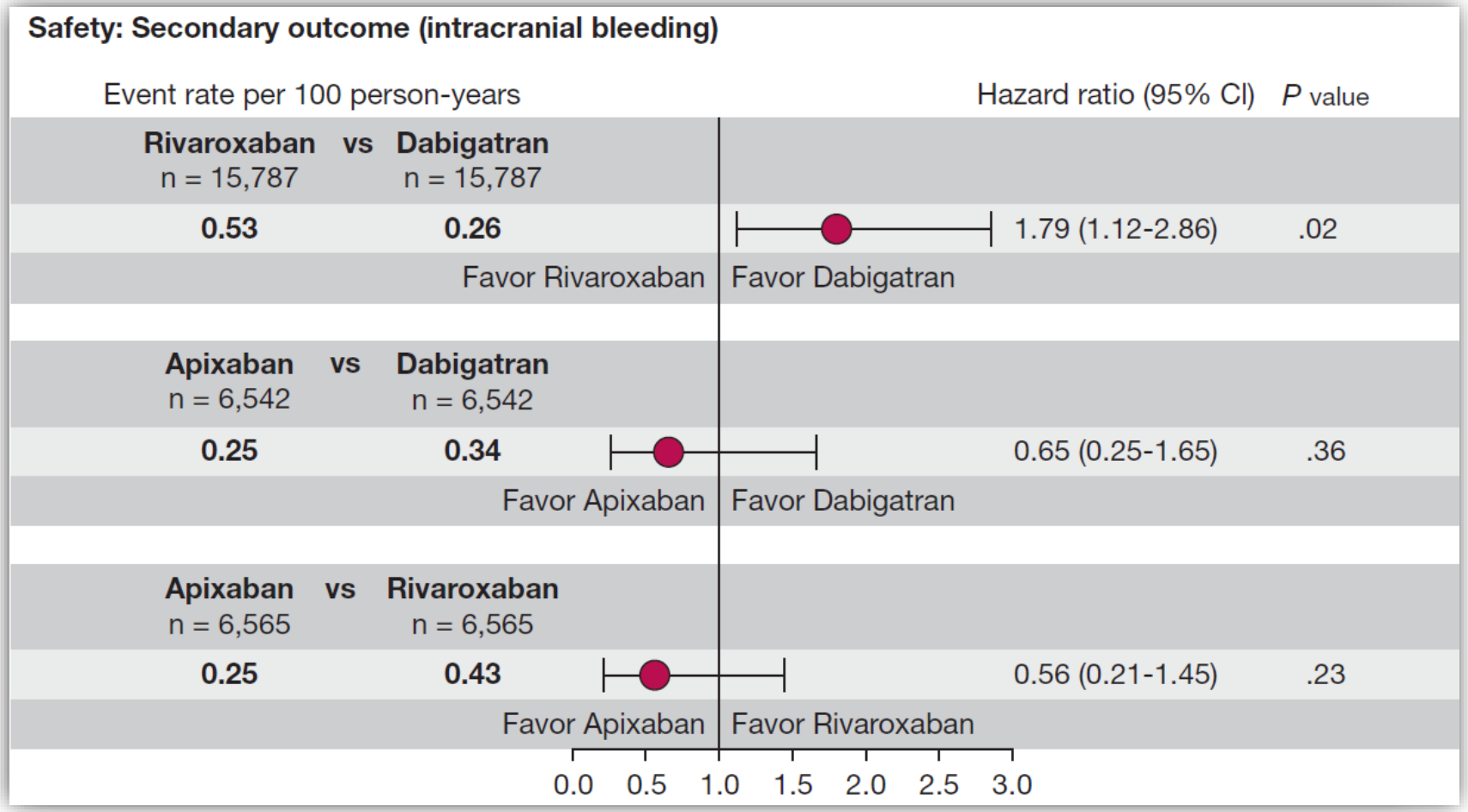
FIGURE 2 Adjusted Adherence of OAC Cohorts[a]: PDC Percentages at 6 Months



[a]*Adjusted adherence was calculated as the predicted probability of PDC≥0.80 or PDC≥0.90 based on multivariable logistic regression.*
OAC=oral anticoagulant; PDC=proportion of days covered.

McHorney CA. JMCP 2017

Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation



Noseworthy PA. Chest 2016

Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis

Dabigatran vs Warfarina

	HR	IC 95%
Ictus isquémico	0,96	0,8-1,16
Ictus isquémico y embolismo sistémico	1,17	0,92-1,5
Cualquier ictus y embolismo sistémico	0,93	0,77-1,14
Infarto de miocardio	0,96	0,77-1,21

	HR	IC 95%
Hemorragia intracraneal	**0,42**	**0,37-0,49**
Hemorragia gastrointestinal	**1,20**	**1,06-1,36**
Hemorragia grave	0,83	0,65-1,05
Muerte	**0,63**	**0,52-0,76**

Ntaios G. Stroke 2017

Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis

Rivaroxaban vs Warfarina

	HR	IC 95%
Ictus isquémico	0,89	0,76-1,04
Ictus isquémico y embolismo sistémico	0,73	0,52-1,04
Cualquier ictus y embolismo sistémico	0,87	0,71-1,07
Infarto de miocardio	1,02	0,54-1,89

	HR	IC 95%
Hemorragia intracraneal	**0,64**	**0,47-0,86**
Hemorragia gastrointestinal	**1,24**	**1,08-1,41**
Hemorragia grave	1	0,92-1,08
Muerte	0,67	0,35-1,3

Ntaios G. Stroke 2017

Real-World Setting Comparison of Nonvitamin-K Antagonist Oral Anticoagulants Versus Vitamin-K Antagonists for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis

Apixaban vs Warfarina

	HR	IC 95%
Ictus isquémico	0,95	0,75-1,19
Ictus isquémico y embolismo sistémico	1,07	0,87-1,31
Cualquier ictus y embolismo sistémico	**0,67**	**0,46-0,98**
Infarto de miocardio	ND	ND

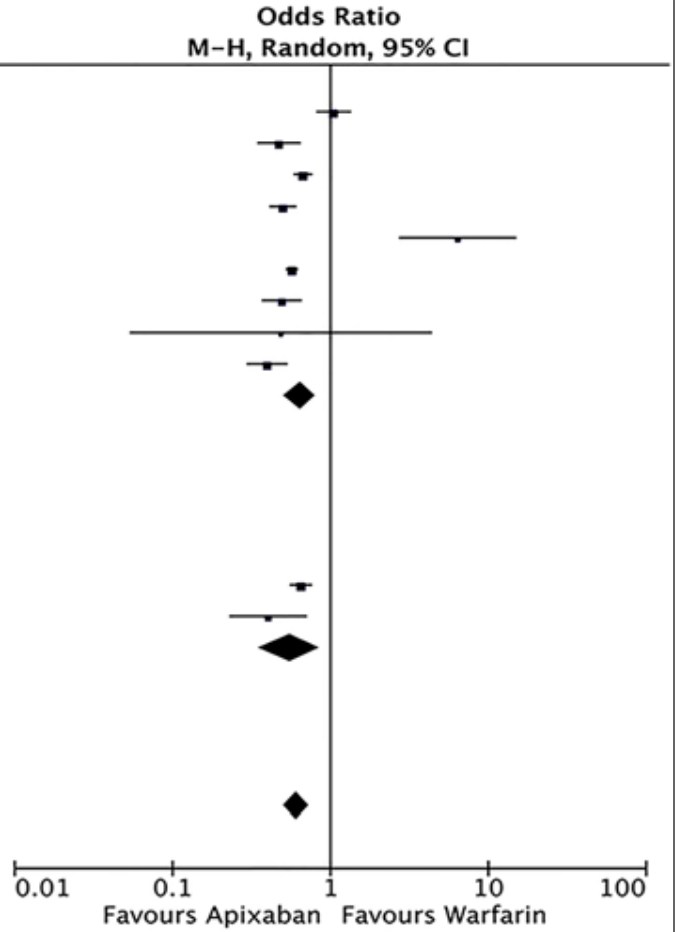
	HR	IC 95%
Hemorragia intracraneal	**0,45**	**0,31-0,63**
Hemorragia gastrointestinal	**0,63**	**0,42-0,95**
Hemorragia grave	**0,55**	**0,48-0,63**
Muerte	**0,65**	**0,56-0,75**

Ntaios G. Stroke 2017

Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis

Major Bleeding

Study or Subgroup	Apixaban Events	Apixaban Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 Regular or Any Dose						
Forslund 2017	79	3587	272	12919	10.8%	1.05 [0.81, 1.35]
Halvorsen 2017	49	6506	181	11427	9.7%	0.47 [0.34, 0.65]
Lamberts 2017	252	7963	1128	24230	12.4%	0.67 [0.58, 0.77]
Larsen 2016	109	6349	1198	35436	11.6%	0.50 [0.41, 0.61]
Lee 2015	9	53	18	580	3.6%	6.39 [2.71, 15.05]
Li 2017	753	38470	1303	38470	12.9%	0.57 [0.52, 0.62]
Lip 2016	68	6964	137	6964	10.1%	0.49 [0.37, 0.66]
Shiga 2015	1	102	4	200	0.7%	0.49 [0.05, 4.40]
Yao 2016	58	6302	176	7695	10.0%	0.40 [0.29, 0.53]
Subtotal (95% CI)		**76296**		**137921**	**81.8%**	**0.64 [0.51, 0.80]**
Total events	1378		4417			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 66.16$, df = 8 ($P < 0.00001$); $I^2 = 88\%$						
Test for overall effect: Z = 3.82 (P = 0.0001)						
1.4.2 Reduced Dose						
Nielsen 2017	160	4400	2136	38893	12.1%	0.65 [0.55, 0.76]
Yao 2016	13	1393	176	7695	6.1%	0.40 [0.23, 0.71]
Subtotal (95% CI)		**5793**		**46588**	**18.2%**	**0.55 [0.36, 0.86]**
Total events	173		2312			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 2.54$, df = 1 ($P = 0.11$); $I^2 = 61\%$						
Test for overall effect: Z = 2.62 (P = 0.009)						
Total (95% CI)		**82089**		**184509**	**100.0%**	**0.62 [0.51, 0.75]**
Total events	1551		6729			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 69.07$, df = 10 ($P < 0.00001$); $I^2 = 86\%$						
Test for overall effect: Z = 4.99 ($P < 0.00001$)						
Test for subgroup differences: $Chi^2 = 0.32$, df = 1 ($P = 0.57$), $I^2 = 0\%$						

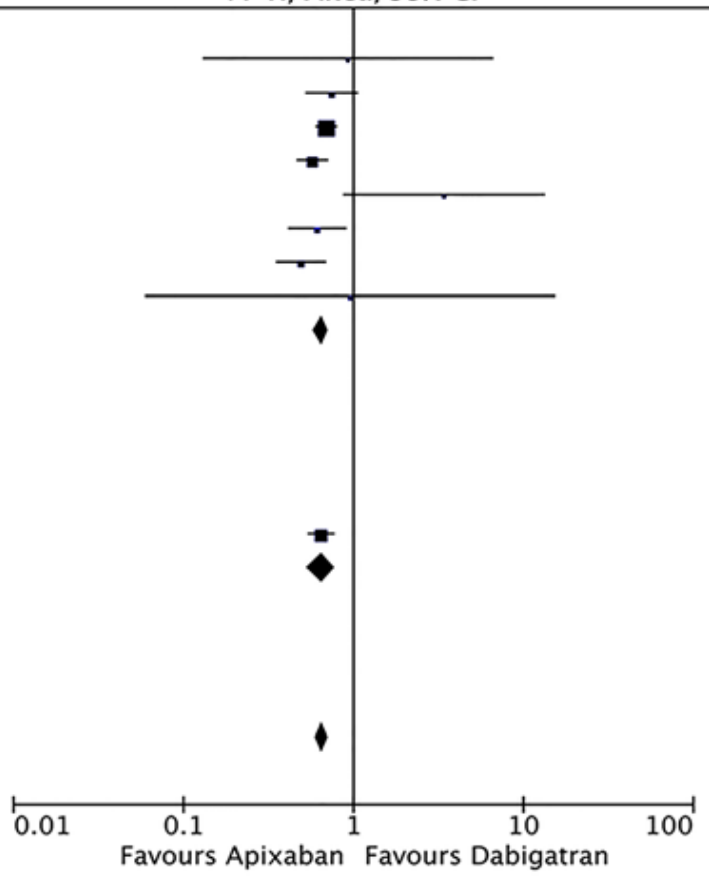


Proietti M. Stroke 2018

Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis

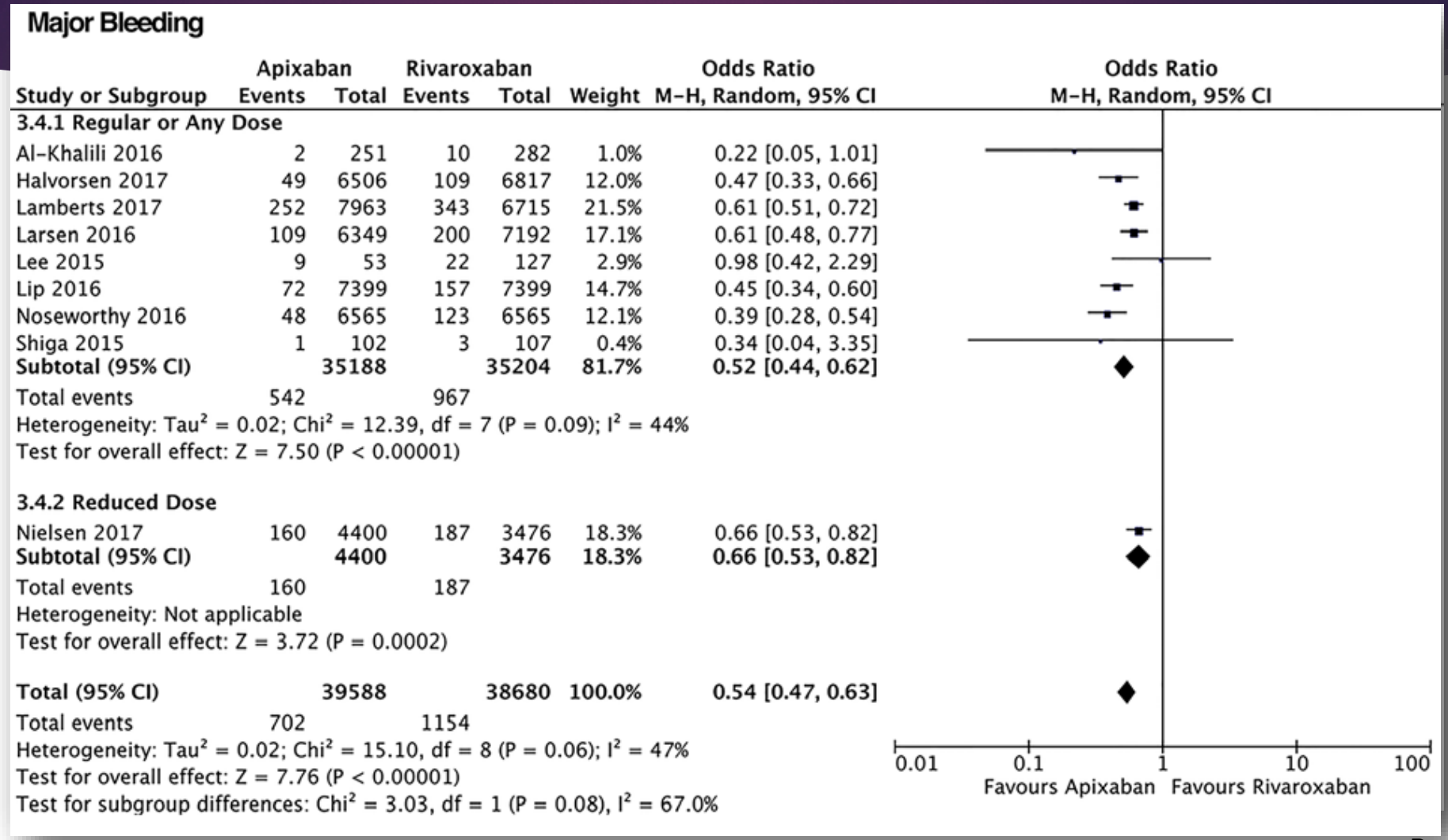
Major Bleeding

Study or Subgroup	Apixaban Events	Apixaban Total	Dabigatran Events	Dabigatran Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Regular or Any Dose						
Al-Khalili 2016	2	251	2	233	0.2%	0.93 [0.13, 6.64]
Halvorsen 2017	49	6506	80	7925	5.7%	0.74 [0.52, 1.06]
Lamberts 2017	252	7963	695	15413	36.4%	0.69 [0.60, 0.80]
Larsen 2016	109	6349	376	12701	19.5%	0.57 [0.46, 0.71]
Lee 2015	9	53	3	53	0.2%	3.41 [0.87, 13.39]
Lip 2016	40	4407	65	4407	5.1%	0.61 [0.41, 0.91]
Noseworthy 2016	50	6542	101	6542	8.0%	0.49 [0.35, 0.69]
Shiga 2015	1	201	1	192	0.1%	0.95 [0.06, 15.38]
Subtotal (95% CI)		**32272**		**47466**	**75.1%**	**0.65 [0.58, 0.72]**
Total events	512		1323			
Heterogeneity: $Chi^2 = 11.10$, df = 7 (P = 0.13); $I^2 = 37\%$						
Test for overall effect: Z = 8.22 (P < 0.00001)						
2.3.2 Reduced Dose						
Nielsen 2017	160	4400	491	8875	24.9%	0.64 [0.54, 0.77]
Subtotal (95% CI)		**4400**		**8875**	**24.9%**	**0.64 [0.54, 0.77]**
Total events	160		491			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.73 (P < 0.00001)						
Total (95% CI)		**36672**		**56341**	**100.0%**	**0.65 [0.59, 0.71]**
Total events	672		1814			
Heterogeneity: $Chi^2 = 11.10$, df = 8 (P = 0.20); $I^2 = 28\%$						
Test for overall effect: Z = 9.49 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.98), $I^2 = 0\%$						



Proietti M. Stroke 2018

Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis



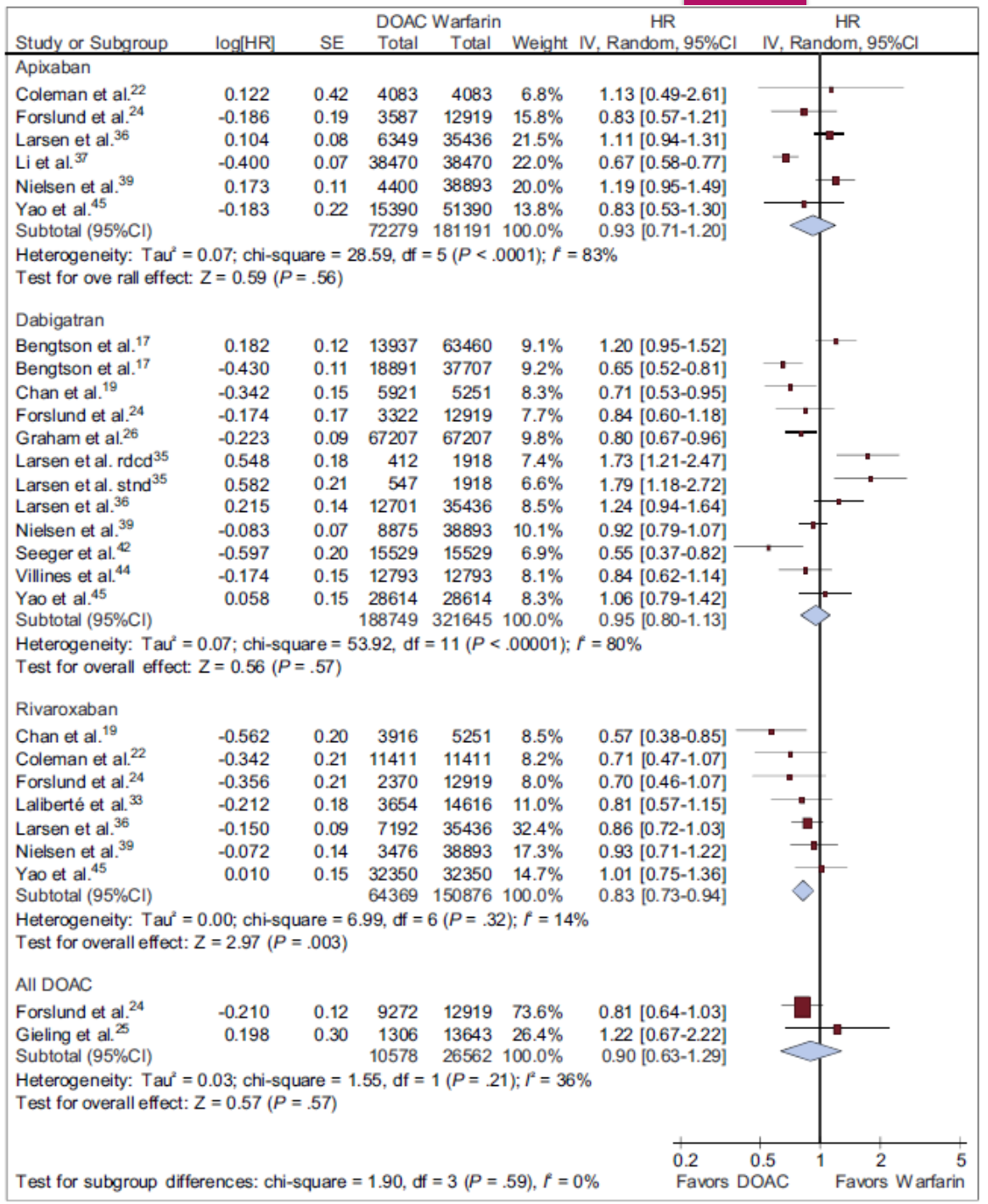
Proietti M. Stroke 2018

Direct Oral Anticoagulants Versus Vitamin K Antagonists in Real-life Patients With Atrial Fibrillation. A Systematic Review and Meta-analysis

Ictus isquémico

Rivaroxaban redujo significativamente el riesgo de ictus isquémico en comparación con warfarina (HR 0.83, 95% CI 0.73–0.94). **Este hallazgo resultó ser muy consistente entre estudios.**

Rivaroxaban
RRR
17 %



Escobar et al. Rev Esp Cardiol 2018

Direct Oral Anticoagulants Versus Vitamin K Antagonists in Real-life Patients With Atrial Fibrillation. A Systematic Review and Meta-analysis

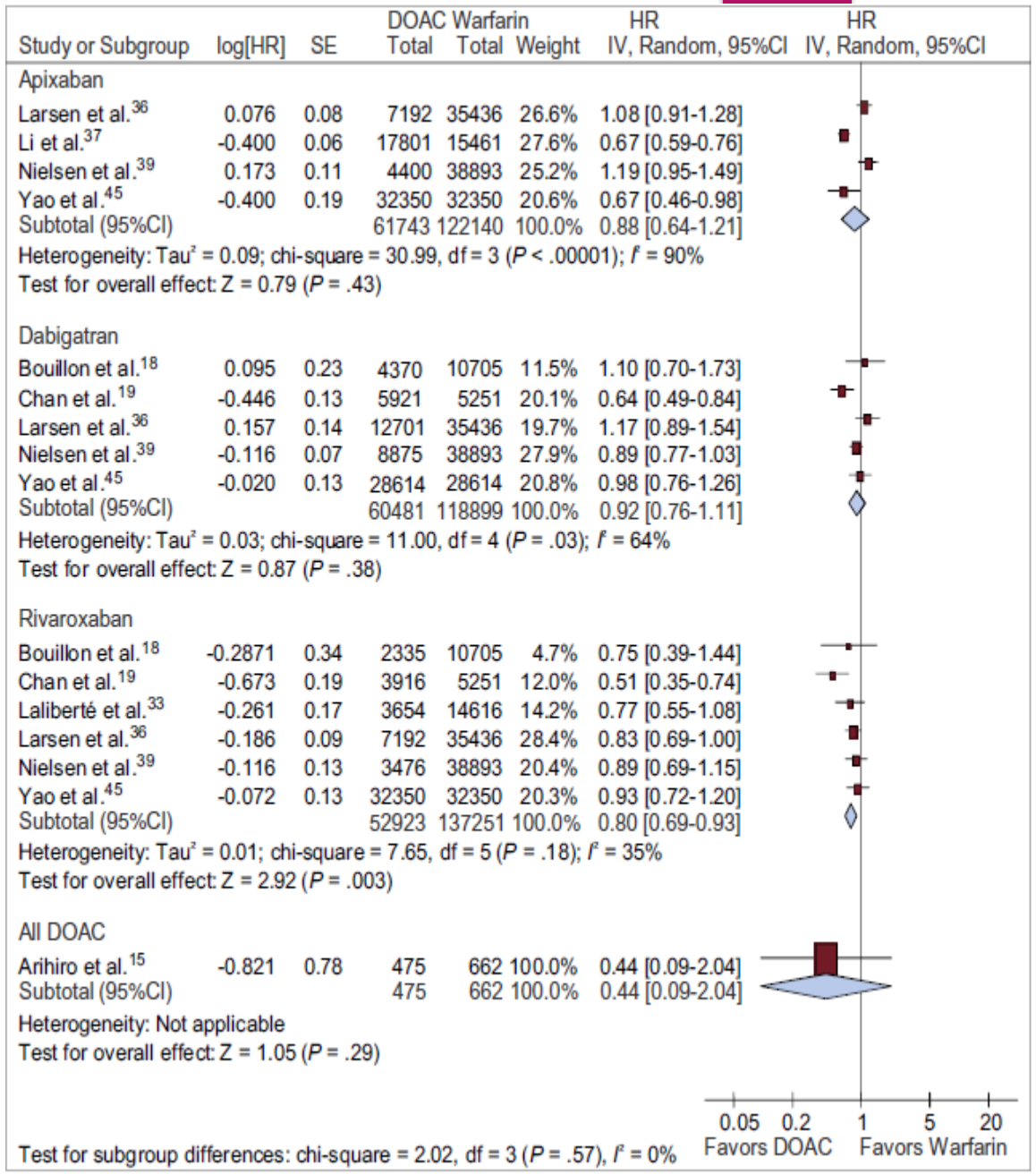
Ictus isquémico/ES

Rivaroxaban redujo significativamente el riesgo de eventos isquémicos (ictus/ES) en comparación con warfarina (HR 0.80, 95% CI 0.69–0.93), **un hallazgo consistente entre estudios.**

Rivaroxaban

RRR

20 %



Escobar et al. Rev Esp Cardiol 2018

Direct Oral Anticoagulants Versus Vitamin K Antagonists in Real-life Patients With Atrial Fibrillation. A Systematic Review and Meta-analysis

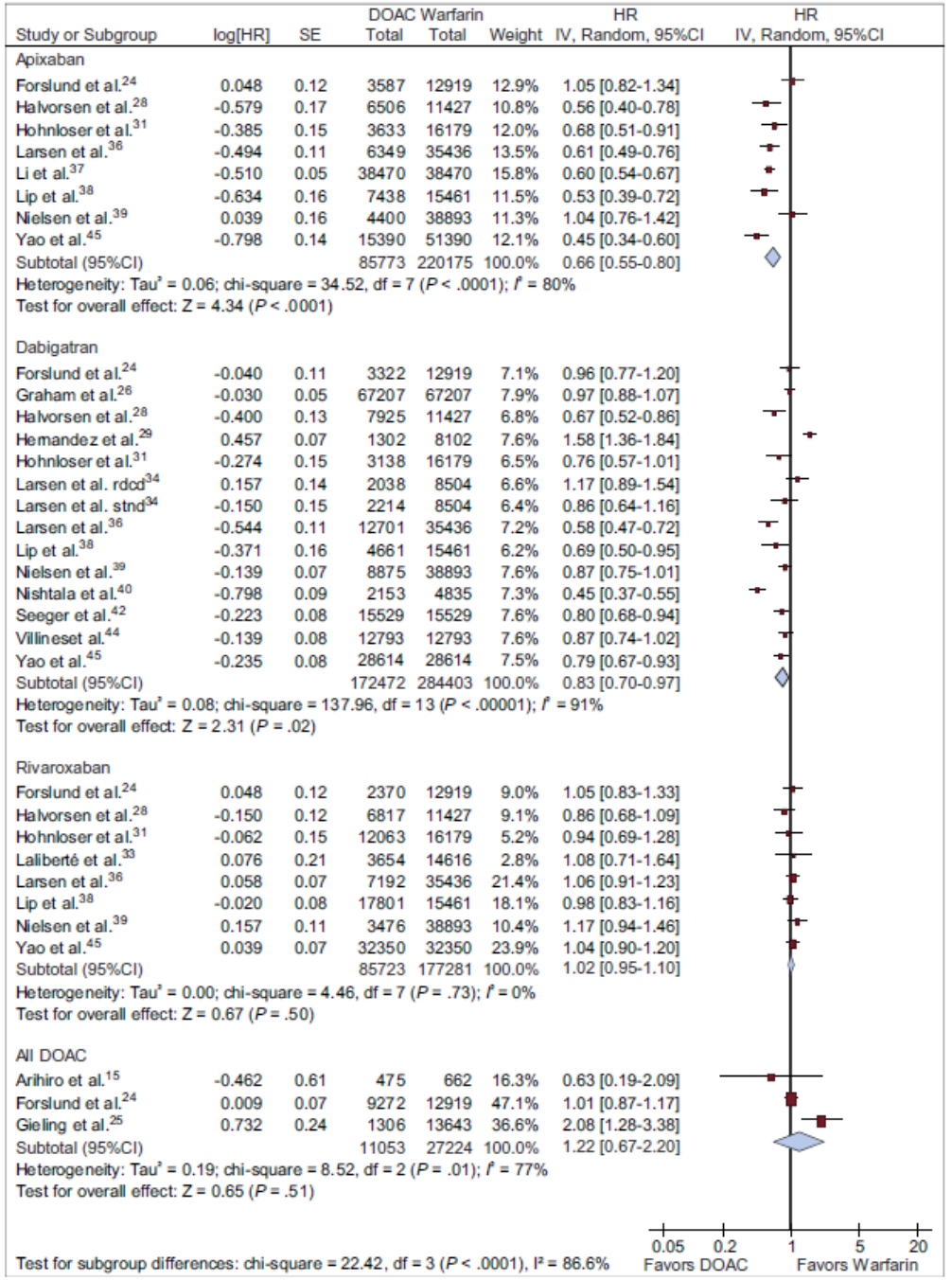
Hemorragia grave

Se observó una **reducción del riesgo de Hemorragia Grave tanto con apixaban como con dabigatran** en comparación con warfarina (HR 0.66, 95% CI 0.55–0.80; HR 0.81, 95% CI 0.69 to –0.95, respectivamente), **sin embargo la heterogeneidad estadística fue muy elevada entre los estudios.**

Apixaban
RRR
34%

Dabigatran
RRR
19%

Rivaroxaban no mostró una reducción del riesgo de Hemorragia Grave en comparación con warfarina (HR 1.02, 95% CI 0.95–1.10).



Escobar et al. Rev Esp Cardiol 2018

Hemorragia Intracraneal

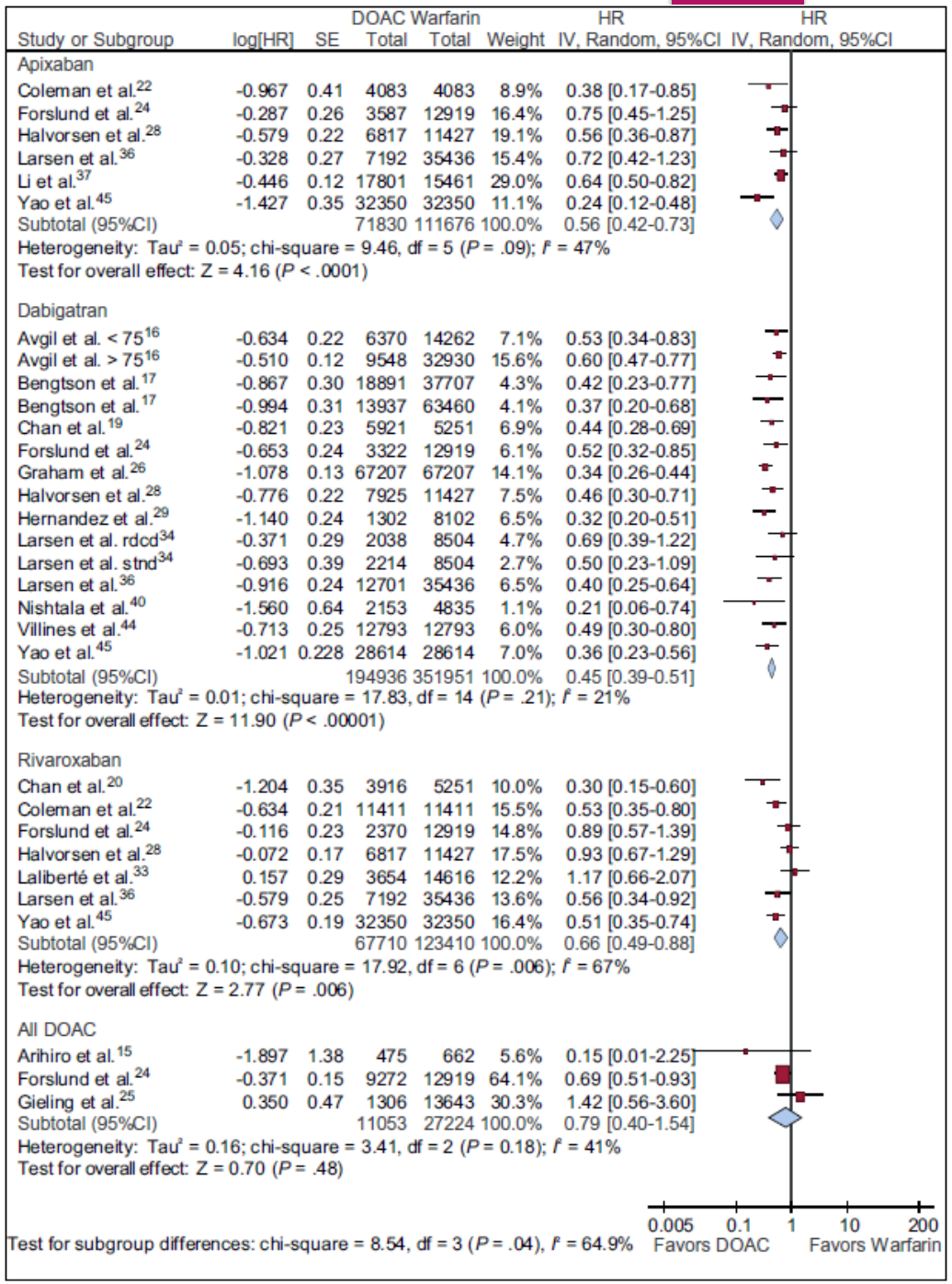
Tanto **apixaban como dabigatran y rivaroxaban redujeron significativamente el riesgo de HIC** en comparación con warfarina (HR 0.56, 95% CI 0.42–0.73; HR 0.42, 95% CI 0.37– 0.48; HR 0.66, 95% CI 0.49–0.88; respectivamente).

Apixaban
RRR
44%

Dabigatran
RRR
58%

Rivaroxaban
RRR
34 %

Escobar et al. Rev Esp Cardiol 2018



NACO: Farmacocinética

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Administración	Oral	Oral	Oral	Oral
Biodisponibilidad	6,5%	>80%	>50%	60%
Tmax (h)	1,25-3	2-4	1-3	1-2
Vida media (h)	12-14	9-13	8-15	9-10
Metabolismo hepático	No	CYP3A4	CYP3A4	CYP3A4
Eliminación renal	85%	66% (1/3 activa)	25%	33%
Interferencia con alimentos	No	No	No	No

Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease (Review)

Analysis 1.8. Comparison 1 Direct oral anticoagulants versus warfarin, Outcome 8 Intracranial haemorrhage.

Review: Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease

Comparison: 1 Direct oral anticoagulants versus warfarin

Outcome: 8 Intracranial haemorrhage

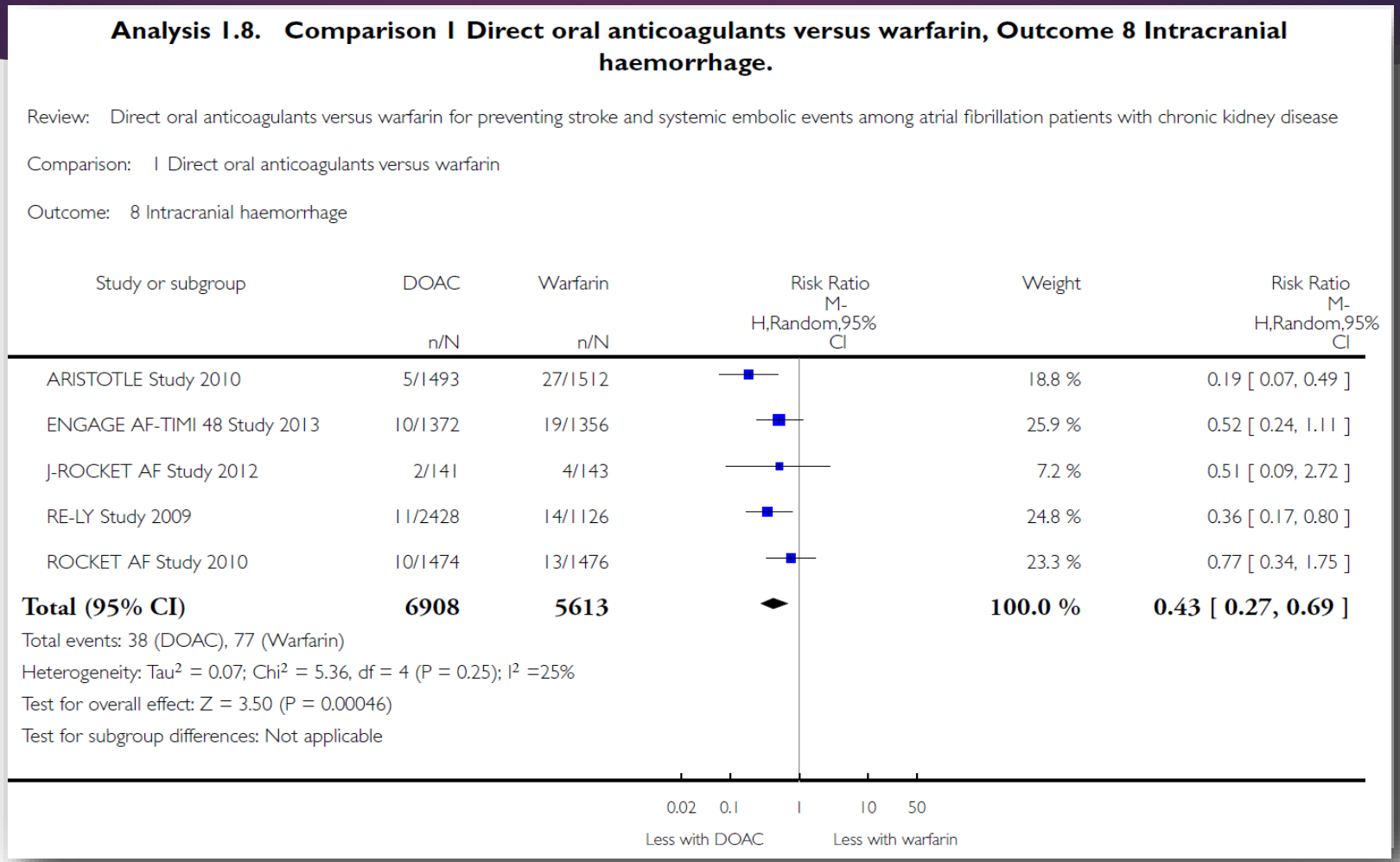
Study or subgroup	DOAC n/N	Warfarin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ARISTOTLE Study 2010	5/1493	27/1512		18.8 %	0.19 [0.07, 0.49]
ENGAGE AF-TIMI 48 Study 2013	10/1372	19/1356		25.9 %	0.52 [0.24, 1.11]
J-ROCKET AF Study 2012	2/141	4/143		7.2 %	0.51 [0.09, 2.72]
RE-LY Study 2009	11/2428	14/1126		24.8 %	0.36 [0.17, 0.80]
ROCKET AF Study 2010	10/1474	13/1476		23.3 %	0.77 [0.34, 1.75]
Total (95% CI)	**6908**	**5613**		**100.0 %**	**0.43 [0.27, 0.69]**

Total events: 38 (DOAC), 77 (Warfarin)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 5.36$, df = 4 (P = 0.25); $I^2 = 25\%$

Test for overall effect: Z = 3.50 (P = 0.00046)

Test for subgroup differences: Not applicable

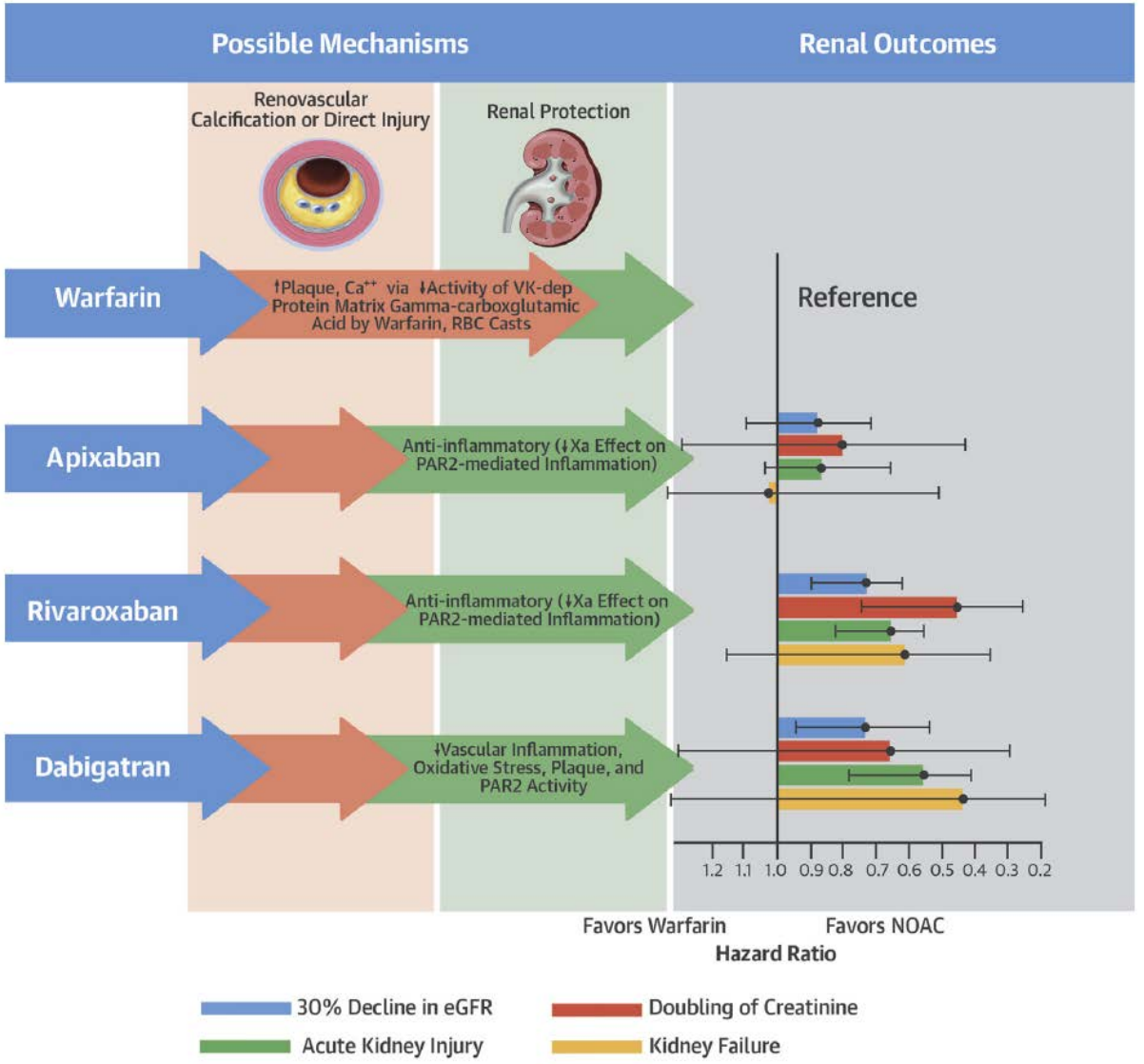


Kimachi M. Cochrane Database of Systematic Reviews 2017

Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation

The cumulative risk at the end of 2 years for each outcome was 24.4%, 4.0%, 14.8%, and 1.7% for >30% decline in eGFR, doubling of serum creatinine, AKI, and kidney failure, respectively.

CENTRAL ILLUSTRATION Renal Outcomes Associated With the Various Oral Anticoagulant Agents: Possible Mechanisms and Outcomes



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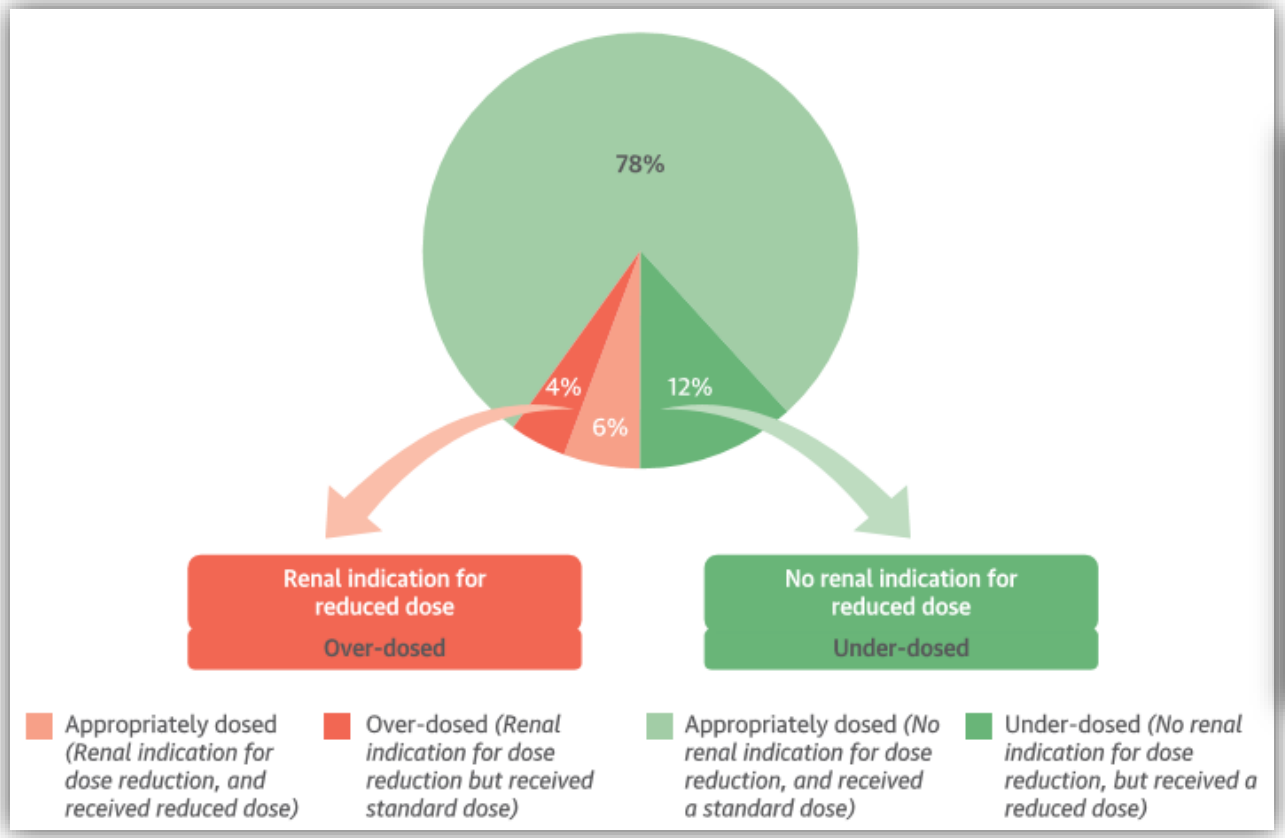
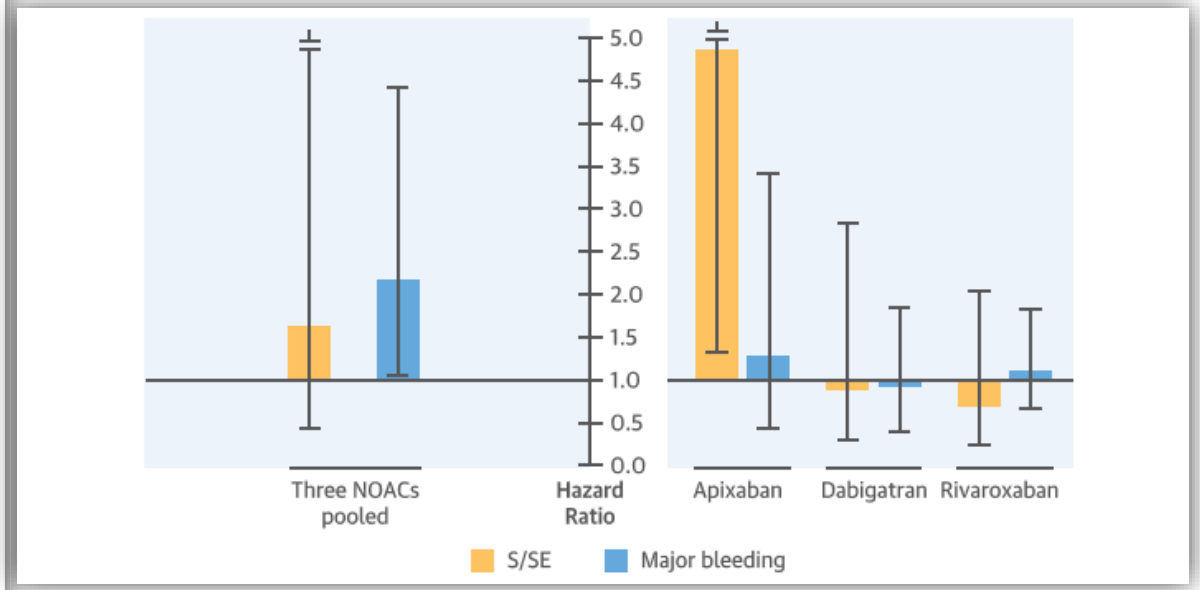
Non–Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction

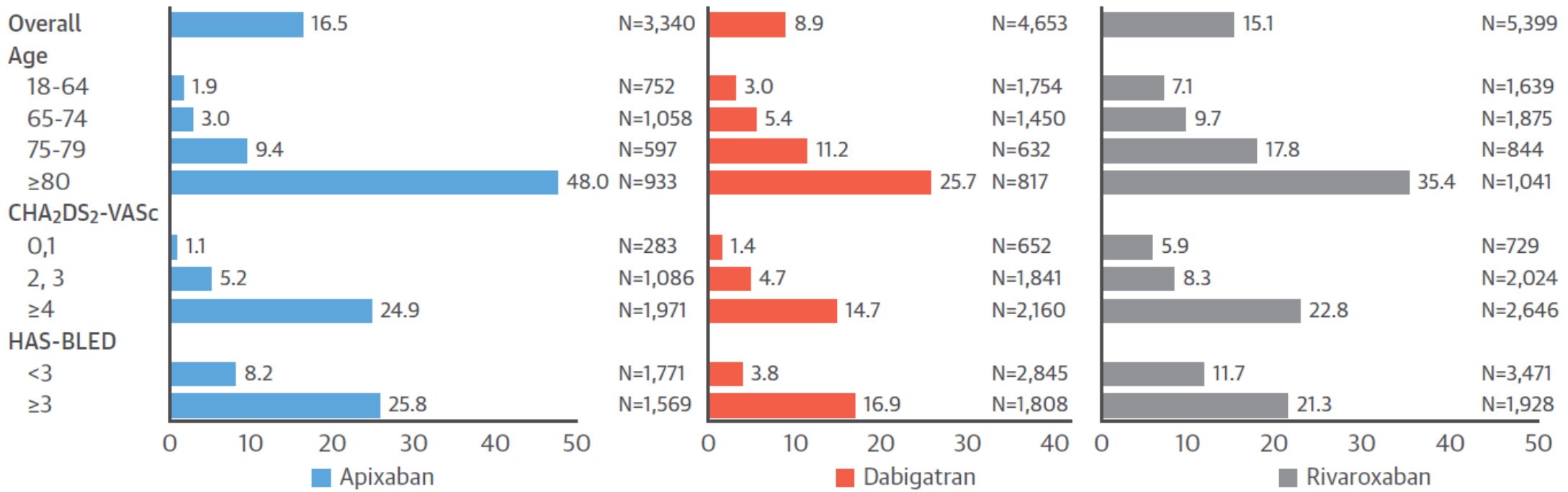




Yao X. J Am Coll Cardiol 2017

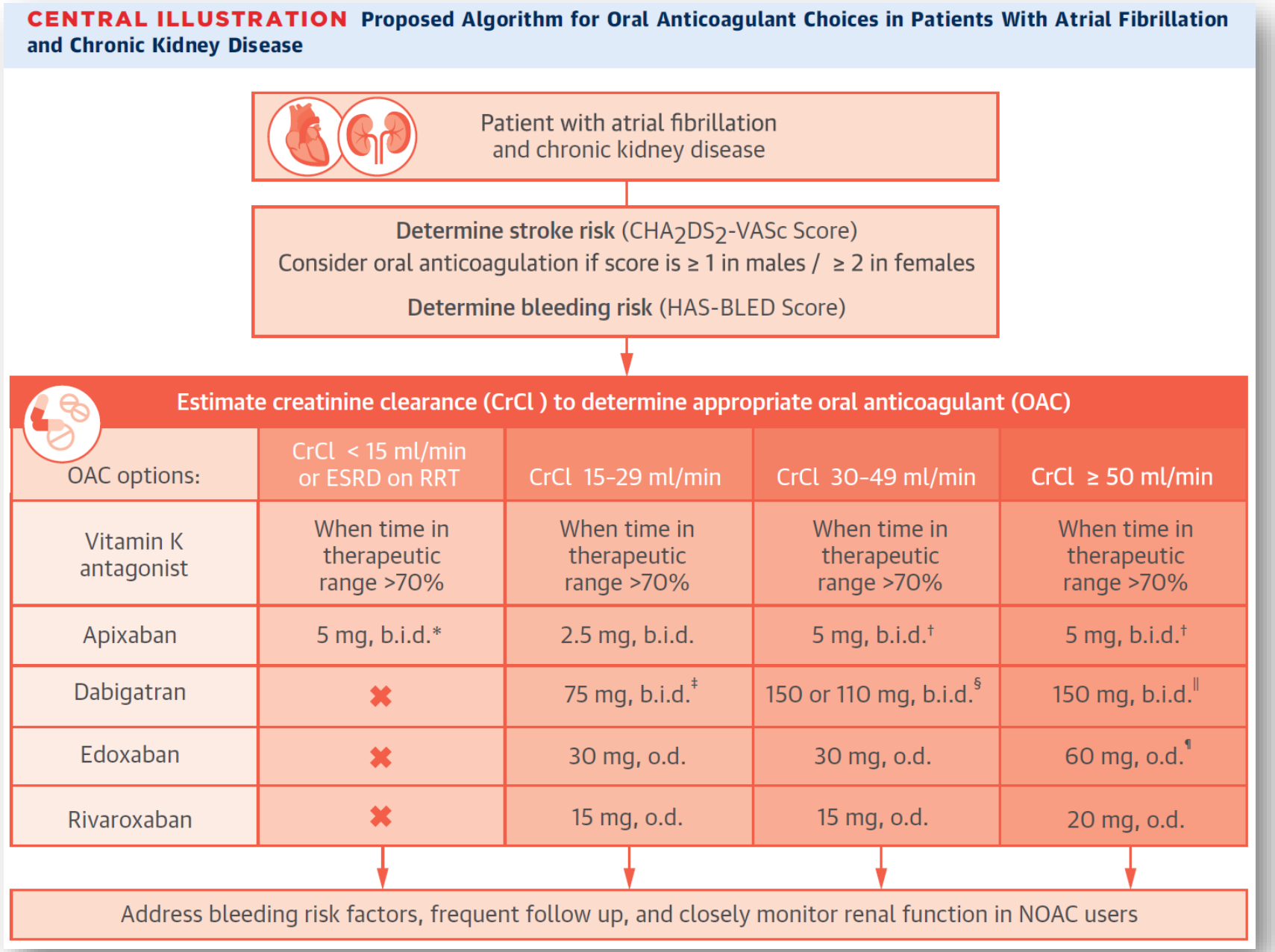
Non–Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction

FIGURE 2 Percentage of Patients Underdosed



Yao X. J Am Coll Cardiol 2017

CENTRAL ILLUSTRATION **Proposed Algorithm for Oral Anticoagulant Choices in Patients With Atrial Fibrillation and Chronic Kidney Disease**



OAC options:	CrCl < 15 ml/min or ESRD on RRT	CrCl 15–29 ml/min	CrCl 30–49 ml/min	CrCl ≥ 50 ml/min
Vitamin K antagonist	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%
Apixaban	5 mg, b.i.d.*	2.5 mg, b.i.d.	5 mg, b.i.d.†	5 mg, b.i.d.†
Dabigatran	✖	75 mg, b.i.d.‡	150 or 110 mg, b.i.d.§	150 mg, b.i.d.‖
Edoxaban	✖	30 mg, o.d.	30 mg, o.d.	60 mg, o.d.¶
Rivaroxaban	✖	15 mg, o.d.	15 mg, o.d.	20 mg, o.d.

Lau YC et al. J Am Coll Cardiol 2016

Conclusiones

- Actualmente los NACOS son el tratamiento anticoagulante de elección en pacientes con fibrilación auricular no valvular.
- Todos los estudios en la práctica clínica habitual siguen demostrando que son tan o más eficaces que los anti-vitamina K e igual o más seguros.
- Entre ellos el perfil de eficacia parece similar.
- Todos reducen de forma significativa la hemorragia intracraneal, aunque Apixaban parece mostrar un mejor perfil de seguridad respecto a las hemorragias graves.
- Se debe utilizar siempre la dosis adecuada de cualquier NACO de acuerdo con la función renal del paciente para evitar los efectos de la infra o sobredosificación.