Àrea Integral de Salut Barcelona Esquerra

Actualización en Fibrilación Auricular

Novedades en Anticoagulación

Elena Arbelo
Unidad de Arritmias – Hospital Clínic

IV JORNADA D'ATENCIÓ COMPARTIDA EN CARDIOLOGIA

9 de Novembre de 2017

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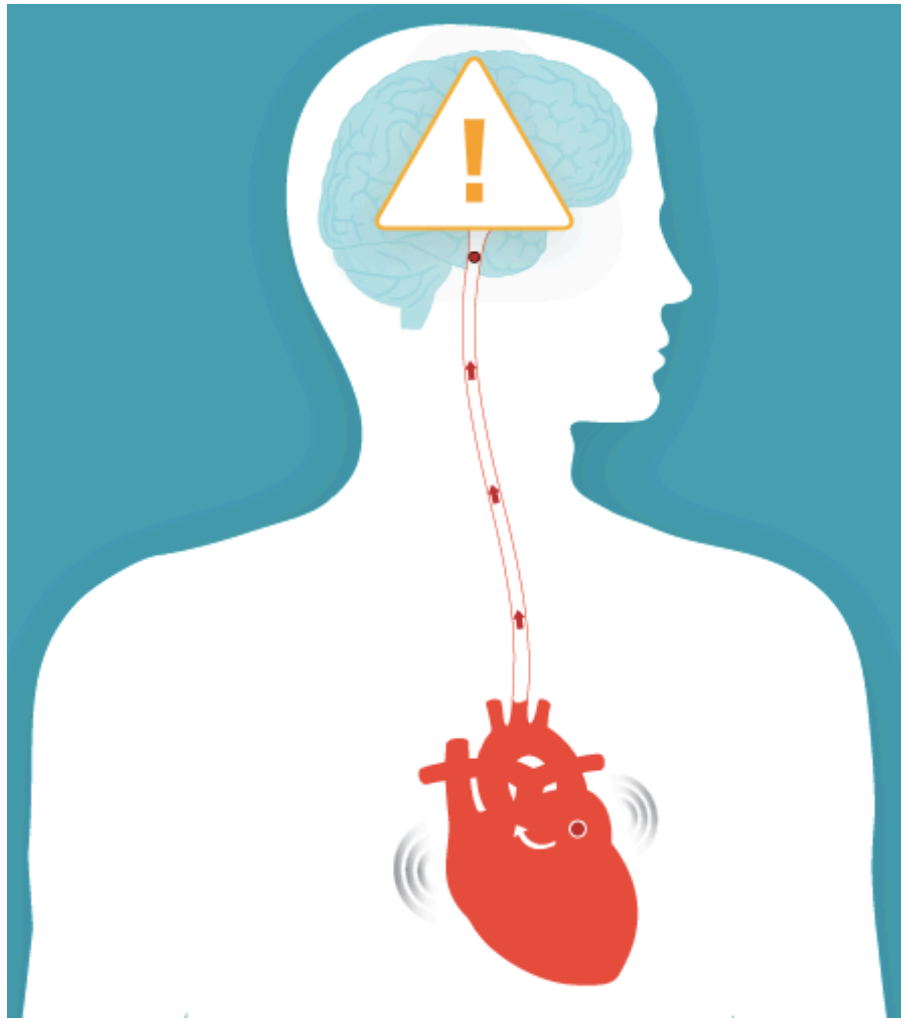
Overview

1. Real-world evidence:
    1. Use of oral anticoagulants
    2. Effectiveness and safety of oral anticoagulants
2. Guidelines recommendations on thromboprofilaxis
3. Oral anticoagulation in special situations
    1. Cardioversion
    2. Ablation
    3. Percutaneous coronary interventions
4. Conclusions



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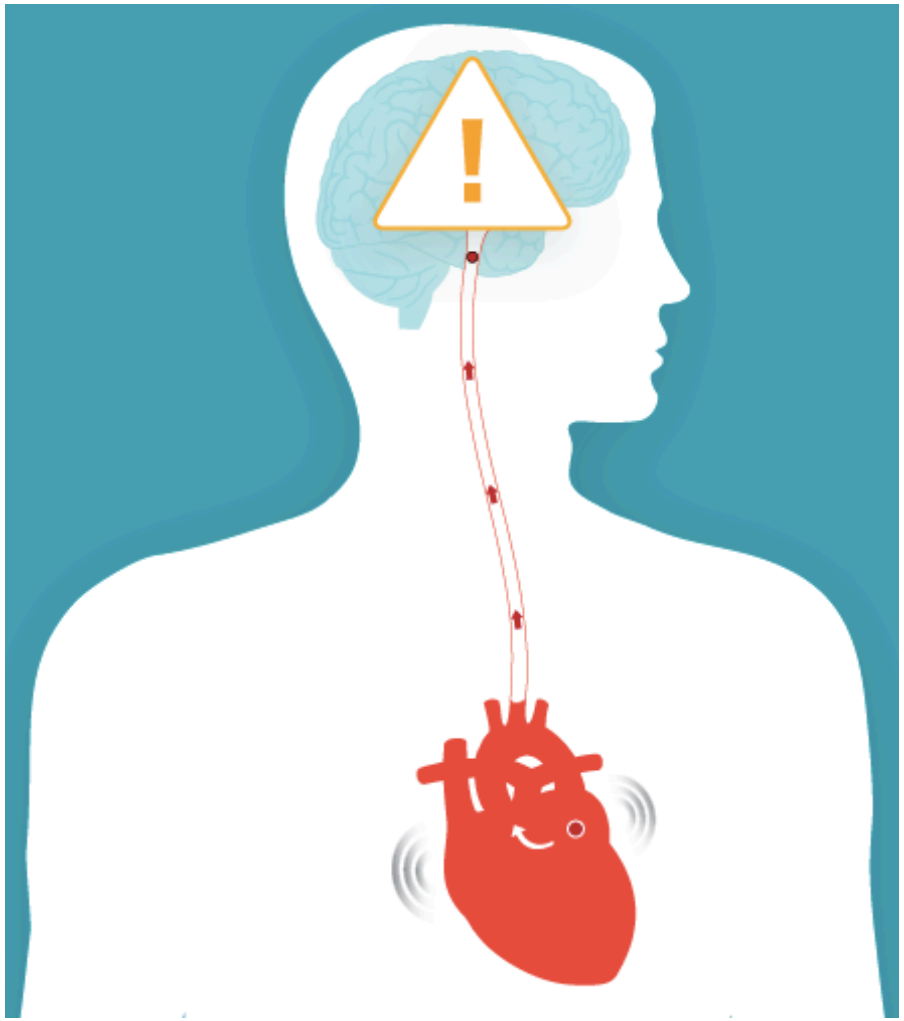

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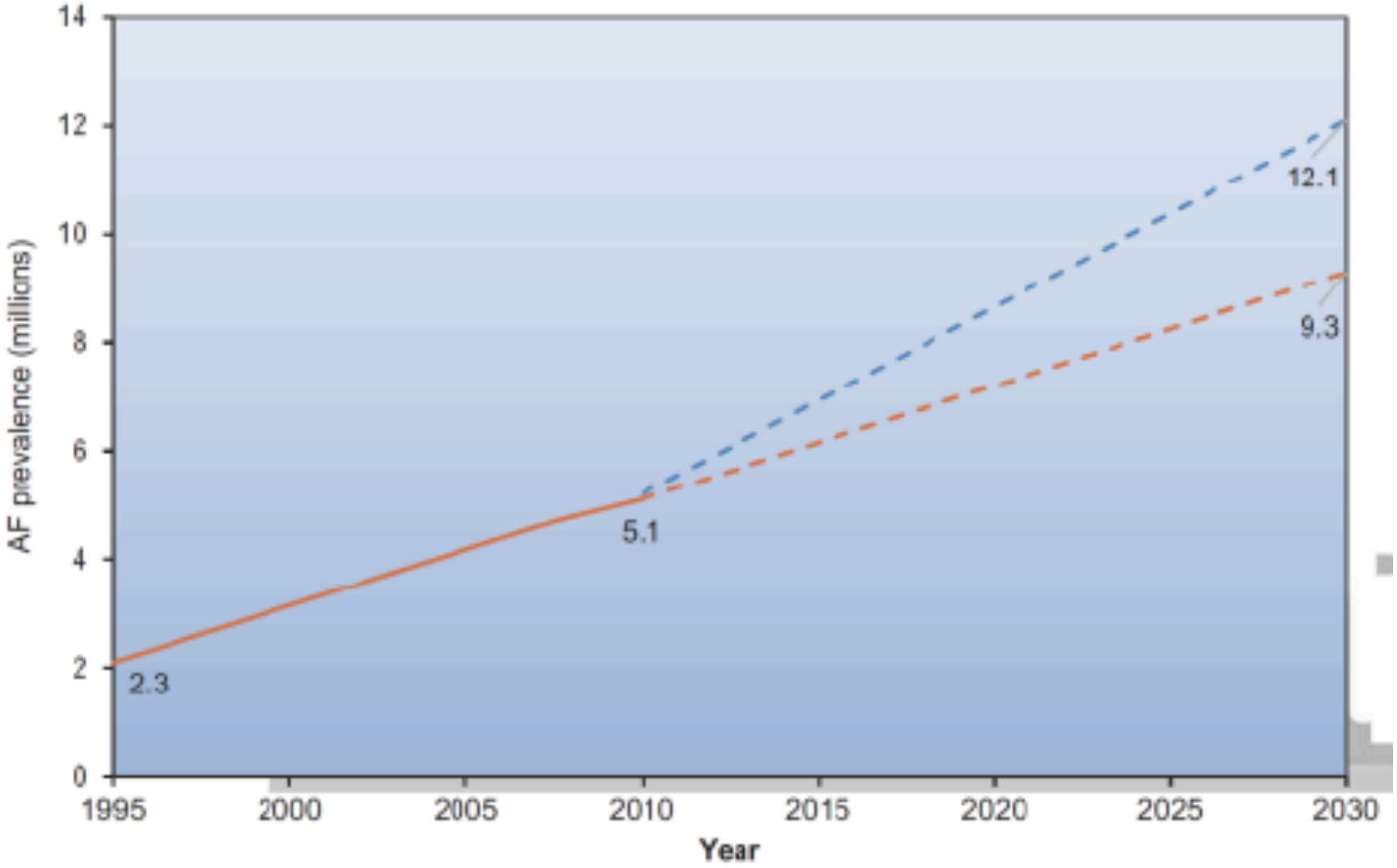
Temporal trends in AF



Benjamin Circulation 2017;135:e146

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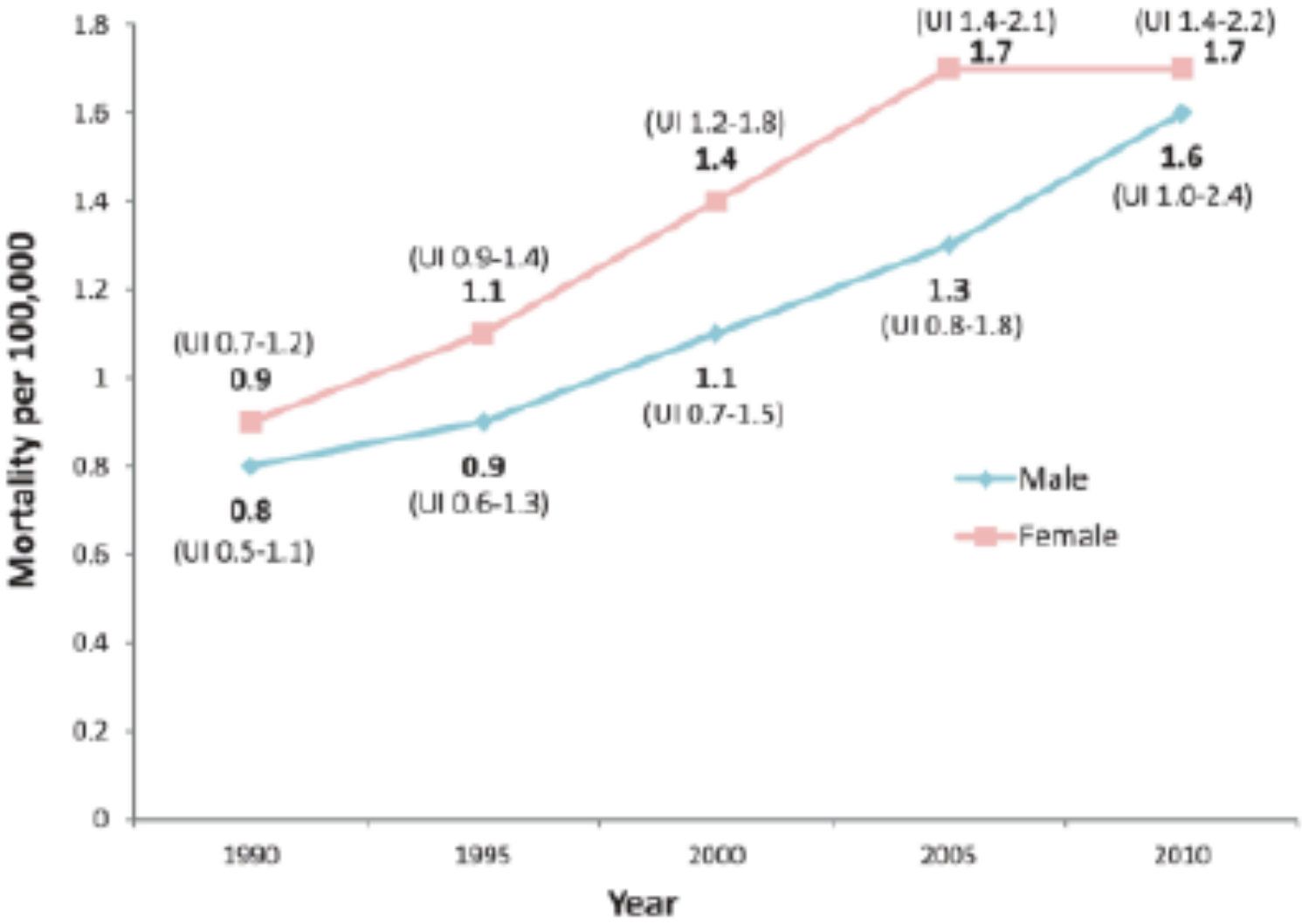
Temporal trends in AF



Chugh Circulation 2014;129:837

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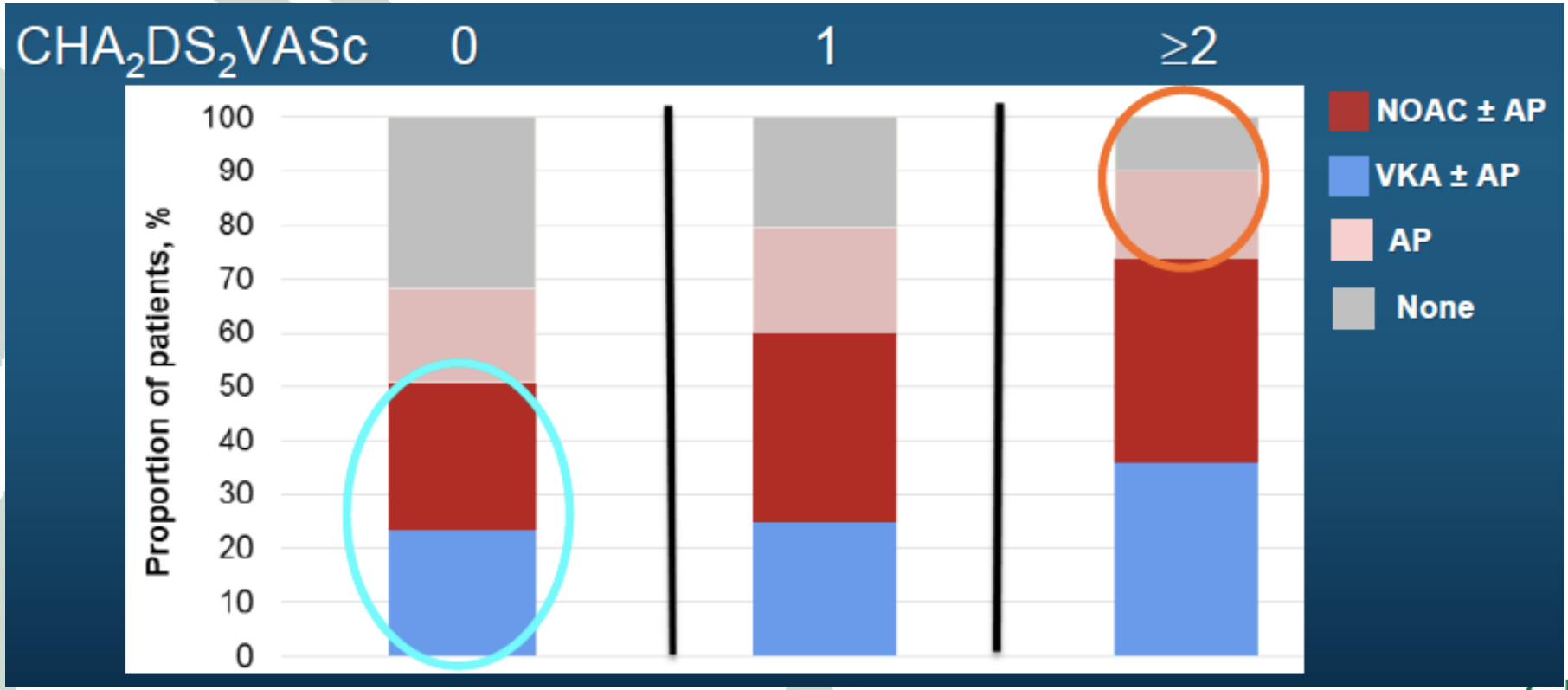
Suboptimal management of OAC in AF:
The GARFIELD Registry

- ✓ 28% high-risk patients (CHA2DS2VASc ≥2) are not anticoagulated
- ✓ 51% of very low-risk patients (CHA2DS2VASc 0) are anticoagulated



Camm AJ, et al. Heart 2017;103:307-14

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Changes in Thromboembolic Risk Profile and Antithrombotic Therapy Use Over a Decade:

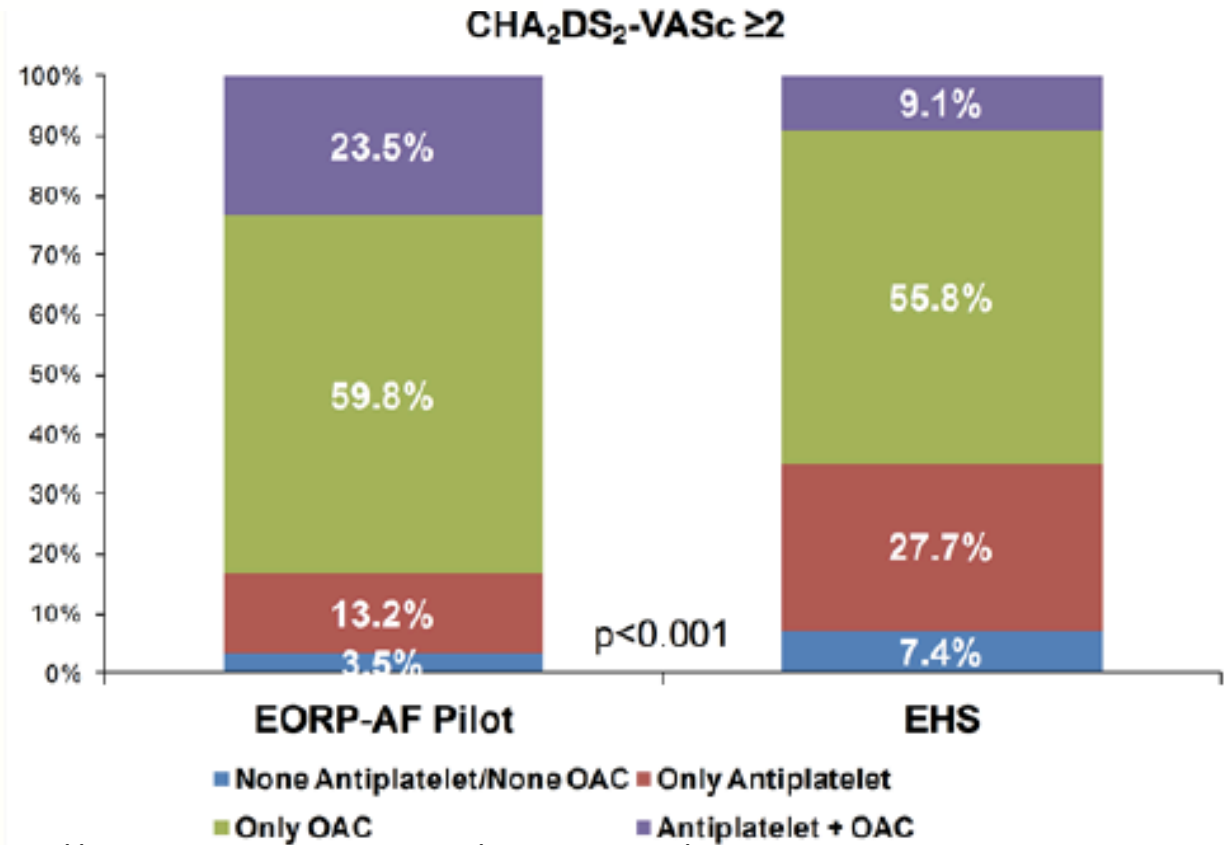
A Comparison of Euro Heart Survey on AF and EURObservational Research Programme Atrial Fibrillation Pilot Registry

Marco Proietti, Paul-Edouard Bouvet, Cécile Laroche, Robby Nieuwlaat, Harry J.G.M. Crijns, Aldo P. Maggioni, Deirdre A. Lane, Giuseppe Boriani, Gregory Y.H. Lip. on behalf of EORP-AF General Pilot Registry and Euro Heart Survey on AF Investigators

2005: Euro Heart Survey on AF (EHS)
2013: EURObservational Research Programme AF Pilot Registry (EORP-AF)

Propensity score matching

Overall cohort: 5206 patients



ESC Congres 2017. Available at http://congress365.escardio.org/Presentation/156607?_ga=2.228620764.1595826504.1510074363-1107808288.1478801549#.WgQCDrZDn-Y

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ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry

$CHADS_2$, %	
0	53.1
1	69.0
>1	81.6

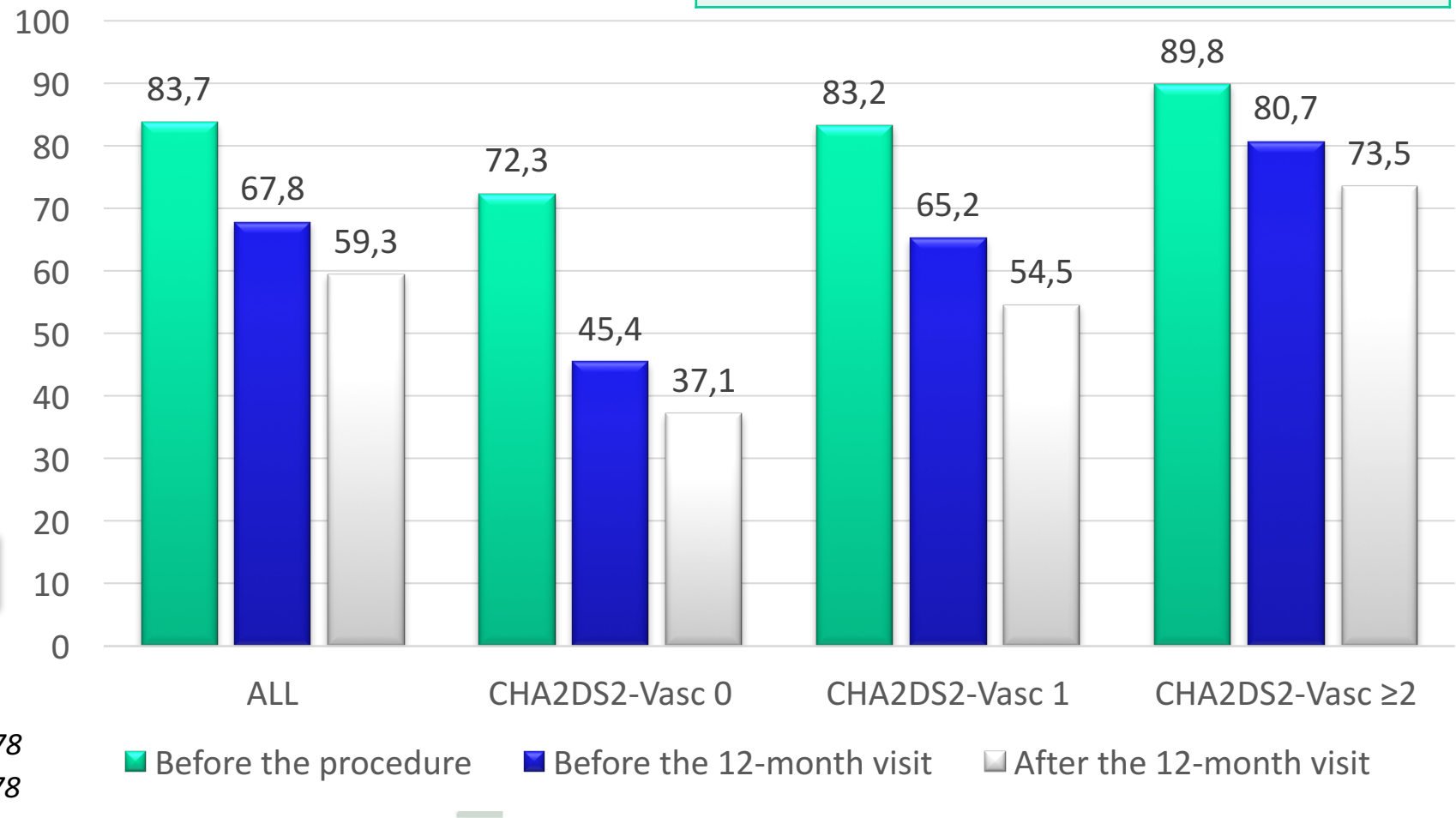
$CHADS_2$-Vasc, %	
0	48.0
1	63.3
>1	76.2

Pilot study

	AFA Pilot Study	AFA Long-term Study
Inclusion period	2010-2011	2012-2015
N at inclusion	1410	3630
N at 12-month FU	1300	3180

Anticoagulation at 12-m FU according to cardioembolic risk

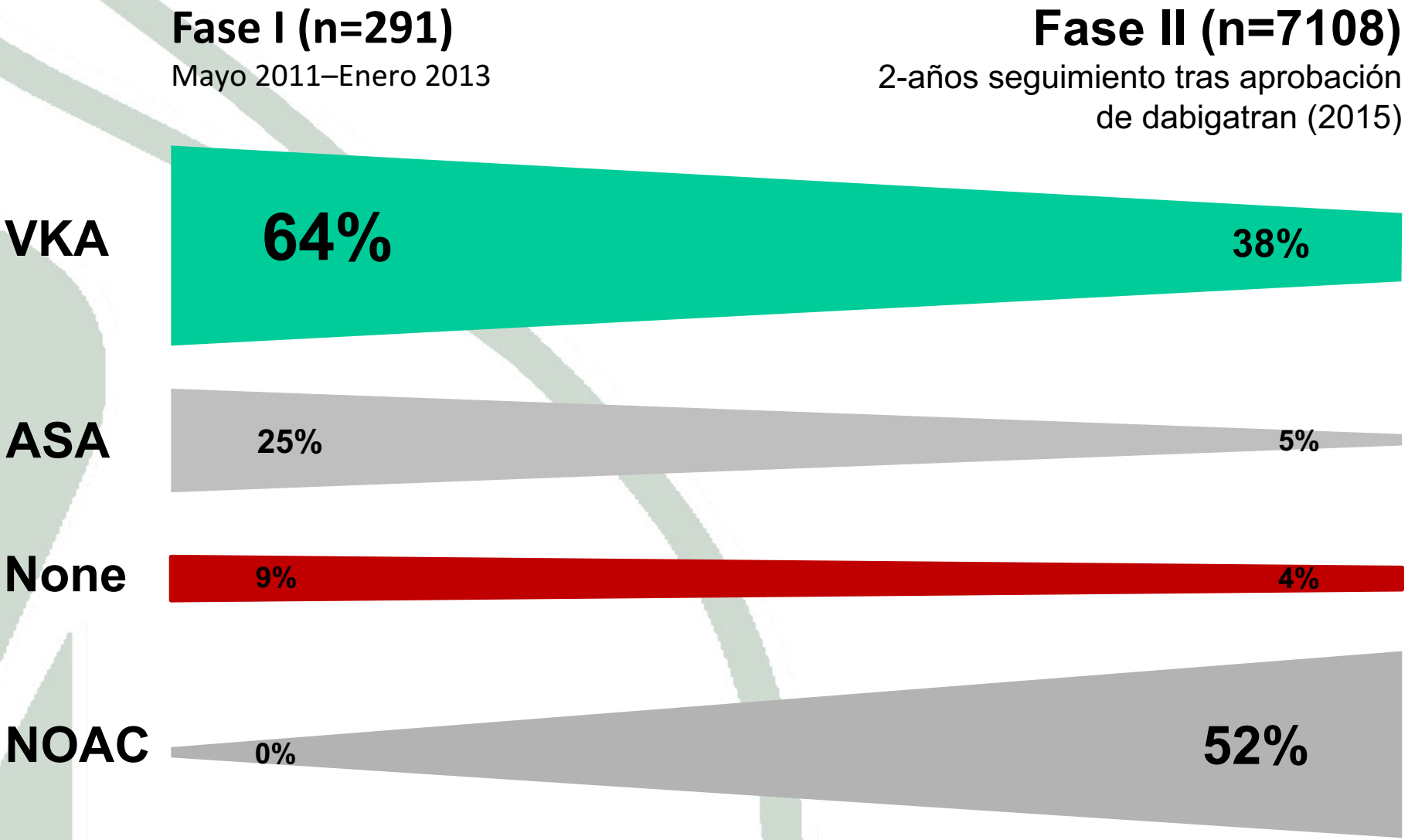
Long-term registry



Arbelo E et al. Eur Heart J 2014; 35:1466-1478

Arbelo E et al. Eur Heart J 2014; 35:1466-1478

Registro GLORIA^{TM}-AF Phase II (Europe): tendencia en tratamientos ACOs en Europa (AVK>ACODs)



Huisman MV et al. Presented at ESC 2015

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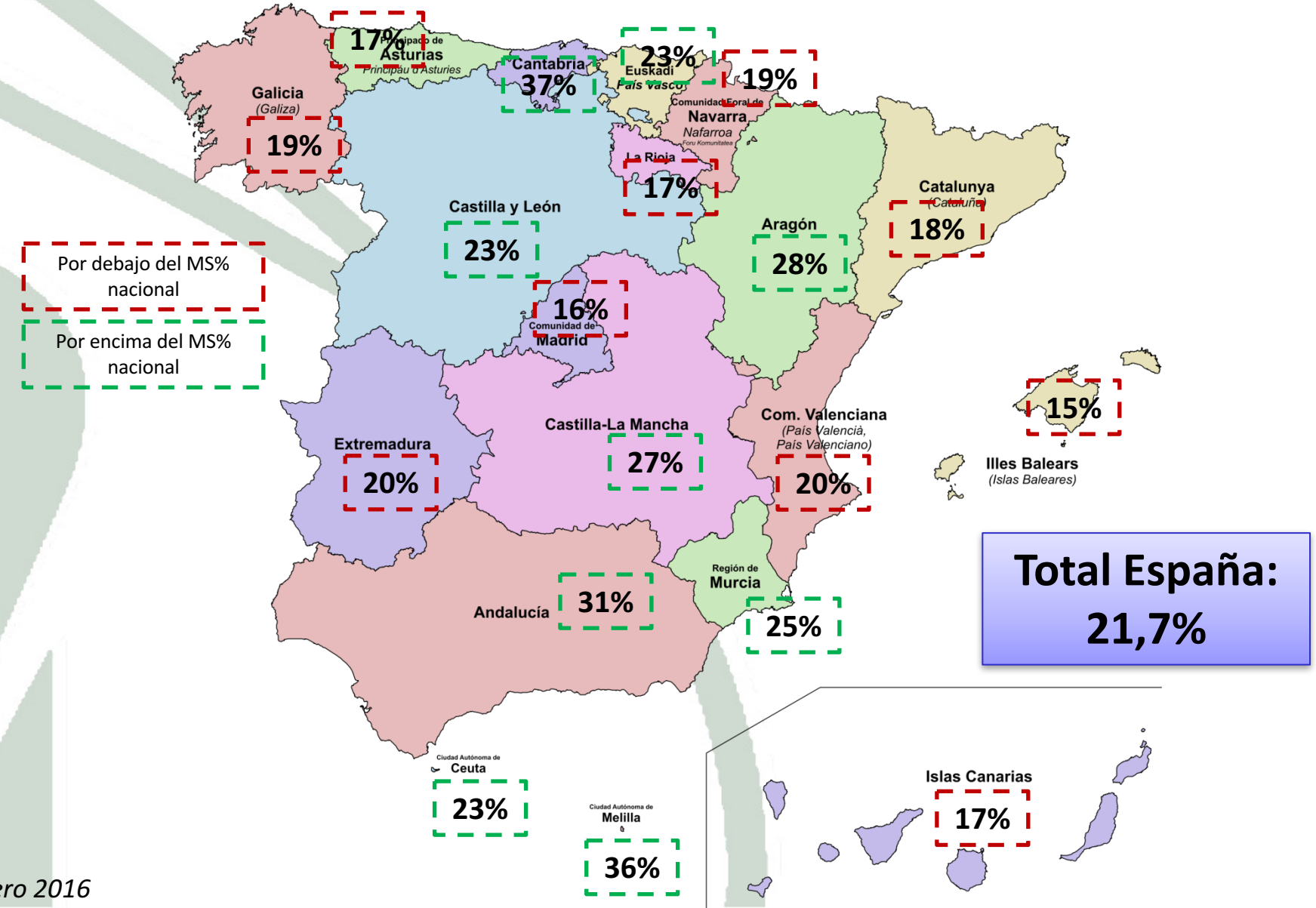
Utilización de ACOD en España
Diferencias de uso de los ACOD en España y otros países europeos

	ACOD Q1'16	AVK
EU5	43.2%	56.8%
Alemania	64.4%	35.6%
Reino Unido	29.8%	70.3%
Francia	43.4%	56.6%
Italia	43.9%	56.1%
España	23.9%	76.1%
Austria	65.5%	34.5%
Bélgica	69.3%	30.7%
Finlandia	22.1%	77.9
Suiza	63.2%	36.8
Portugal	57.0%	43.0%
Irlanda	46.4%	53.6%
Holanda	17.4%	82.6%
Suecia	50.6%	49.4%
Noruega	62.8%	37.2%
Dinamarca	56.8%	43.2%
Grecia	66.1%	33.1%
Rusia	27.3%	72.7%
Turquía	47.6%	52.4%
Polonia	54.2%	47.5%
República Checa	64.3%	35.7%

Fuente: IMS MIDAS Q1'16

Datos mercado NACOs vs Sintrom en España

Market Share (MS%) en Unidades por CCAA



Total España: 21,7%

Fuente: IMS - Enero 2016

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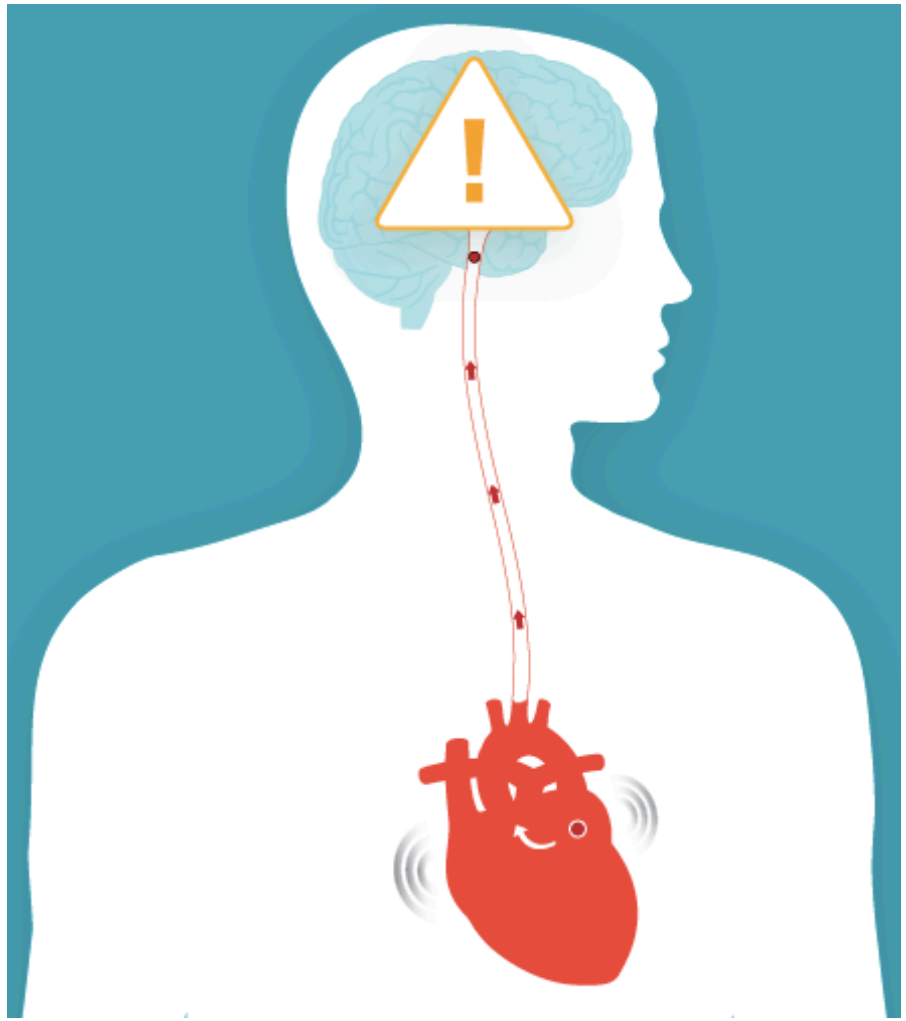

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Perfil de eficacia y seguridad de los ACOD

	Dabigatran[1] 150 mg	Dabigatran[1] 110 mg	Apixaban[2] 5/2.5 mg	Rivaroxaban[3,4] 20/15 mg	Edoxaban[5] 60/30 mg
HIC	↓ 59%	↓ 70%	↓ 58%	↓ 33%	↓ 53%
Sangrado mayor	↔	↓ 20%	↓ 31%	↔	↓ 20%
Sangrado GI *	↑ 48%	↔	↔	↑ 66%	↑ 23%
Ictus/ES	↓ 35%	↔	↓ 21%	↔	↔
Mortalidad	↔	↔	↓ 11%	↔	↔

* Los criterios utilizados para clasificar sangrado mayor GI diferían entre los ensayos.

No disponemos de estudios *head-to-head*, por lo que no se deben hacer comparaciones directas entre los distintos fármacos

1. Connolly et al. N Engl J Med 2009; 2. Granger et al. N Engl J Med 2011; 3. Patel et al. N Engl J Med 2011; 4. Sherwood et al. J Am Coll Cardiol 2015; 5. Giugliano et al. N Engl J Med 2013;

RCTs of NOACs for Stroke Prevention in AF:
Differences in patient risk profile and study protocol

	ROCKET AF n=14,264	ENGAGE AF n=21,105	ARISTOTLE n=18,201	RE-LY n=18,113
Mean $CHADS_2$	3.5	2.8	2.1	2.1
Heart failure*	64%	57%	35%	32%
Hypertension	91%	94%	87%	79%
Age ≥75 y	44%	40%	31%	40%
Diabetes mellitus	40%	36%	25%	23%
Prior stroke/TIA	52%	28%	19%	20%
Moderate CKD	21%	19%	15%	19%
Tested doses	1	2	1	2
Permanent drug discontinuation	25.3%	34.4%/33.0%	25.3	21.2%/20.7%

ROCKET-AF: Patel MR et al. NEJM 2011;365(10):883-891; ENGAGE-AF: Giugliano RP4 .e2t %al. N Engl J Med 2013;369(22):2093-2104
ARISTOTLE: Granger CB et al. N Engl J Med. 2011;365(11):981–992; RE-LY: Connolly SJ et al. N Engl J Med. 2009;361(12):1139–1151

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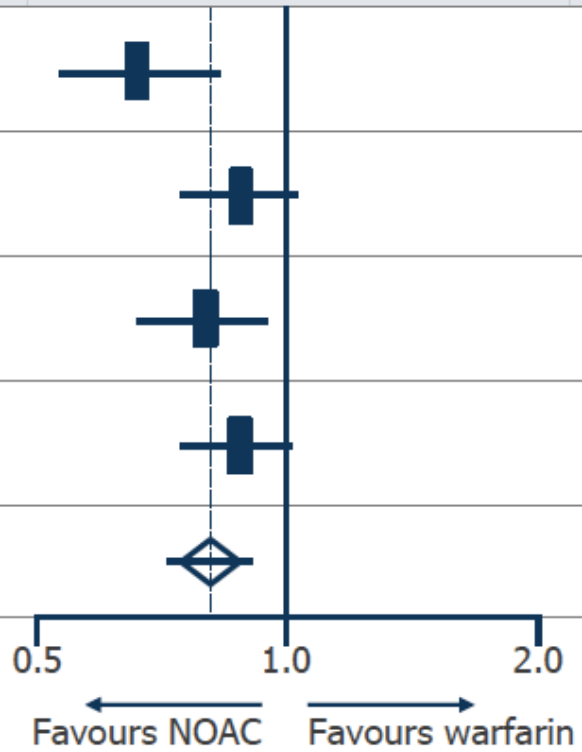
Meta-analysis: Efficacy of NOACs vs warfarin for stroke prevention in patients with NVAF

Stroke or systemic embolism						
Study	NOAC (events)	Warfarin (events)	RR (95% CI)	RR (95% CI)	p-value for interaction	p-value for heterogeneity
RE-LY (dabigatran)*	134/6076	199/6022		0.66 (0.53–0.82)	0.0001	
ROCKET AF (rivaroxaban)†¶	269/7081	306/7090		0.88 (0.75–1.03)	0.12	
ARISTOTLE (apixaban)‡¶	212/9120	265/9081		0.80 (0.67–0.95)	0.012	0.13
ENGAGE AF-TIMI 48 (edoxaban)§¶	296/7035	337/7036		0.88 (0.75–1.02)	0.10	
Combined (random)	911/29 312	1107/29 229		0.81 (0.73–0.91)	<0.0001	

Data are n/N, unless otherwise indicated



Head-to-head studies do not exist, and direct comparisons between agents may not be made

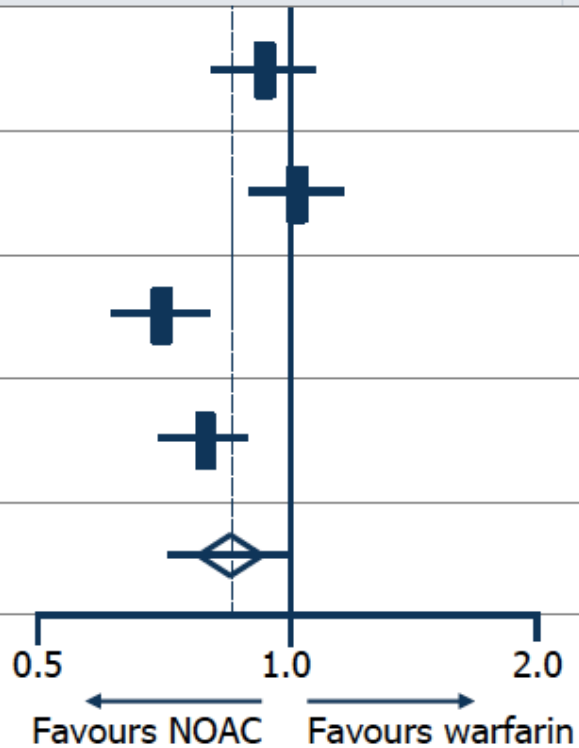
*150 mg BID; †20 mg OD; ‡5 mg BID; §60 mg OD; ¶Lower dose in selected patients. CI: confidence interval; NVAF: non-valvular atrial fibrillation; RR: relative risk

Ruff CT, et al. Lancet 2014;383:955–96

Meta-analysis: Safety of NOACs vs warfarin for stroke prevention in patients with NVAF

Major bleeding						
Study	NOAC (events)	Warfarin (events)	RR (95% CI)	RR (95% CI)	p-value for interaction	p-value for heterogeneity
RE-LY (dabigatran)*	375/6076	397/6022		0.94 (0.82–1.07)	0.34	0.001
ROCKET AF (rivaroxaban)†¶	395/7111	386/7125		1.03 (0.90–1.18)	0.72	
ARISTOTLE (apixaban)‡¶	327/9088	462/9052		0.71 (0.61–0.81)	<0.0001	
ENGAGE AF-TIMI 48 (edoxaban)§¶	444/7012	557/7012		0.80 (0.71–0.90)	0.0002	
Combined (random)	1541/29 287	1802/29 211		0.86 (0.73–1.00)	0.06	

Data are n/N, unless otherwise indicated



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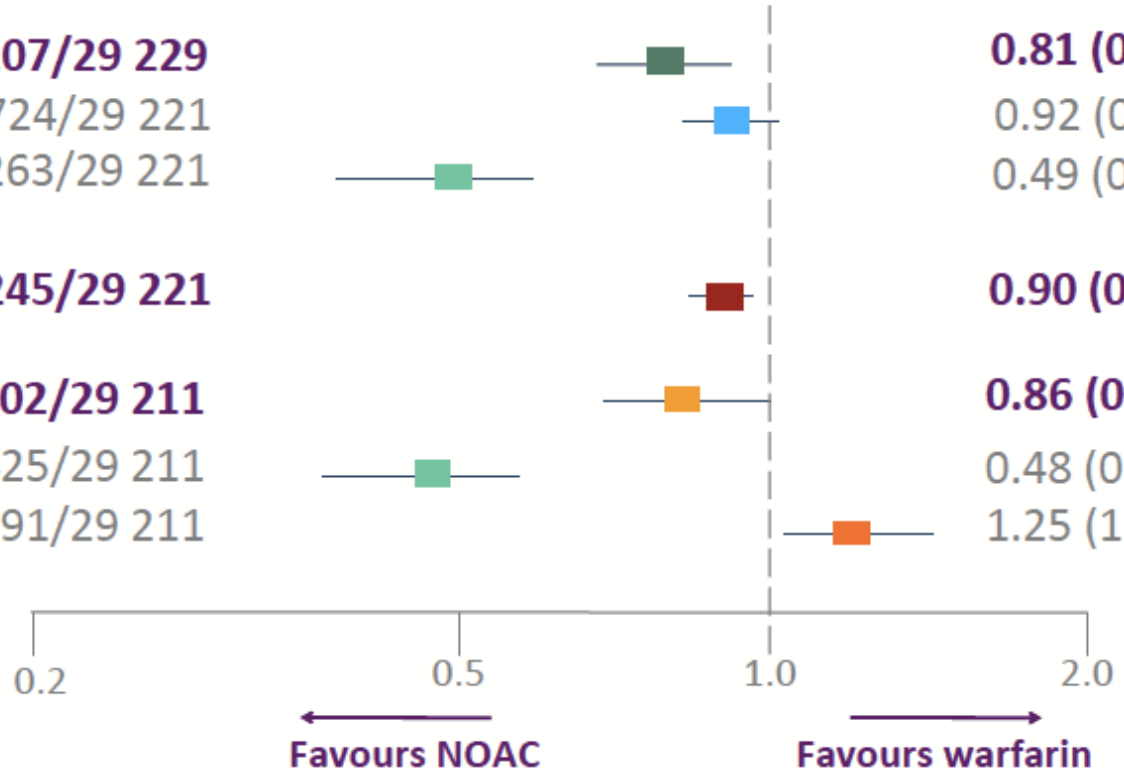
Ruff CT, et al. Lancet 2014;383:955–96

RCTs of NOACs for Stroke Prevention in AF:
Meta-analysis de estudios randomizados

OUTCOME	NOAC (events)	Warfarin (events)	Relative Risk (95% CI)	p
STROKE/SE	**911/29 312**	**1 107/29 229**	**0.81 (0.73–0.91)**	**<0.0001**
Ischemic stroke	665/29 292	724/29 221	0.92 (0.83–1.02)	0.10
Hemorrhagic stroke	130/29 292	263/29 221	0.49 (0.38–0.64)	<0.0001
MORTALITY	**2022/29 292**	**2245/29 221**	**0.90 (0.85–0.95)**	**0.0003**
MAJOR BLEEDING	**1 541/29 287**	**1 802/29 211**	**0.86 (0.73–1.00)**	**0.06**
ICH	204/29 287	425/29 211	0.48 (0.39–0.59)	<0.0001
GI bleeding	751/29 287	591/29 211	1.25 (1.01–1.55)	0.043



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

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Randomized Clinical Trials: Strengths and Limitations

RCT

Clinical practice

- Uncertain generalizability
- Limited data on the interactions of investigated treatment with concomitant illnesses
- Unknown adherence to treatment outside the trial setting
- Residual safety concerns (e.g., unexpected SAEs)
- Limited follow-up
- The effect of different dosing regimens

Effectiveness of NOACS in the real-world setting

28 estudios usando bases de datos nacionales o de seguros de salud (hasta Enero 2017)

A: Any stroke or systemic embolism

	Dabigatran*	Rivaroxaban	Apixaban
RCT	0.66 (0.53-0.82) 0.91 (0.74-1.11)	0.88 (0.75-1.03)	0.79 (0.66-0.95)
RWD	**0.93 (0.77-1.14)**	**0.87 (0.71-1.07)**	**0.67 (0.46-0.98)**
Studies	n=2	n=2	n=1
	I^2 = 0%	I^2 = 0%	---

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

Ntaios G, et al. Stroke 2017; doi:10.1161/STROKEAHA.117.017549

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Effectiveness of NOACS in the real-world setting

A: Ischemic stroke

	Dabigatran	Rivaroxaban	Apixaban
RCT	0.76 (0.60-0.98) 1.11 (0.89-1.40)	0.94 (0.75-1.17)	0.92 (0.74-1.13)
RWD	**0.96 (0.80-1.16)**	**0.89 (0.76-1.04)**	**0.95 (0.75-1.19)**
Studies	n=12	n=5	n=3
	I^2 = 83%	I^2 = 0%	I^2 = 0%

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

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All-cause mortality of NOACS in the real-world setting

Apixaban y dabigatran se asocian con menor riesgo de mortalidad

A: All-cause mortality

	Dabigatran	Rivaroxaban	Apixaban
RCT	0.88 (0.77-1.00) 0.91 (0.80-1.03)	0.85 (0.70-1.02)	0.89 (0.80-0.998)
RWD	**0.63 (0.52-0.79)**	**0.67 (0.35-1.30)**	**0.65 (0.56-0.75)**
Studies	n=6	n=2	n=1
	I^2 = 83%	I^2 = 92%	---

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

Ntaios G, et al. Stroke 2017; doi:10.1161/STROKEAHA.117.017549

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Safety of NOACS in the real-world setting

apixaban con menor sangrado mayor

A: Major bleeding

	Dabigatran*	Rivaroxaban	Apixaban
RCT	0.93 (0.81-1.07) 0.80 (0.69-0.93)	1.04 (0.90-1.20)	0.69 (0.60-0.80)
RWD	**0.83 (0.65-1.05)**	**1.00 (0.92-1.08)**	**0.55 (0.48-0.63)**
Studies	n=15	n=8	n=4
	I^2 = 93%	I^2 = 0%	I^2 = 0%

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

Ntaios G, et al. Stroke 2017; doi:10.1161/STROKEAHA.117.017549

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Safety of NOACS in the real-world setting

apixaban con menor sangrado gastrointestinal

A: ICH

	Dabigatran	Rivaroxaban	Apixaban
RCT	0.40 (0.27-0.60) 0.31 (0.20-0.47)	0.67 (0.47-0.93)	0.42 (0.30-0.58)
RWD	**0.42 (0.37-0.49)**	**0.64 (0.47-0.86)**	**0.45 (0.31-0.63)**
Studies	n=15	n=7	n=4
	I^2 = 28%	I^2 = 63%	I^2 = 34%

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Ntaios G, et al. Stroke 2017; doi:10.1161/STROKEAHA.117.017549

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Safety of NOACS in the real-world setting

dabigatran y rivaroxaban con mayor riesgo de hemorragia gastrointestinal

A: GI bleeding

	Dabigatran	Rivaroxaban	Apixaban
RCT	1.50 (1.19-1.89) 1.10 (0.86-1.41)	1.66 (1.34-2.05)	0.89 (0.70-1.15)
RWD	**1.20 (1.06-1.36)**	**1.24 (1.08-1.41)**	**0.63 (0.42-0.95)**
Studies	n=13	n=4	n=2
	I^2 = 72%	I^2 = 0%	I^2 = 73%

*Upper row: HR for 150mg bid, Lower row: HR for 110mg bid

Systematic review and meta-analysis of 28 observational studies comparing ≥1NOAC vs. VKA, published until January 2017

Ntaios G, et al. Stroke 2017; doi:10.1161/STROKEAHA.117.017549

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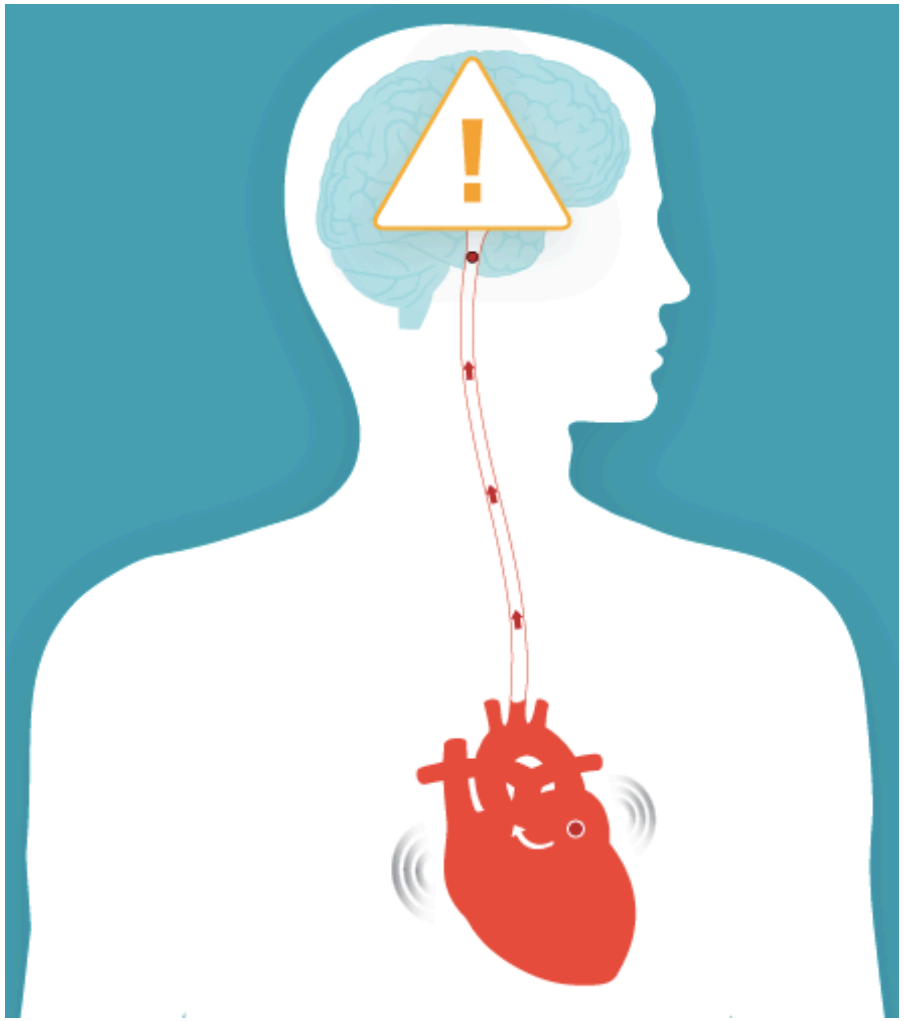

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Recommendations for prediction of stroke and bleeding risk

Recommendations	Class[a]	Level[b]
The CHA_2DS_2-VASc score is recommended for stroke risk prediction in patients with AF.	I	A
Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.	IIa	B
Biomarkers such as high-sensitivity troponin and natriuretic peptide may be considered to further refine stroke and bleeding risk in AF patients.	IIb	B

Kirchov P et al. Eur Heart J 2016;37:2893-2962.

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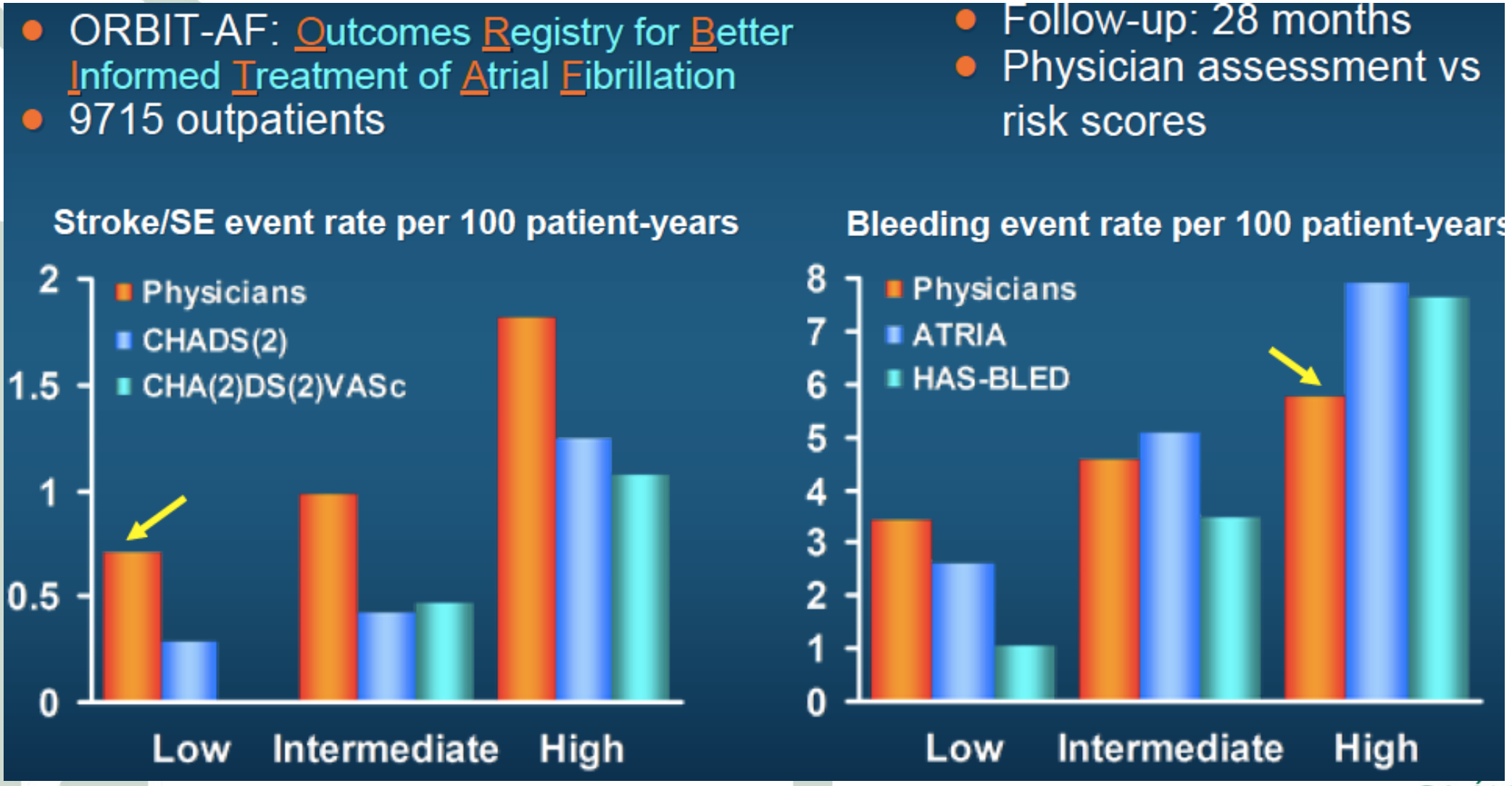
Do Physicians Need a Risk Score?

- ORBIT-AF: Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
- 9715 outpatients
- Follow-up: 28 months
- Physician assessment vs risk scores



Steinberg BA, et al. Am Heart J 2016;181:145-52

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Clinical risk factors for stroke, transient ischemic attack, and systemic embolism in the CHA2DS2-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

Kirchov P et al. Eur Heart J 2016;37:2893-2962.

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Contemporary guidelines in Europe and North America

CLINICAL PRACTICE GUIDELINE

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

ESC EUROPEAN SOCIETY OF CARDIOLOGY®

	The US guideline recommendations		ESC guideline recommendations	
	Women	Men	Women	Men
CHA_2DS_2-VASc = 0	N/A*	No therapy	N/A*	No therapy
CHA_2DS_2-VASc = 1	OAC, aspirin, or no therapy		No therapy	Consider OAC
CHA_2DS_2-VASc = 2	Recommend OAC		Consider OAC	Recommend OAC
CHA_2DS_2-VASc ≥ 3	Recommend OAC		Recommend OAC	Recommend OAC

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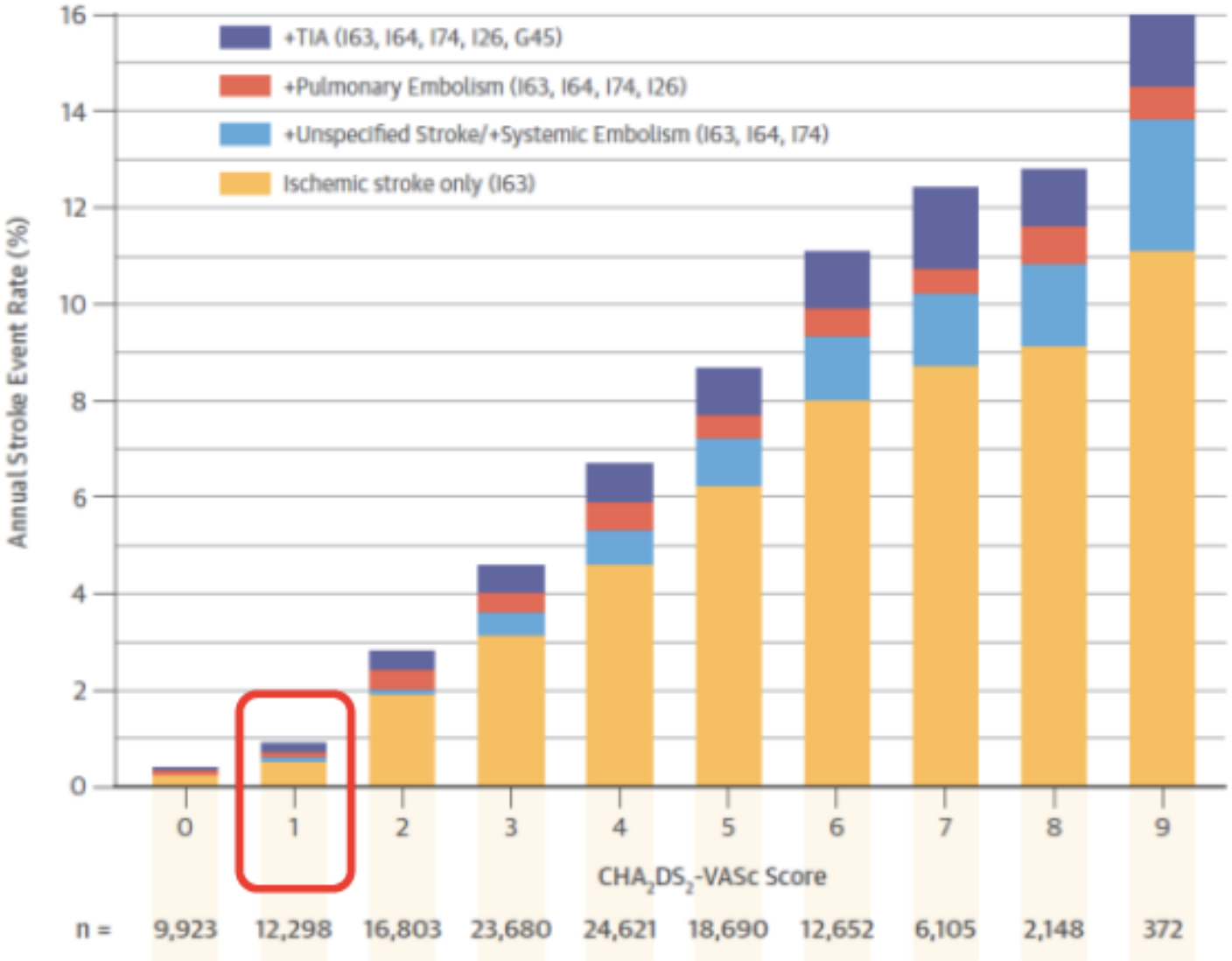
http://dx.doi.org/10.1016/j.jacc.2014.10.052

ORIGINAL INVESTIGATIONS

Benefit of Anticoagulation Unlikely in Patients With Atrial Fibrillation and a CHA_2DS_2-VASc Score of 1

After having studied the prevalence of anticoagulant treatment at baseline, all patients who had been exposed to warfarin any time within 6 months before the index date or during the study period (n = 144,111) were excluded from further study.



Friberg et al. J Am Coll Cardiol; 2015: 65(3):225-32

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Should we provide antithrombotics?

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ORIGINAL INVESTIGATIONS

Oral Anticoagulation, Aspirin, or No Therapy in Patients With Nonvalvular AF With 0 or 1 Stroke Risk Factor Based on the CHA_2DS_2-VASc Score

CONCLUSIONS

Low-risk patients (i.e., CHA_2DS_2-VASc = 0 [male], = 1 [female]) have a truly low risk for stroke, intracranial bleeding, and major bleeding. With 1 additional stroke risk factor (i.e., CHA_2DS_2-VASc = 1 [male], = 2 [female]), there was a significant increase in event rates, particularly mortality, if nonanticoagulated.

	No Treatment		Aspirin Initiated		Warfarin Initiated	
	Events/PY	Rate	Events/PY	Rate	Events/PY	Rate
No risk factors						
ITT						
Stroke	65/13,370	0.49	16/2,048	0.78	27/3,078	0.88
Ischemic stroke	58/13,372	0.43	16/2,048	0.78	23/3,080	0.75
Bleeding	144/13,329	1.08	31/2,038	1.52	51/3,067	1.66
ICH	20/13,387	0.15	2/2,053	0.10	5/3,093	0.16
Death	519/13,401	3.87	64/2,054	3.12	68/3,093	2.20
1 risk factor*						
ITT						
Stroke	133/8,571	1.55	43/2,964	1.45	55/5,172	1.06
Ischemic stroke	129/8,573	1.50	43/2,964	1.45	53/5,173	1.02
Bleeding	233/8,516	2.74	68/2,949	2.31	124/5,130	2.42
ICH	31/8,611	0.36	6/2,981	0.20	23/5,189	0.44
Death	978/8,630	11.3	169/2,984	5.66	208/5,197	4.00

Lip et al. J Am Coll Cardiol 2015;65(14)

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Net Clinical Benefit for Oral Anticoagulation, Aspirin, or No Therapy in Nonvalvular Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA_2DS_2-VASc Score (Beyond Sex)

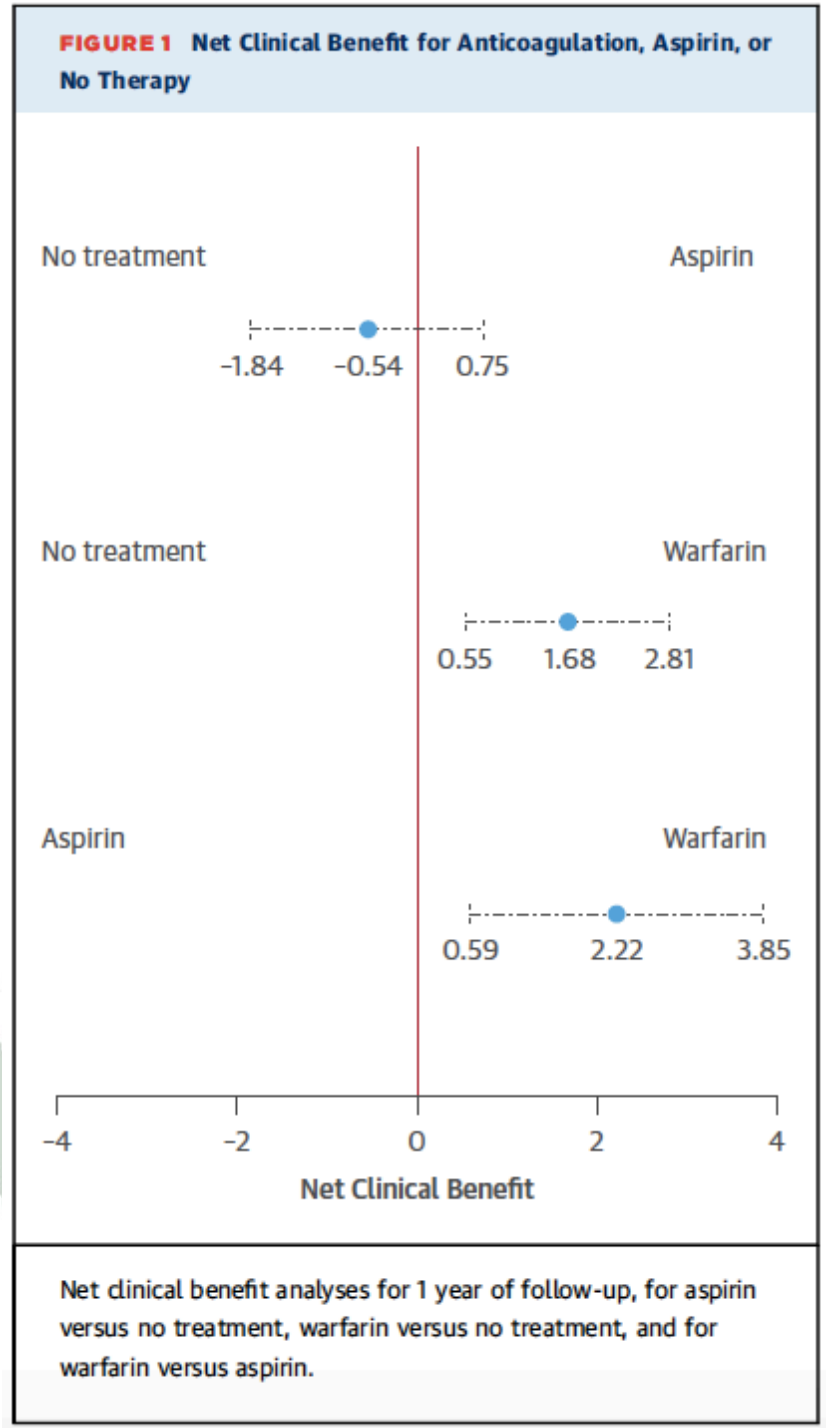
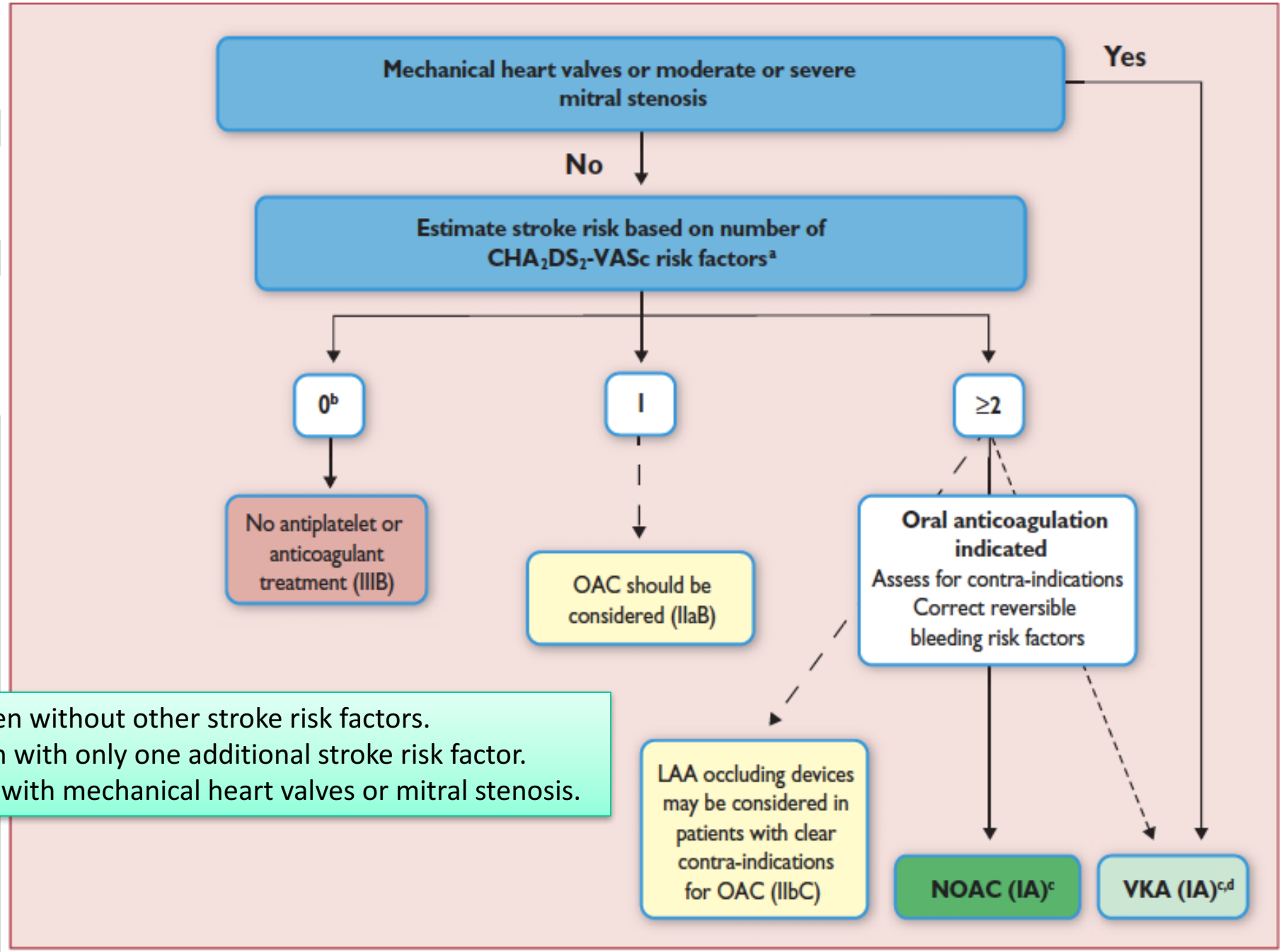


FIGURE 1 Net Clinical Benefit for Anticoagulation, Aspirin, or No Therapy

Net clinical benefit analyses for 1 year of follow-up, for aspirin versus no treatment, warfarin versus no treatment, and for warfarin versus aspirin.

Lip GH et al. J Am Coll Cardiol 2015;66(4):488-490



[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.

Kirchov P et al. Eur Heart J 2016;37:2893-2962.

Recommendations for stroke prevention in patients with AF

Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B
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
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	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
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C

Kirchov P et al. Eur Heart J 2016;37:2893-2962.

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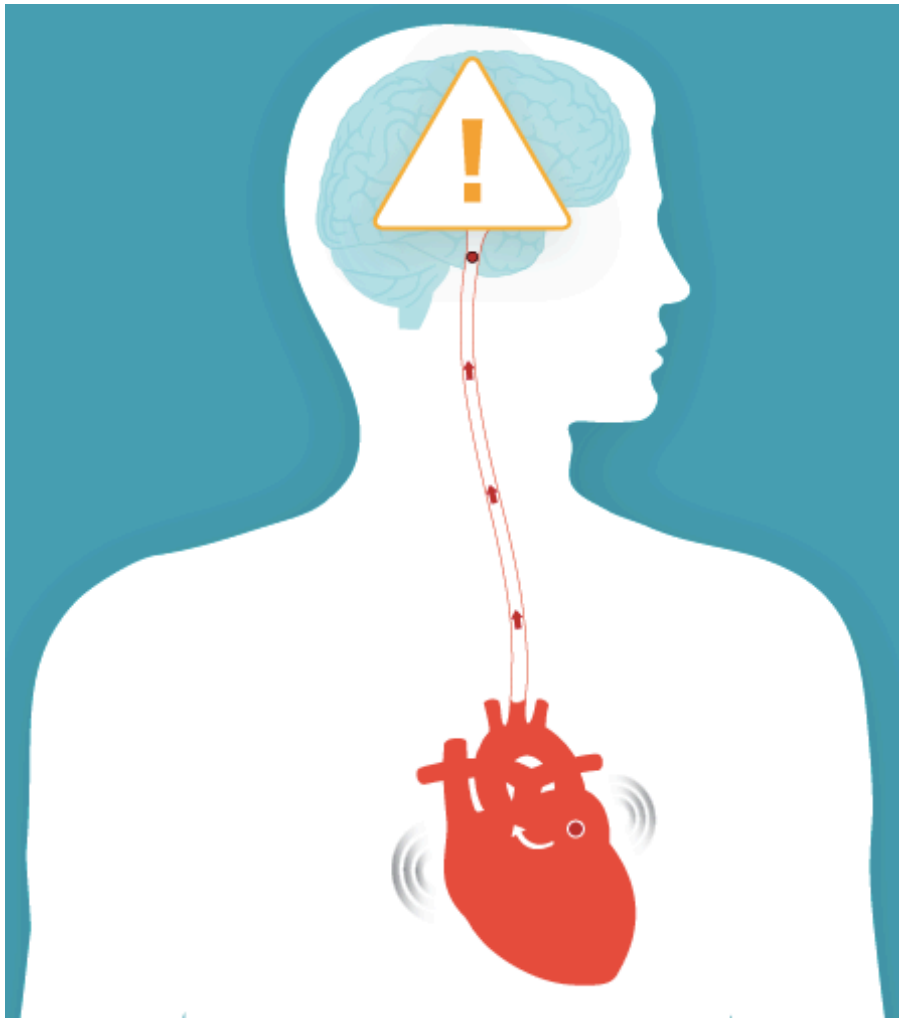
Overview

1. Real-world evidence:
    1. Use of oral anticoagulants
    2. Effectiveness and safety of oral anticoagulants
2. Guidelines recommendations on thromboprofilaxis
3. Oral anticoagulation in special situations
    1. Cardioversion
    2. Ablation
    3. Percutaneous coronary interventions
    4. Fragile patients
4. Conclusions



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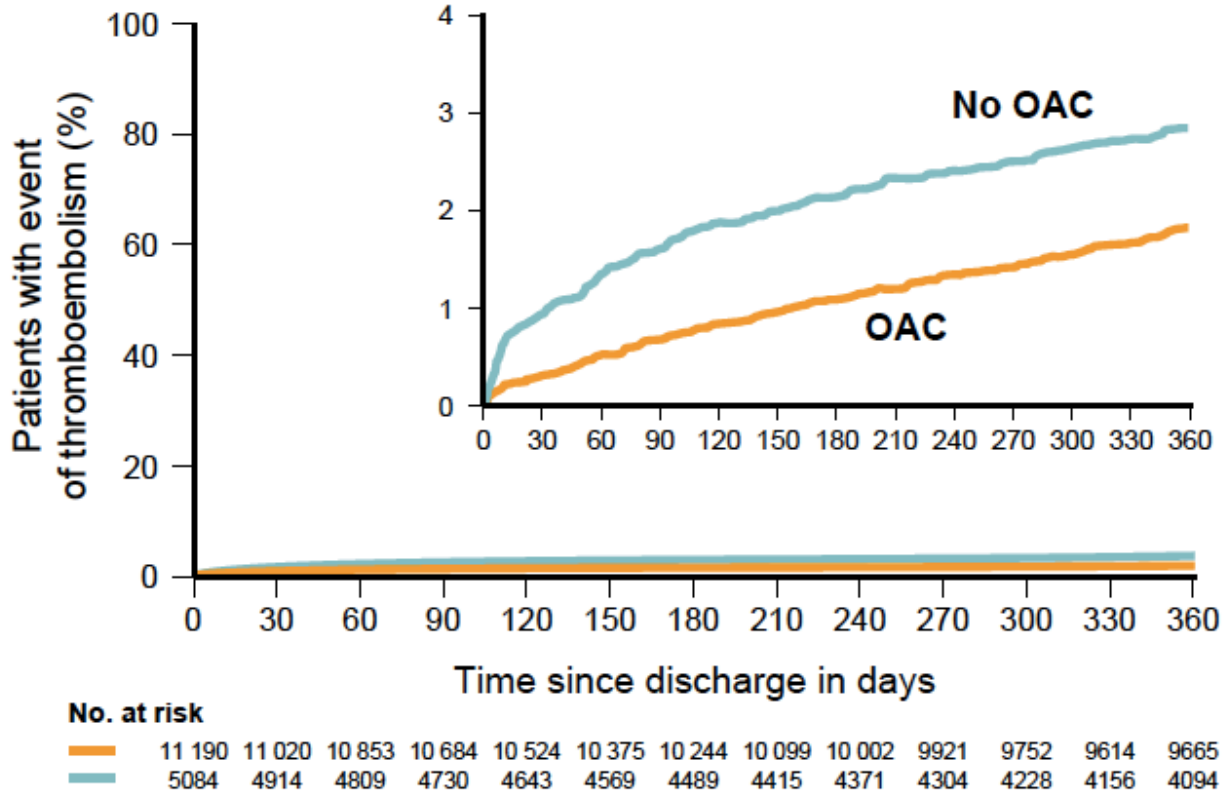
Cardioversion: Increased risk of stroke without appropriate anticoagulation

- Historic data show a high stroke rate in AF patients undergoing cardioversion[1]
- Supported by recent data showing an association between ischaemic events and lack of OAC in AF patients undergoing cardioversion[2,3]

OAC is recommended before, during, and after a cardioversion in all patients with AF[4]

Thromboembolic outcome after cardioversion of AF[2]



1. Resnekov L, McDonald L. Br Heart J 1967;29:926–936; 2. Hansen ML, et al. Europace 2015;17:18–23; 3. Palomäki A, et al. Int J Cardiol 2016;203:269–273; 4. Kirchhof P, et al. Eur Heart J 2016;37:2893–2962

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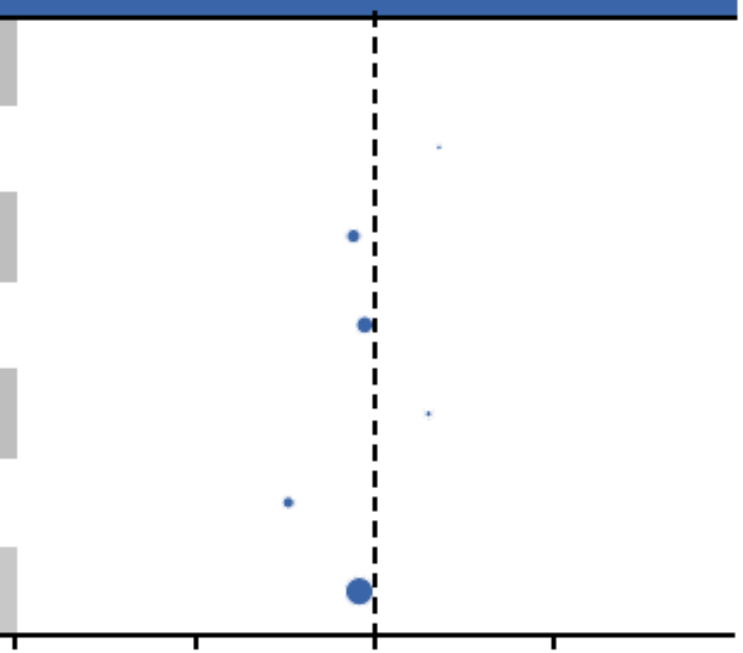
Data from Patients Enrolled in RCTs Showed that NOACs are Effective for Patients with AF Undergoing Cardioversion

Risk of stroke/SE with NOACs versus warfarin in patients with AF undergoing cardioversion

Study/ subgroup	NOAC		Warfarin		Weight, %	OR	95% CI
	Events	Total	Events	Total			
ARISTOTLE	0	331	0	412	-	NE	NE
ENGAGE AF	2	251	0	114	6.4	2.28	0.11–47.15
ENSURE AF	3	1095	4	1104	26.1	0.76	0.17–3.37
RE-LY	7	1319	4	664	38.9	0.88	0.26–3.00
ROCKET AF	2	138	1	132	10.2	1.91	0.18–20.85
X-VERT	2	1002	3	502	18.3	0.33	0.06–1.99
Total	**16**	**4136**	**12**	**2938**	**100.0**	**0.82**	**0.38–1.75**



Heterogeneity: $Tau^2=0.00$; $Chi^2=1.92$, df=4 ($p=0.75$); $I^2=0\%$; test for overall effect: $Z=0.52$ ($p=0.60$)

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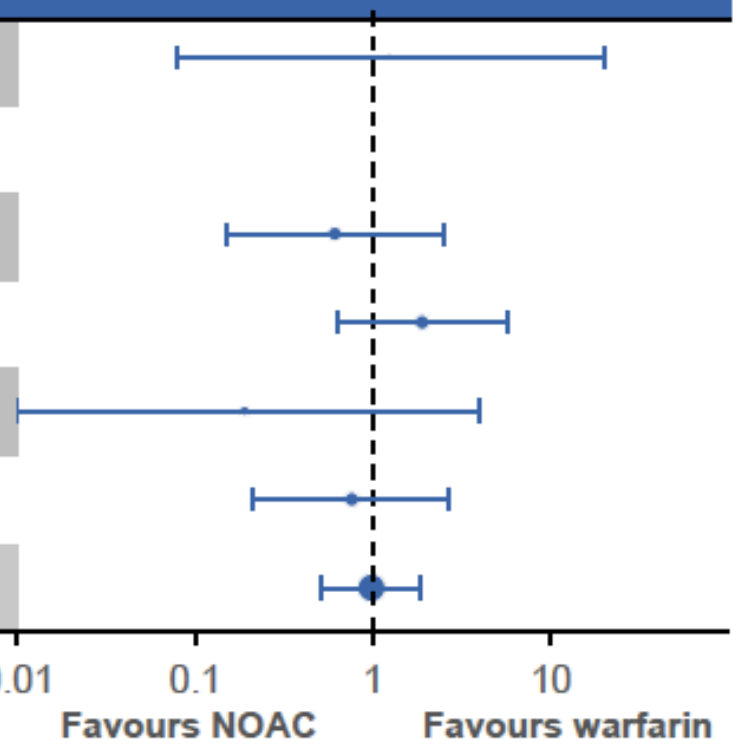
Data from Patients Enrolled in RCTs Showed that NOACs Are Safe for Patients with AF Undergoing Cardioversion

Risk of major bleeding with NOACs versus warfarin in patients with AF undergoing cardioversion

Study/ subgroup	NOAC		Warfarin		Weight, %	OR	95% CI
	Events	Total	Events	Total			
ARISTOTLE	1	331	1	142	4.7	1.24	0.08–19.82
ENGAGE AF	0	251	0	114	-	NE	NE
ENSURE AF	3	1067	5	1082	26.1	0.61	0.15–2.54
RE-LY	15	1319	4	664	27.9	1.89	0.63–5.67
ROCKET AF	0	138	2	132	13.4	0.19	0.01–3.95
X-VERT	6	988	4	499	27.9	0.76	0.21–2.67
Total	**25**	**4094**	**16**	**2903**	**100.0**	**0.98**	**0.51–1.87**

Heterogeneity: Chi^2=3.10, df=4 (p=0.54); I^2=0%; test for overall effect: Z=0.06 (p=0.95)



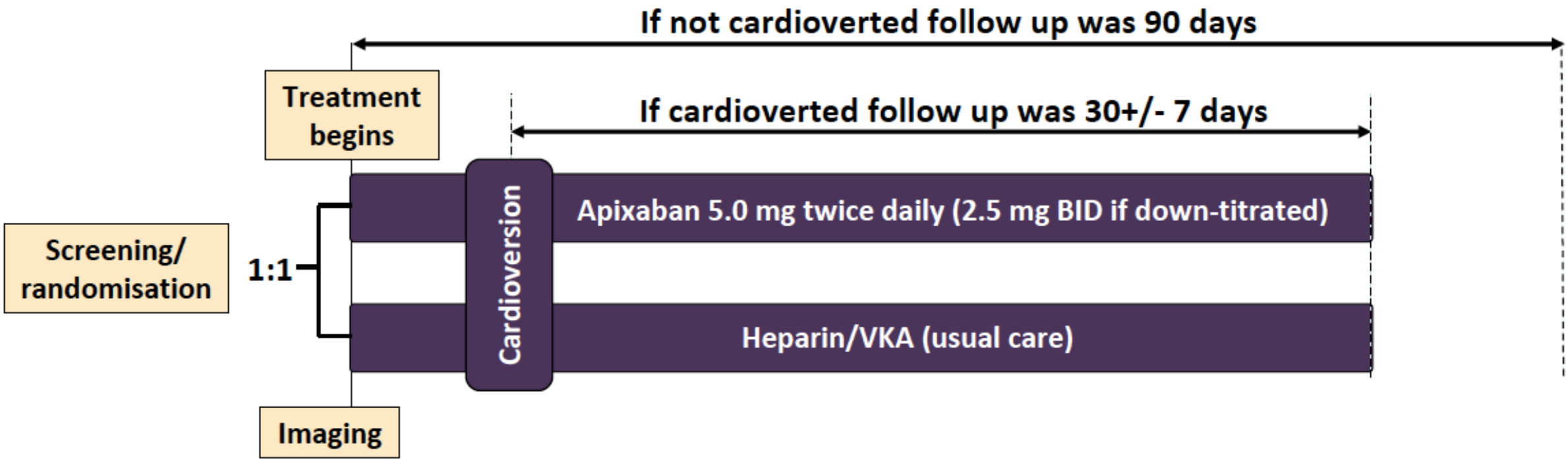
Renda G *et al*, *Am J Med* 2017;130:457–461

Prospective NOAC Studies in Cardioversion

Trial name	NOAC	Study overview	Primary outcome(s)
X-VeRT[1]	Rivaroxaban	◆ Rivaroxaban 20/15 mg od vs VKA in 1504 patients undergoing electrical or pharmacological cardioversion of NVAF (optional use of parenteral anticoagulant with VKA)	◆ Composite of stroke, TIA, peripheral embolism, MI and cardiovascular mortality ◆ Rivaroxaban 0.51% vs VKA 1.02%; RR 0.50 (95% CI 0.15–1.73)
ENSURE AF[2]	Edoxaban	◆ Edoxaban 60/30 mg od vs enoxaparin–warfarin in 2199 patients undergoing electrical cardioversion for NVAF	◆ Composite of stroke, SE, MI and cardiovascular mortality ◆ Edoxaban <1% vs enoxaparin–warfarin 1%; OR 0.46 (95% CI 0.12–1.43)
EMANATE[3]	Apixaban	◆ Ongoing study of efficacy and safety of apixaban vs heparin and/or VKA in patients with NVAF undergoing cardioversion	

1. Cappato R et al, Eur Heart J 2014;35:3346–3355; 2. Goette A et al, Lancet 2016;388:1995–2003; 3. https://clinicaltrials.gov/ct2/show/NCT02100228

EMANATE: Randomised, prospective, active-controlled, open-label study



In patients randomised to apixaban, cardioversion could be performed 2 hours after a loading dose of 10 mg (reduced to 5 mg if 2 of the following present: age ≥80, weight ≤60 kg, serum creatinine ≥1.5 mg/dl [133 micromol/L])

Ezekowitz M, et al. ESC 2017 Hot Line presentation. Available from: congress365.escardio.org

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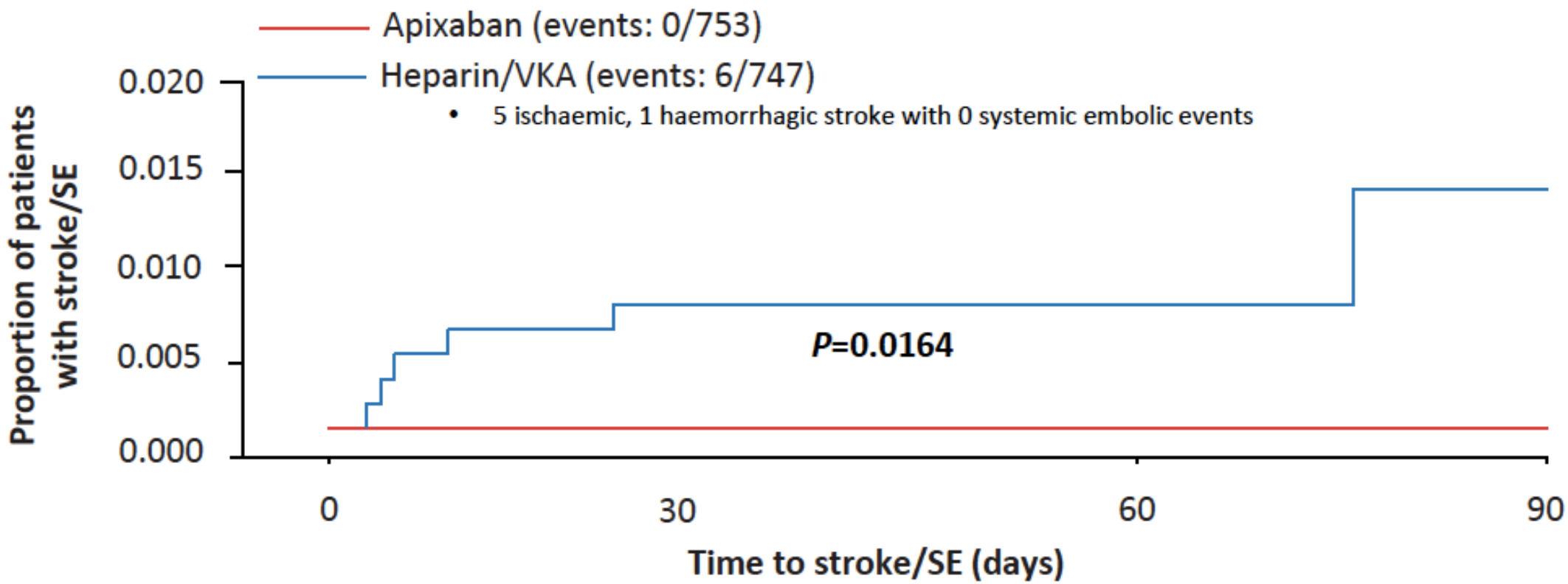
Stroke/systemic embolic outcomes



Number at risk

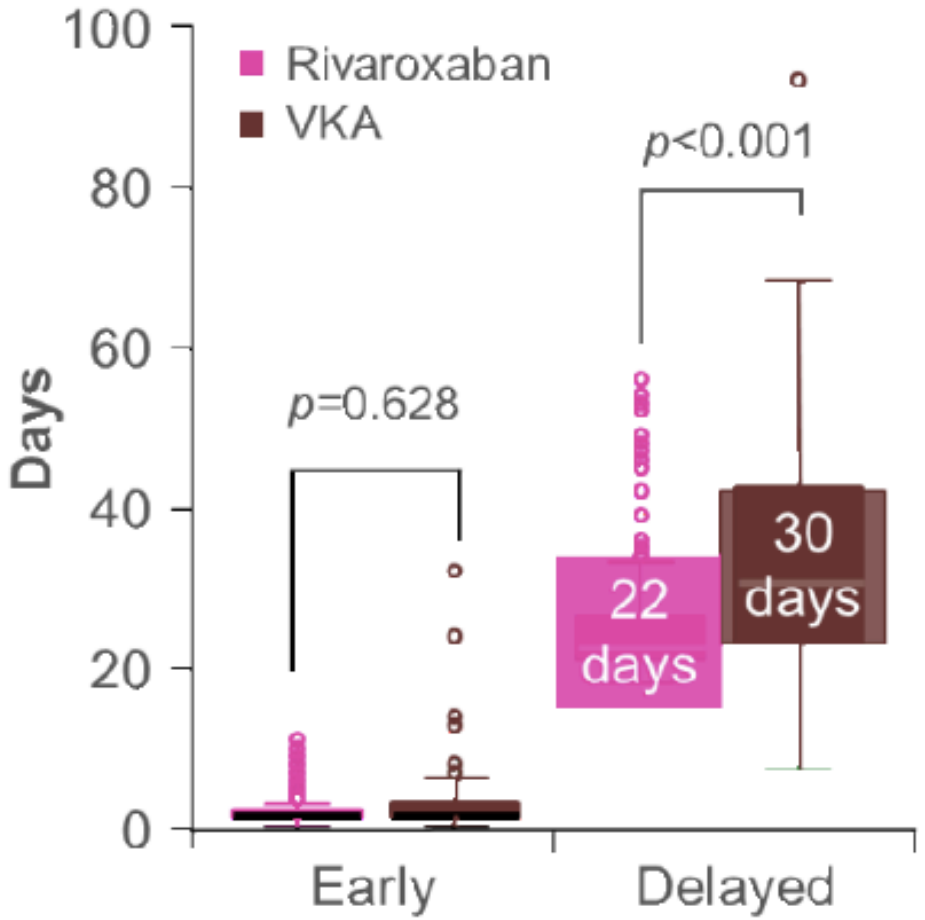
Apixaban	752	6145	199	55
Heparin/VKA	747	65	231	88

One patient's adjudicated stroke date was one day prior to randomisation; thus at Day 0, only 1499 were at risk for stroke.
No patients had SE

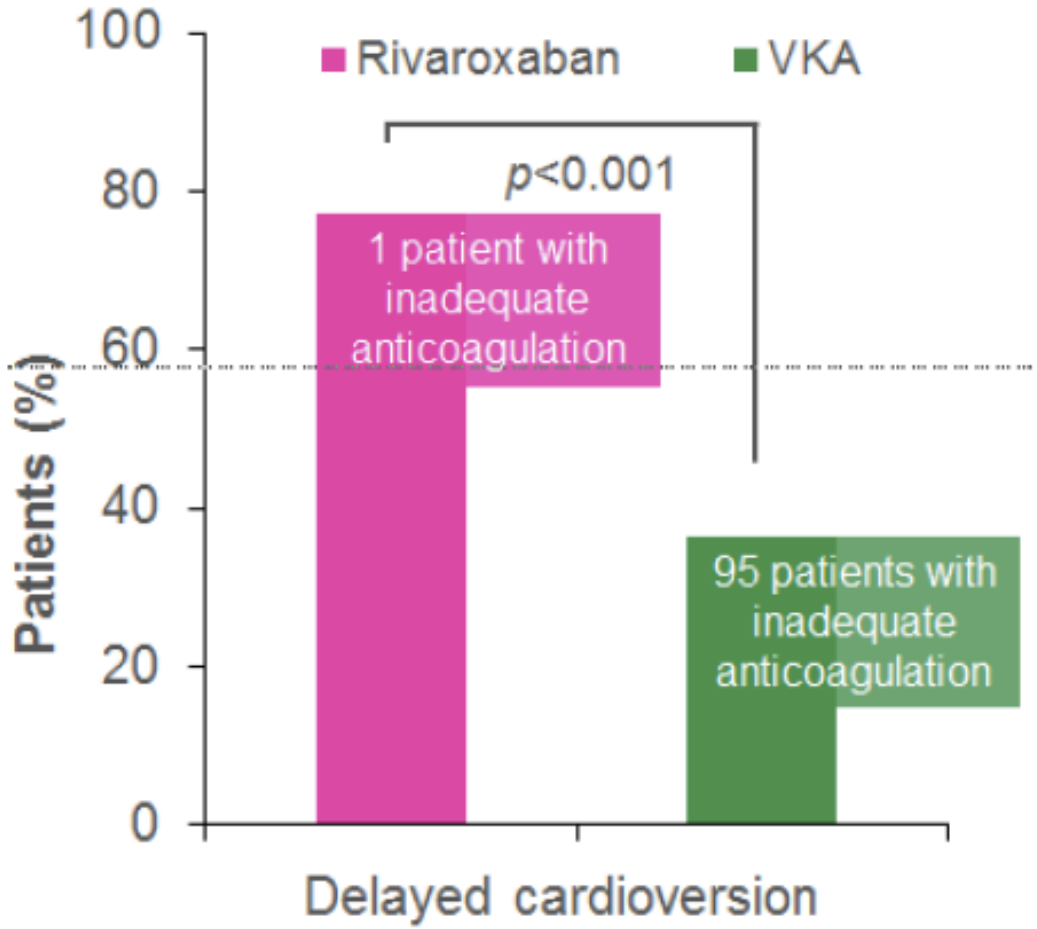
Ezekowitz M, et al. ESC 2017 Hot Line presentation. Available from: congress365.escardio.org

X-VeRT: Time to Cardioversion was Similar (Early Strategy) or Significantly Shorter (Delayed Strategy) Using Rivaroxaban Compared with VKA

Median time to cardioversion[1,2]



Patients cardioverted as scheduled[1*]



1. Cappato R et al, Eur Heart J 2014;35:3346–3355;

2. Cappato R et al, Presented at ESC 2014, slides available at: http://congress365.escardio.org/Presentation/106419#.WWYAz4Tyupp

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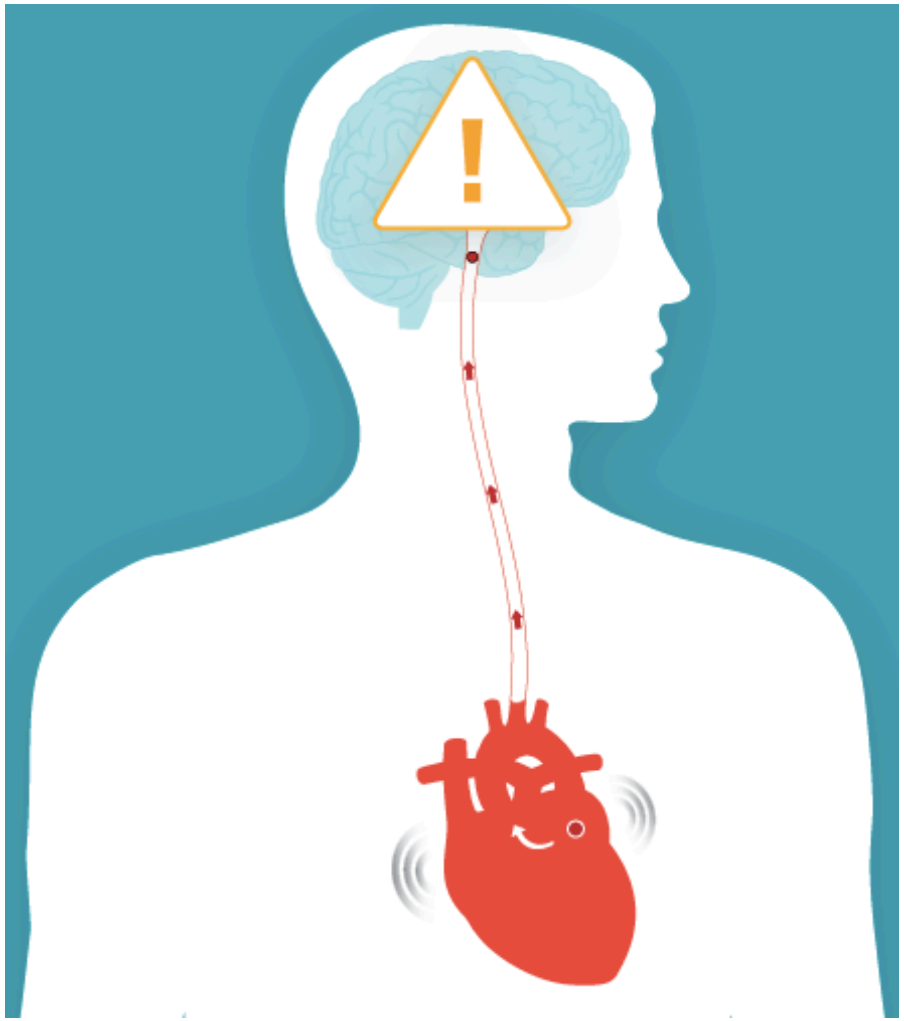

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Pulmonary vein isolation (PVI): Bleeding and thrombotic complications

- Risk of serious and/or frequent bleeding[1–4]
  - tamponade and haemothorax: 1–2%
  - groin bleeding: ?
- Risk of thromboembolism[1–5]
  - cf. pro-thrombotic AF patient (cf. CHA_2DS_2-VASc)
  - cf. extensive endocardial lesions
  - periprocedural stroke: ≤1%
  - asymptomatic cerebral embolism: 5–20%
- Also risks post-procedurally[4]
  - late pericardial tamponade
  - stroke

1. Cappato R, et al. Circ Arrhythm Electrophysiol 2010;3:32–38; 2. Nagao T, et al. Heart Rhythm 2015;12:1972–1978; 3. Camm AJ, et al. Eur Heart J 2012;33:2719–2747; 4. Kirchhof P, et al. Eur Heart J 2016;37:2893–2962; 5. Calkins H, et al. Europace 2012;14:528–606

Las recomendaciones en relación a la anticoagulación periprocedimiento han cambiado en los últimos años

En el pasado se recomendaban las terapias puente…

HRS/EHRA/ECAS
Expert Consensus Statement
'**LMWH or intravenous heparin should be used as a bridge** to resumption of systemic anticoagulation following AF ablation'

2007

2012

HRS/EHRA/ECAS
Expert Consensus Statement
'In patients who are not therapeutically anticoagulated with warfarin at the time of AF ablation, **LMWH or intravenous heparin should be used as a bridge** to resumption of systemic anticoagulation with warfarin'

Hoy en día las guías ya no recomiendan realizar terapias puente

EHRA Position Paper
'In patients receiving a VKA, the ablation should be performed **without interruption** of VKA therapy'

2015

2016

ESC Guidelines
'Continuation of oral anticoagulation with a VKA or NOAC should be considered during the procedure, maintaining effective anticoagulation'

LMWH, low-molecular-weight heparin. Kirchhof P et al. Europace 2016; Sticherling C et al. Europace 2015; Calkins H et al. Europace 2012; Calkins H et al. Europace 2007

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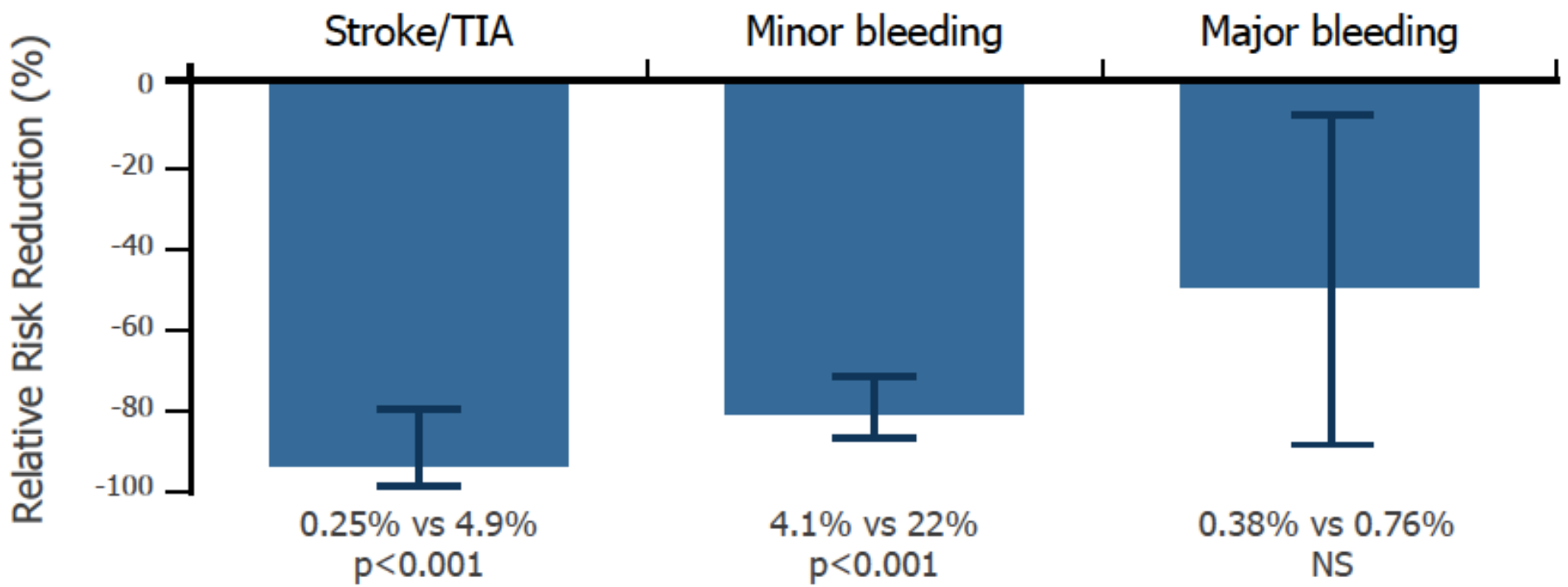
PVI and VKA: COMPARE trial

- 1584 patients
  1:1 prospective randomisation interrupted or uninterrupted warfarin
- Primary endpoint: TEE within 48 hours after PVI
- Uninterrupted VKA vs bridging:



Di Biase L, et al. Circulation 2014;129:2638–2644

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Recommendations for PVI: NOACs

- 2016 ESC AF guidelines[1]

> When catheter ablation of AF is planned, **continuation of OAC** with a VKA (IIaB) **or NOAC (IIaC)** should be considered during the procedure, maintaining effective anticoagulation
>
> All patients should receive OAC for at least 8 weeks after catheter (IIaB) or surgical (IIaC) ablation
>
> Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high risk of stroke (IIaC)

- EHRA practical guidance[2–4]

> Recommend an **institutional protocol** for patients taking NOACs undergoing AF ablation, either:
>
> – changing patients to uninterrupted VKA, or
>
> – uninterrupted NOAC therapy, or
>
> – well-planned cessation of NOAC

1. Kirchhof P, et al. Eur Heart J 2016;37:2893–2962; 2. Heidbuchel H, et al. Europace 2015;17:1467–1507; 3. Sticherling C, et al. Europace 2015;17:1197–1214; 4. Heidbuchel H, et al. Eur Heart J 2017; 38:2137–2149

Evidence for NOACs in PVI patients: Randomised studies

- Two randomised trials with <250 patients completed
  - **VENTURE-AF:** rivaroxaban vs VKA[1]
  - **Japanese RCT:** apixaban vs VKA[2]
- One large randomised trial with >600 patients has been recently completed
  - **RE-CIRCUIT:** dabigatran vs VKA[3]
- Two other larger RCTs ongoing
  - **AXAFA:** apixaban vs VKA[4,5] (n=663; results expected in early 2018)
  - **ELIMINATE-AF:** edoxaban vs VKA[6,7] (n~560; results expected 2019)

1. Cappato R, et al. Eur Heart J 2015;36:1805–1811; 2. Kuwahara T, et al. J Cardiovasc Electrophysiol 2016;27:549–554; 3. Calkins H, et al. New Engl J Med 2017;376:1627–1636; 4. Di Biase L, et al. Europace 2017;19:132–138; 5. https://clinicaltrials.gov/NCT02227550; 6. https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-003069-25; 7. https://clinicaltrials.gov/NCT02942576

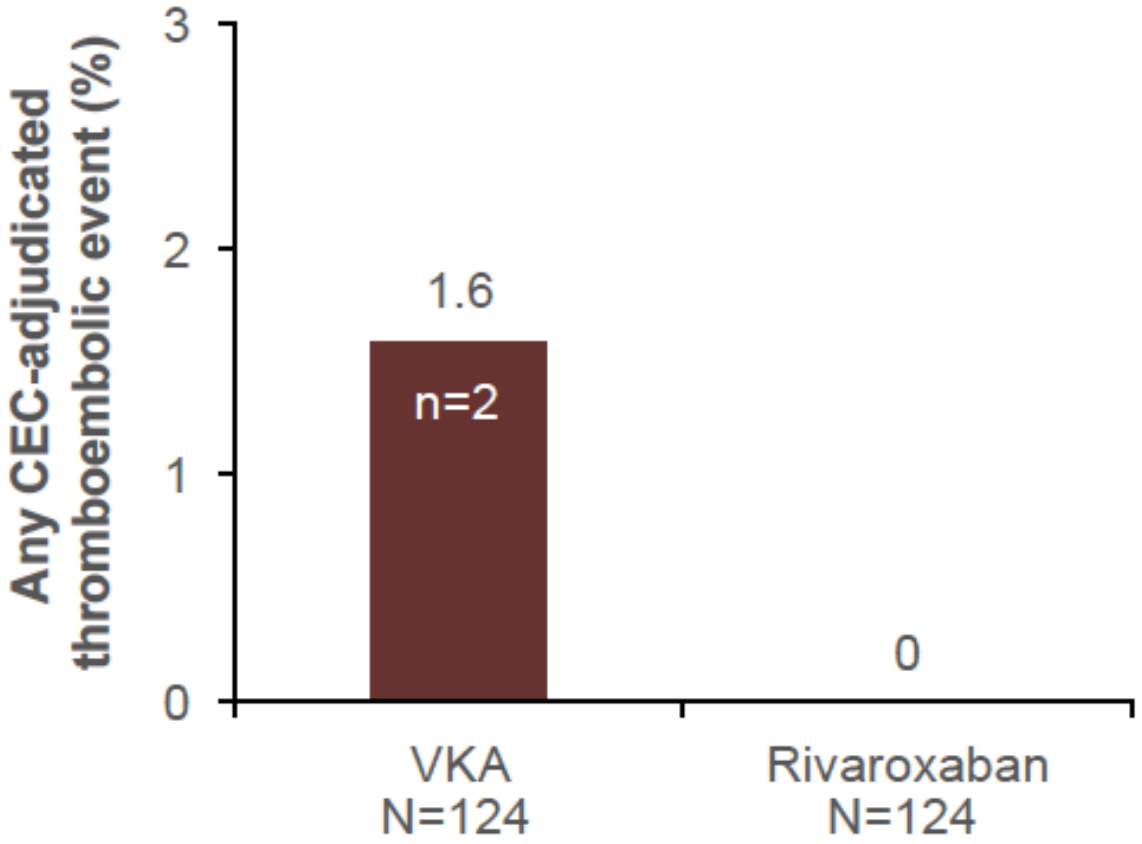
Prospective NOAC Studies in Catheter Ablation

Trial name	NOAC	Study overview	Primary outcome(s)
VENTURE-AF[1]	Rivaroxaban	◆ Uninterrupted rivaroxaban 20 mg od vs VKA in 248 patients undergoing catheter ablation for NVAF	◆ Major bleeding events after catheter ablation; rivaroxaban: 0 vs VKA: 1 ◆ No difference in terms of efficacy outcomes
RE-CIRCUIT[3]	Dabigatran	◆ Uninterrupted dabigatran (150 mg bid) vs warfarin in 635 patients undergoing catheter ablation for NVAF (8-week follow-up)	◆ Major bleeding events during and <8 weeks after ablation; dabigatran 1.6% vs warfarin 6.9%; ARD –5.3% (95% CI –8.4 to –2.2; $p<0.001$) ◆ No difference in terms of efficacy outcomes
AEIOU[3]	Apixaban	◆ Uninterrupted vs interrupted apixaban (prospective RCT) vs non-randomized retrospective matched cohort of uninterrupted warfarin	◆ Ischaemic stroke/SE; uninterrupted apixaban: 0%, interrupted apixaban: 0%, warfarin: 0% ◆ Clinically significant bleeding; uninterrupted apixaban: 11.3%, interrupted apixaban: 9.7%
AXAFA[4]	Apixaban	◆ Ongoing study of efficacy and safety of uninterrupted apixaban vs VKA for patients with NVAF undergoing catheter ablation	

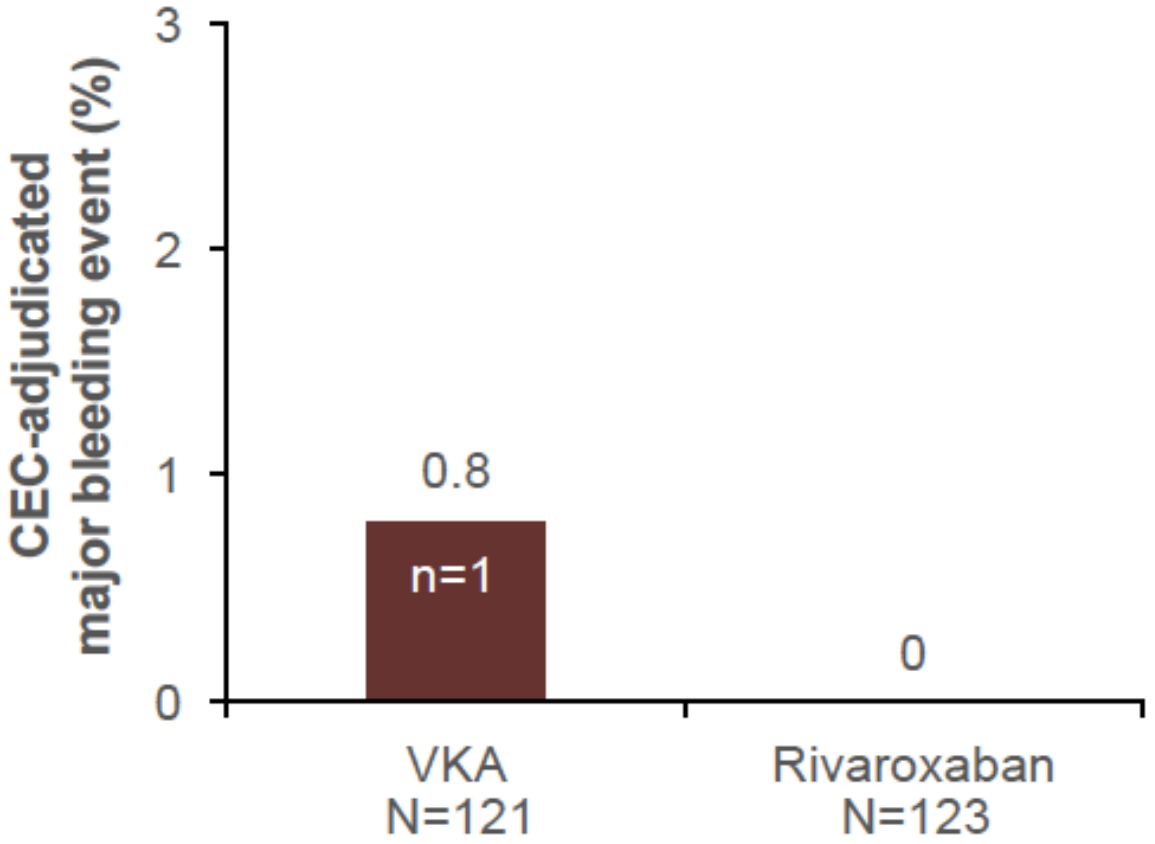
1. Cappato R et al, Eur Heart J 2015;36:1805–1811; 2. Calkins H et al, N Engl J Med 2017; 376:1627–1636; 3. Reynolds MR et al, Presented at HRC 2017; slides available at: http://files.eventpilotadmin.com/doc/clients/OASIS/HRS17/library/xpub/out/C-LBCT01_13589.xpub/index.php?page=0; 4. Di Biase et al,

VENTURE AF: Uninterrupted Rivaroxaban Versus Uninterrupted VKA in Patients with AF Undergoing Ablation

Thromboembolic events



Major bleeding events*



*At least one of: ISTH major bleeding event, GUSTO severe/life-threatening bleeding event or TIMI major bleeding event

Cappato R et al, Eur Heart J 2015;36:1805–1811

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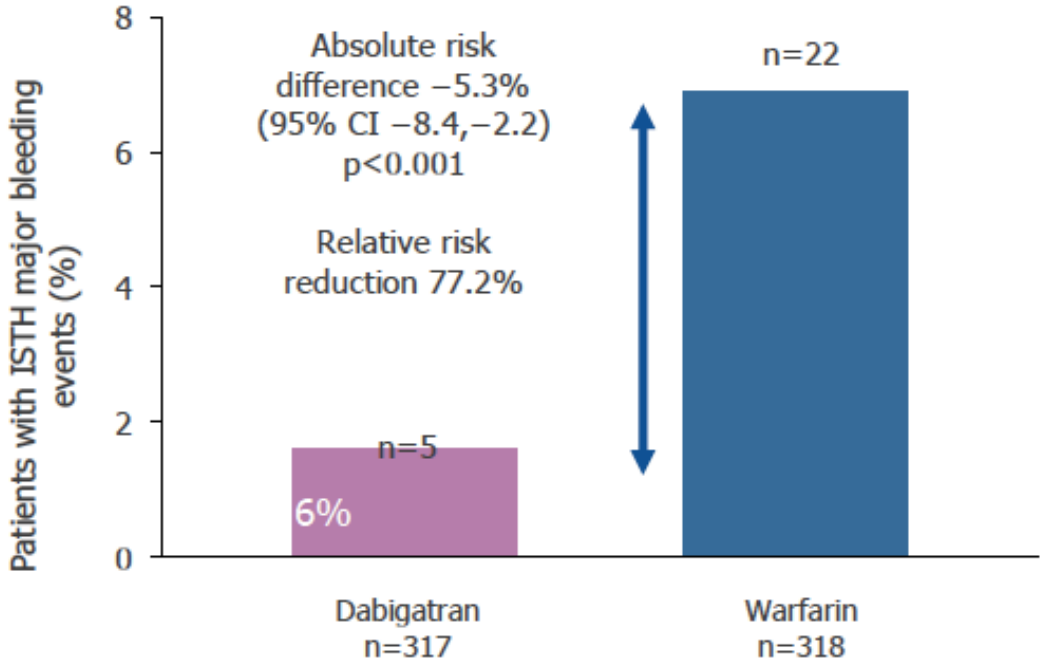
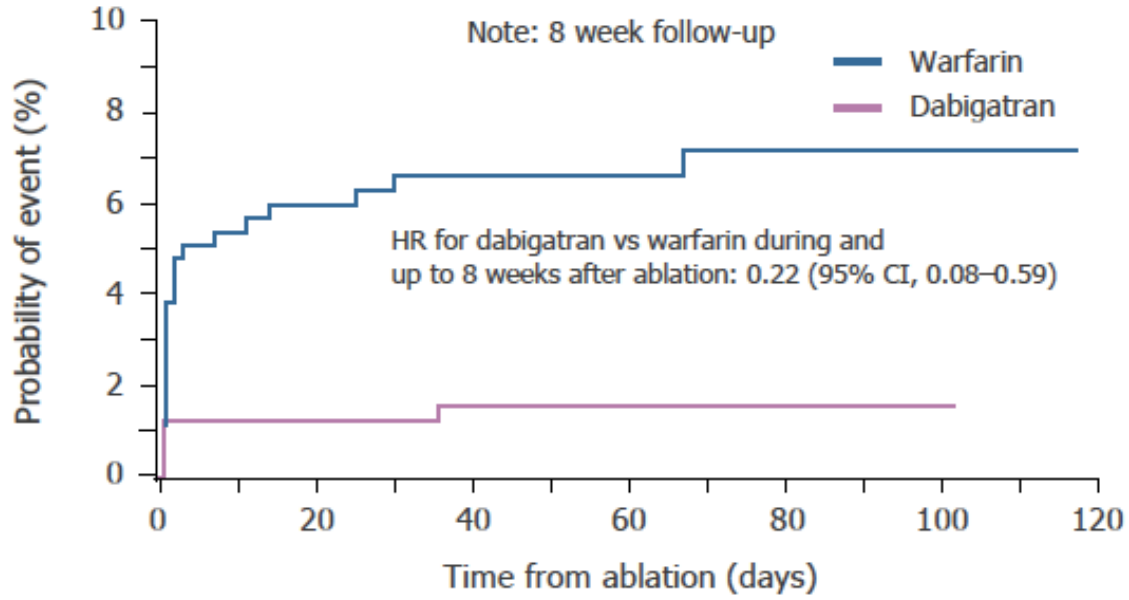
RE-CIRCUIT (dabigatran): Results – major bleeding



Created from Calkins H, et al. 2017



Patients at risk

Dabigatran	317	313	311	311	306	305	297	83	4	2	1	0	0
Warfarin	318	301	297	296	295	295	278	85	13	5	3	1	0

Tamponade: 1 dabigatran vs 6 warfarin

Groin haematoma: 0 dabigatran vs 8 warfarin

Minor bleeding: 18.6% dabigatran vs 17% warfarin

Prolonging hospitalisation: 3.8% dabigatran vs 6.5% warfarin

Calkins H, et al. New Engl J Med 2017;376:1627–1636

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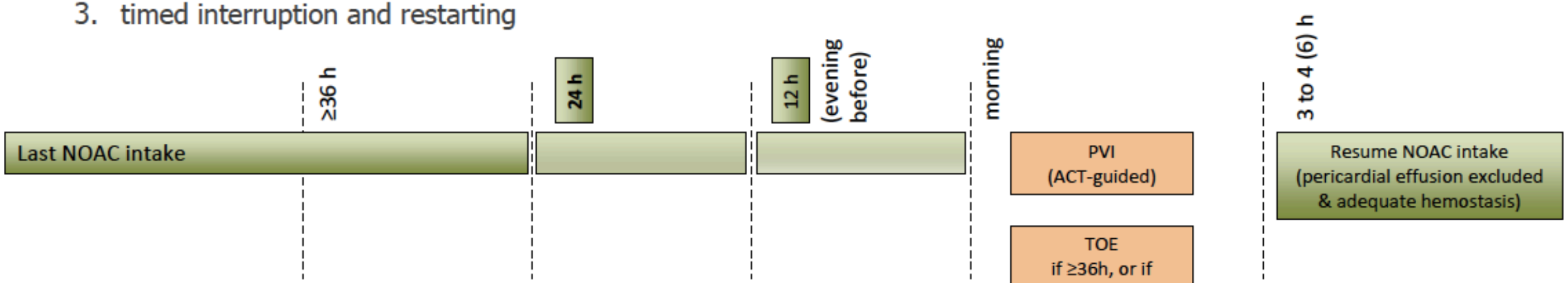
Conclusions: Current guidance on OAC during PVI

- Have an institutional protocol (i.e. no improvisation):[1,2]
  1. switch from NOAC to VKA before PVI, or
  2. fully uninterrupted NOAC (i.e. even on the morning of PVI), or
  3. timed interruption and restarting



Flowchart created from Heidbuchel H, et al. 2015

1. Heidbuchel H, et al. Europace 2015;17:1467–1507; 2. Sticherling C, et al. Europace 2015;17:1197–1214

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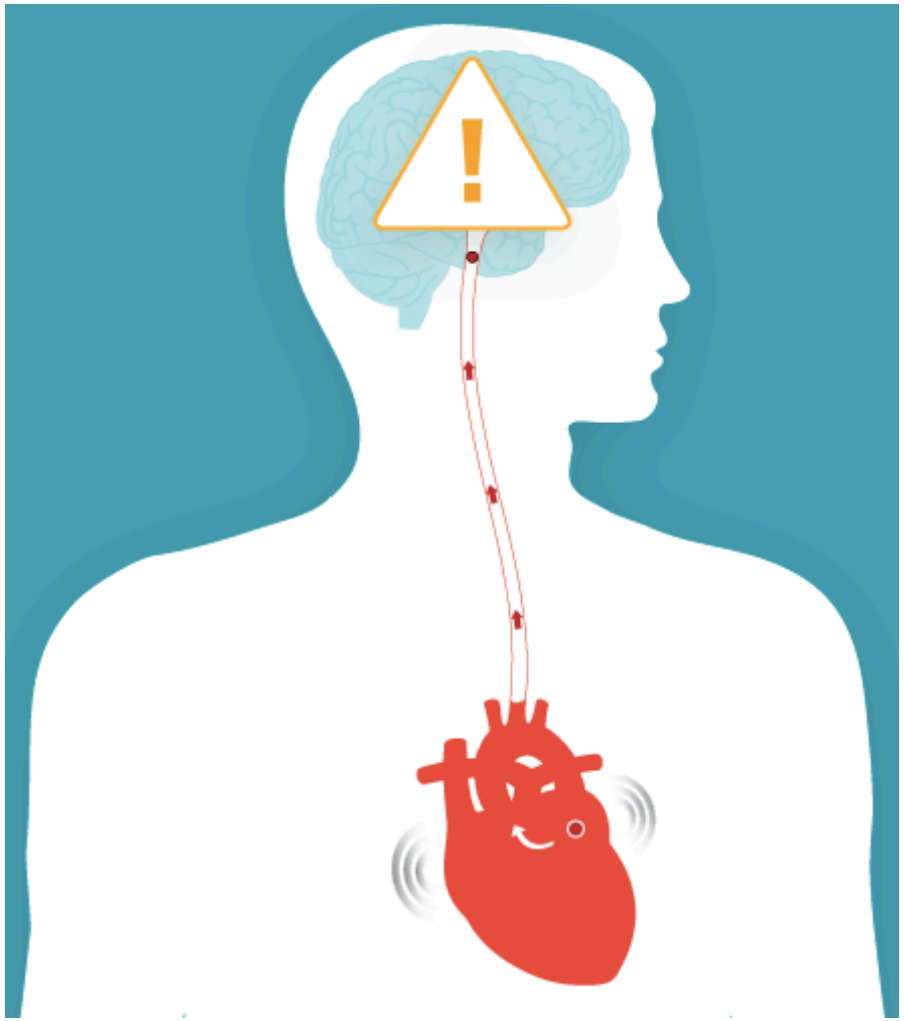
    3. Percutaneous coronary interventions
4. Conclusions



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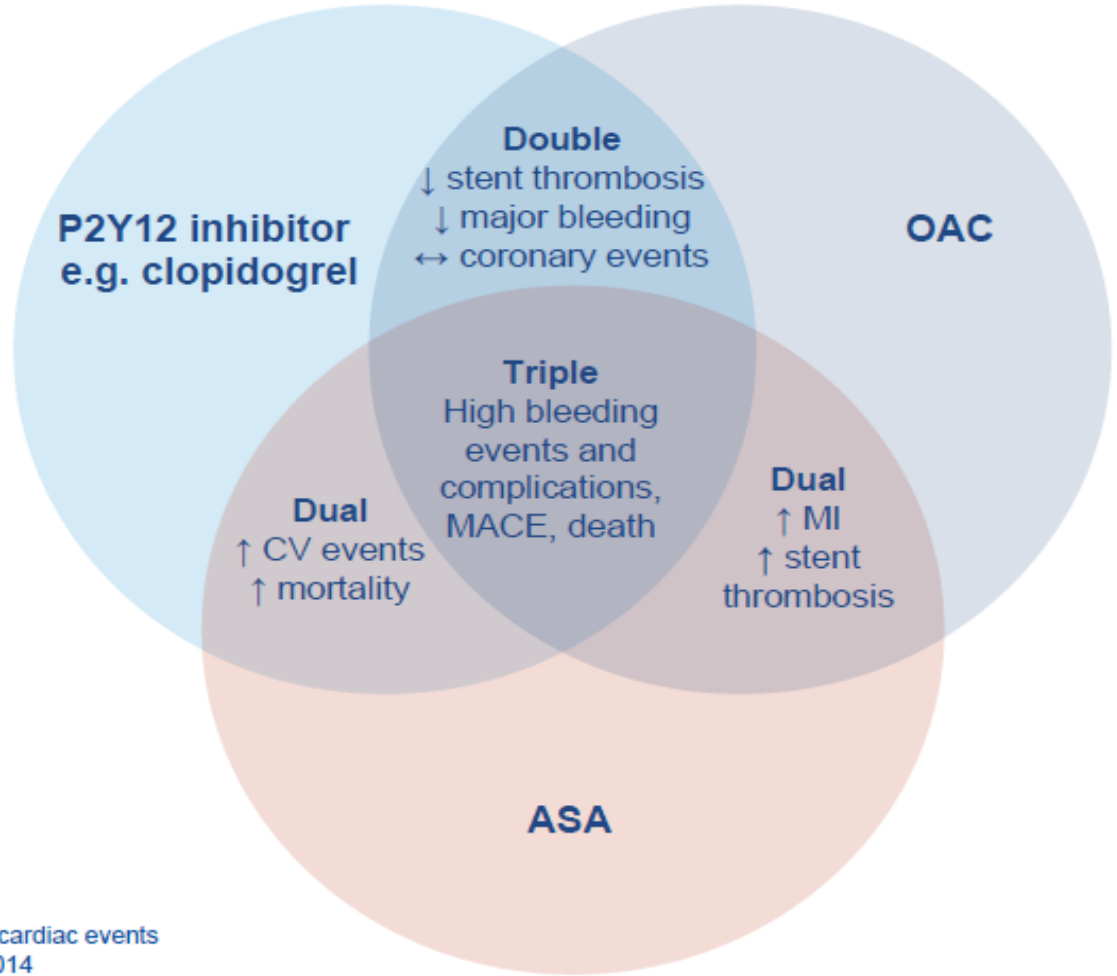
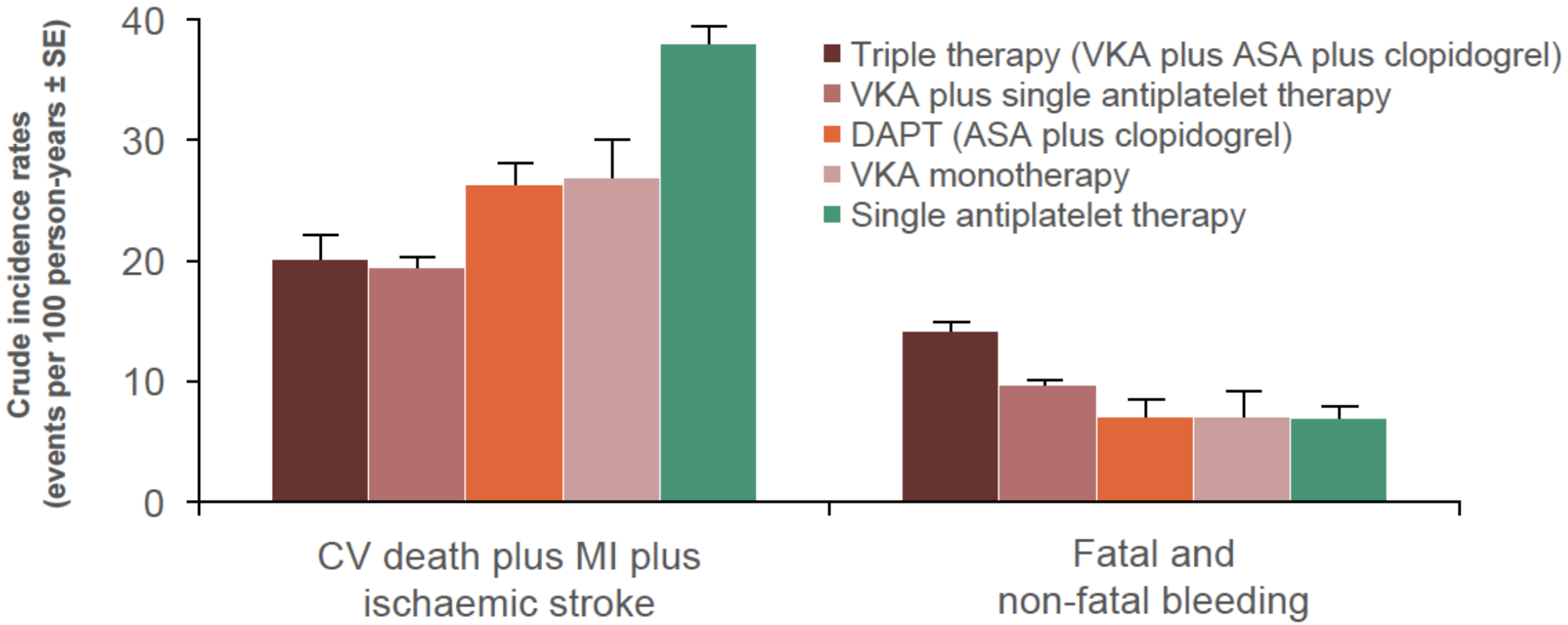
What combination of therapy is optimal for patients with AF after PCI?



ASA, acetylsalicylic acid; MACE, major adverse cardiac events
Adapted from Dewilde et al. J Am Coll Cardiol 2014

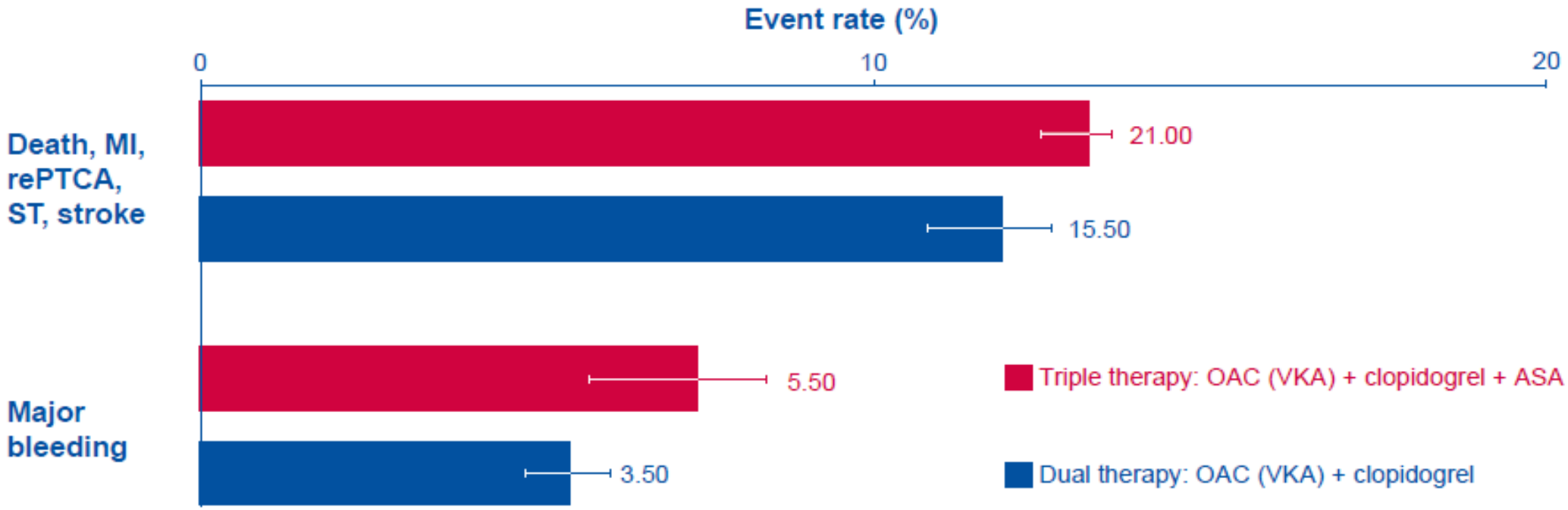
Triple Therapy with a VKA Reduces Thromboembolic Events but Increases Bleeding after PCI in Patients with AF

Danish registry data (2000–2009; N=11,480 patients)



Lamberts M et al, Circulation 2012;126:1185–1193

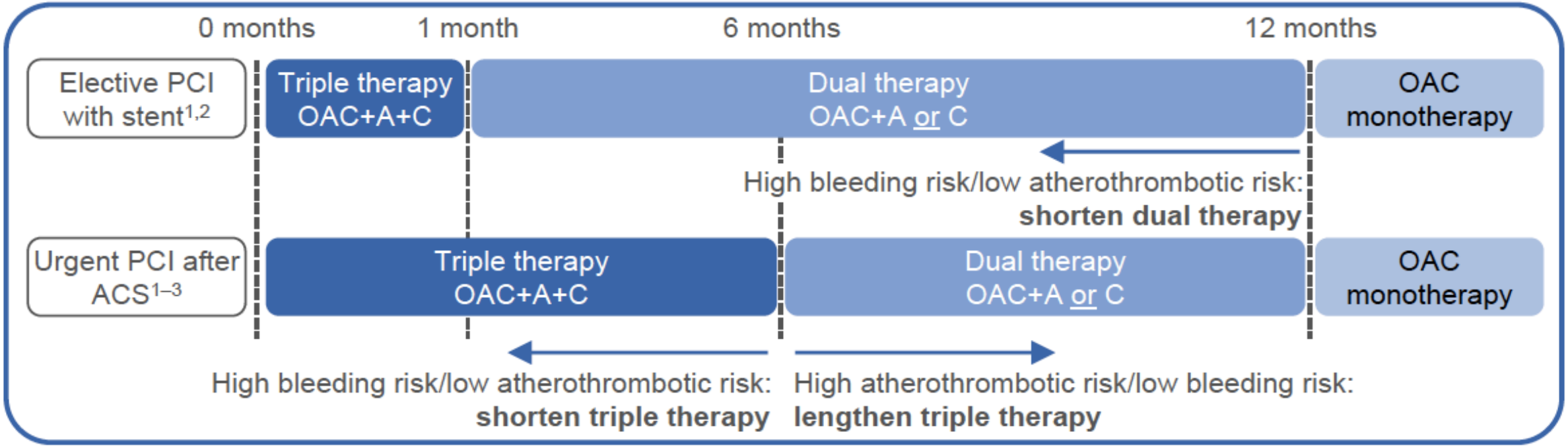
Meta-analysis: oral antithrombotic therapy in patients with AF post-PCI



OAC (VKAs) + clopidogrel associated with reduction in major bleeding and no increase in rates of death, MI, stroke, and stent thrombosis vs OAC + ASA + clopidogrel

Meta-analysis of 15 studies (2 randomized controlled trials and 13 observational registries) including 7182 patients
rePTCA, repeat percutaneous transluminal coronary angioplasty; ST, stent thrombosis
D'Ascenzo et al. Am J Cardiol 2015

Guidelines for the Management of AF and PCI: 'Minimize Triple Therapy Duration'



- In selected patients, dual therapy may be considered instead of triple therapy[1]
- European guidelines suggest that NOACs may be used in triple/dual therapy,[1–3] whereas US guidelines recommend a VKA[4,5]

1. Kirchhof P et al, Eur Heart J 2016; doi:10.1093/eurheartj/ehw210; 2. Heidbuchel H et al, Europace 2015;17:1467–1507;
3. Windecker S et al, Eur Heart J 2014;35:2541–2619; 4. Amsterdam EA et al, Circulation 2014;130:e344–e426;
5. O'Gara PT et al, J Am Coll Cardiol 2013;61:e78–e140

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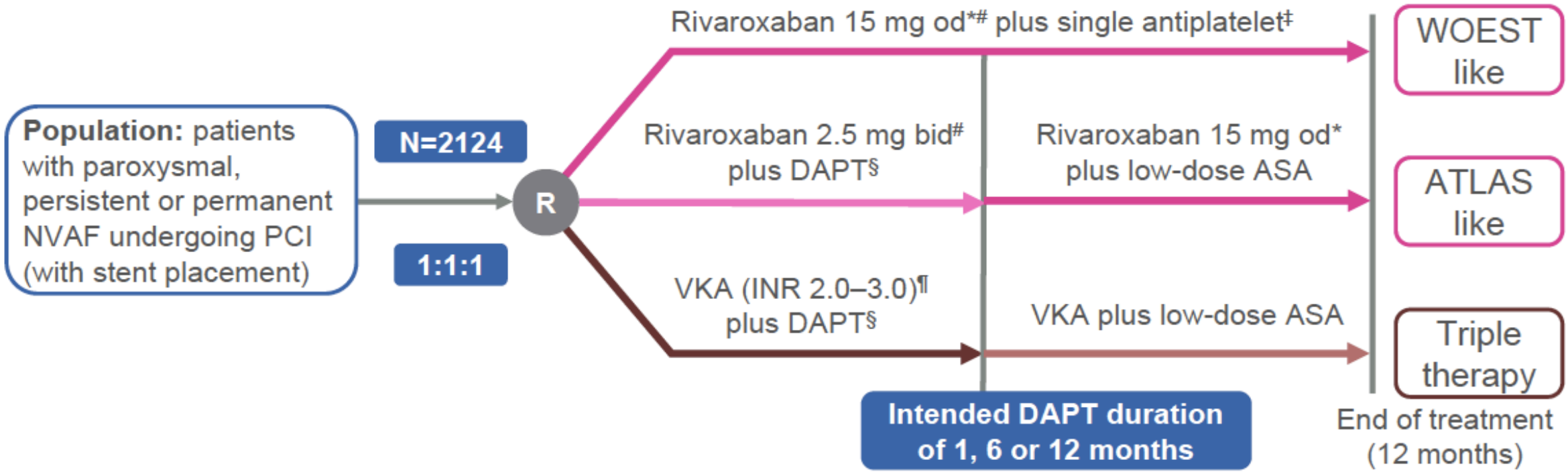
PIONEER AF-PCI: Two Rivaroxaban Strategies Versus VKA Plus DAPT

Design: An open-label, randomized, controlled phase IIIb safety study



*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶first dose 12–72 hours after sheath removal

1. Janssen Scientific Affairs, LLC. 2016. https://clinicaltrials.gov/ct2/show/NCT01830543 [accessed 10 Oct 2016];
2. Gibson CM et al, Am Heart J 2015;169:472–478e5; 3. Gibson CM et al, N Engl J Med 2016; 375:2423-2434

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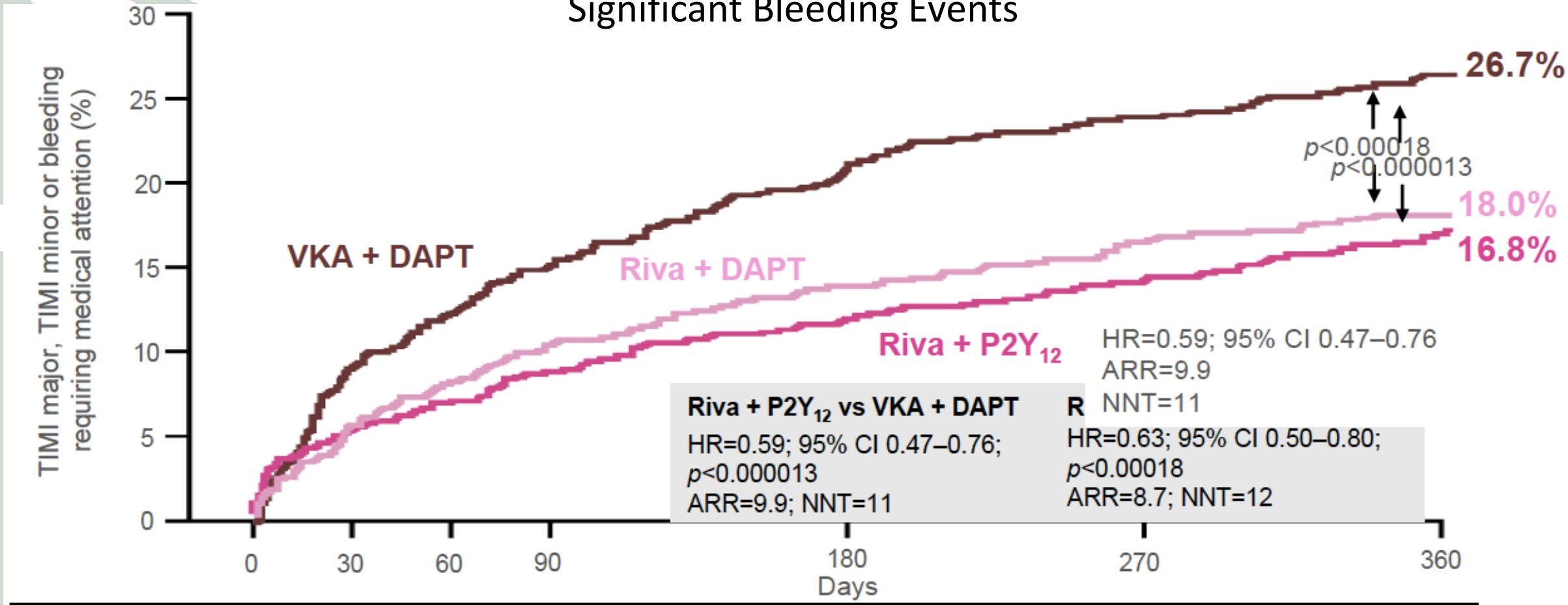
Kaplan–Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



No. at risk							
Riva + P2Y$_{12}$	696	628	606	585	543	510	383
Riva + DAPT	706	636	600	579	543	509	409
VKA + DAPT	697	593	555	521	461	426	329

Gibson CM et al, N Engl J Med 2016;375:2423–2434

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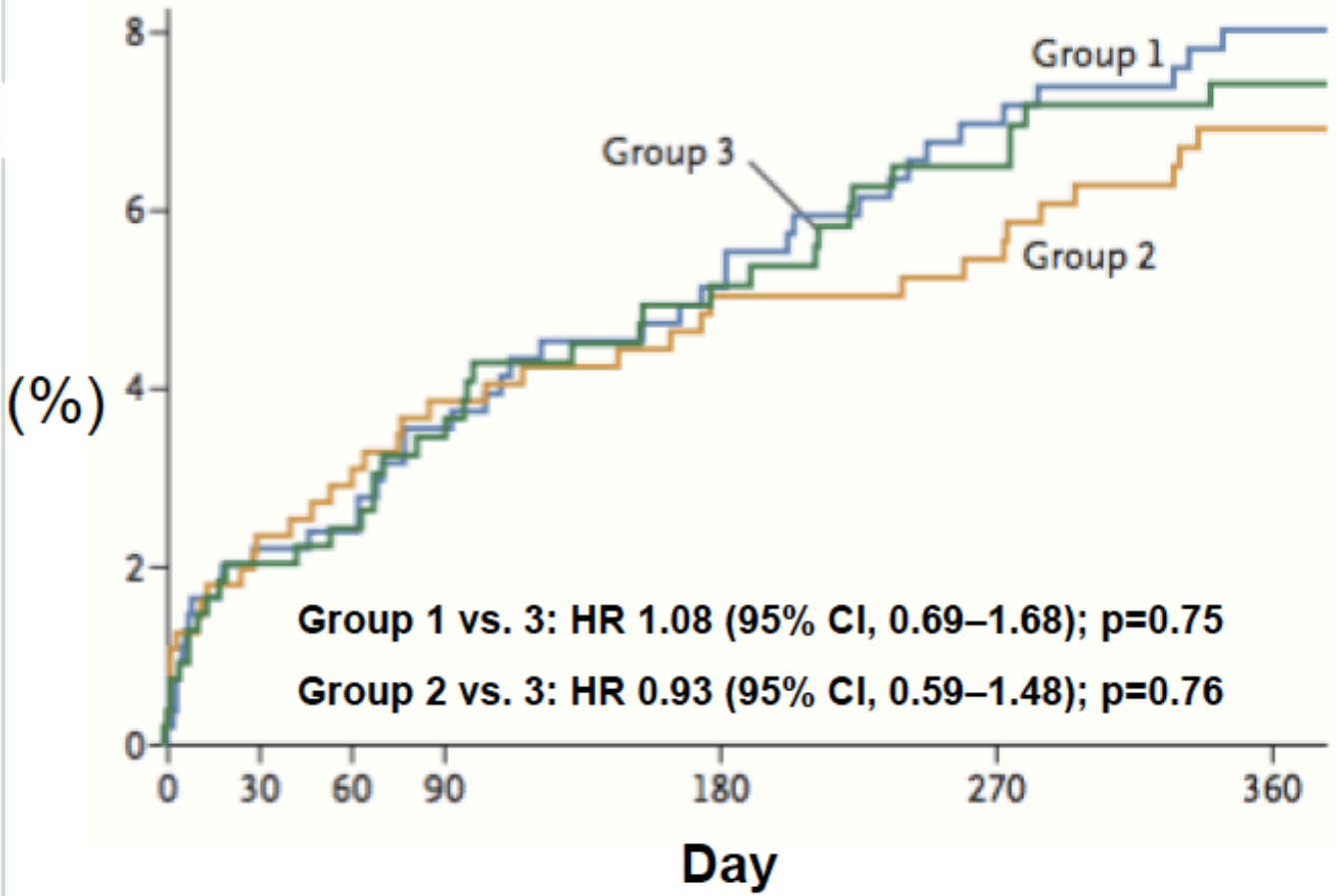
PIONEER AF-PCI trial: secondary efficacy end-point

Group 1: rivaroxaban 15 mg OD + $P2Y_{12}$ inhibitor; **Group 2**: rivaroxaban 2.5 mg BID + DAPT; **Group 3**: adjusted-dose VKA + DAPT



MACE:

composite of CV death, MI, or stroke

Gibson CM et al. Am Heart J 2015;169:472-8.e5

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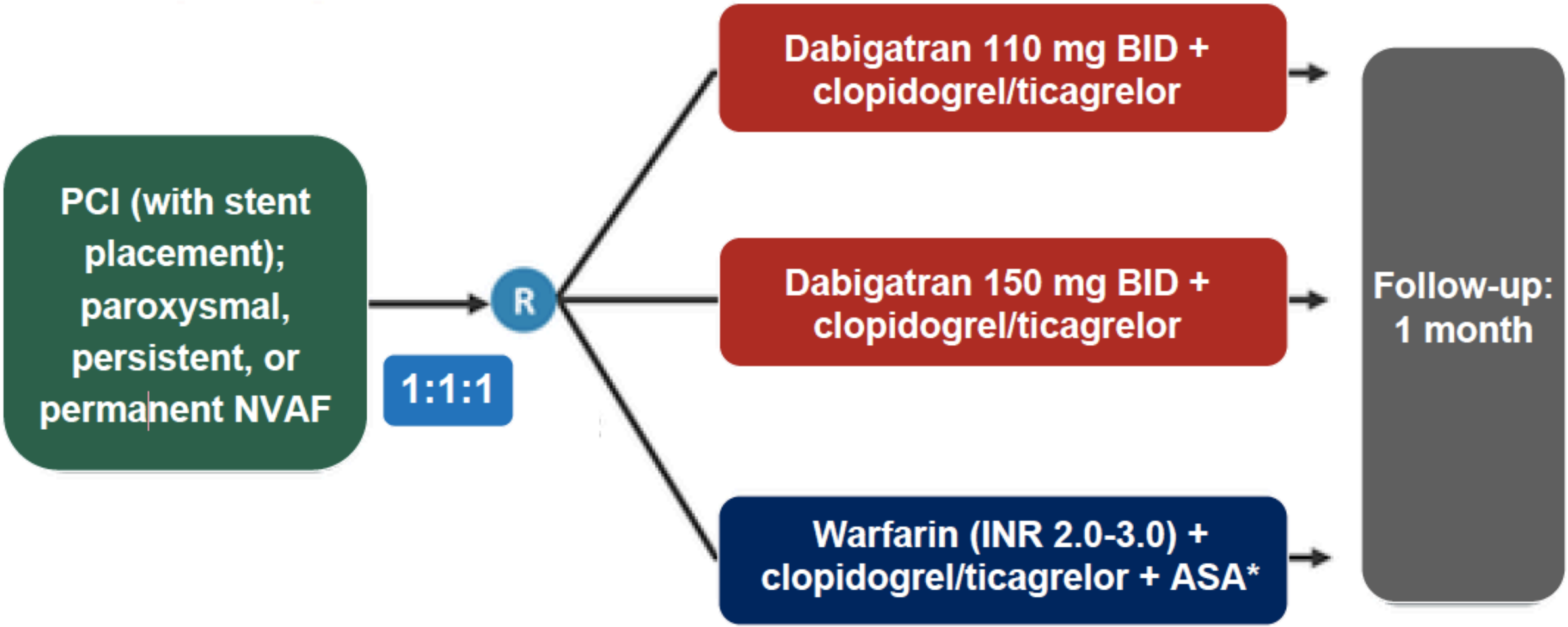
RE-DUAL PCI trial: design



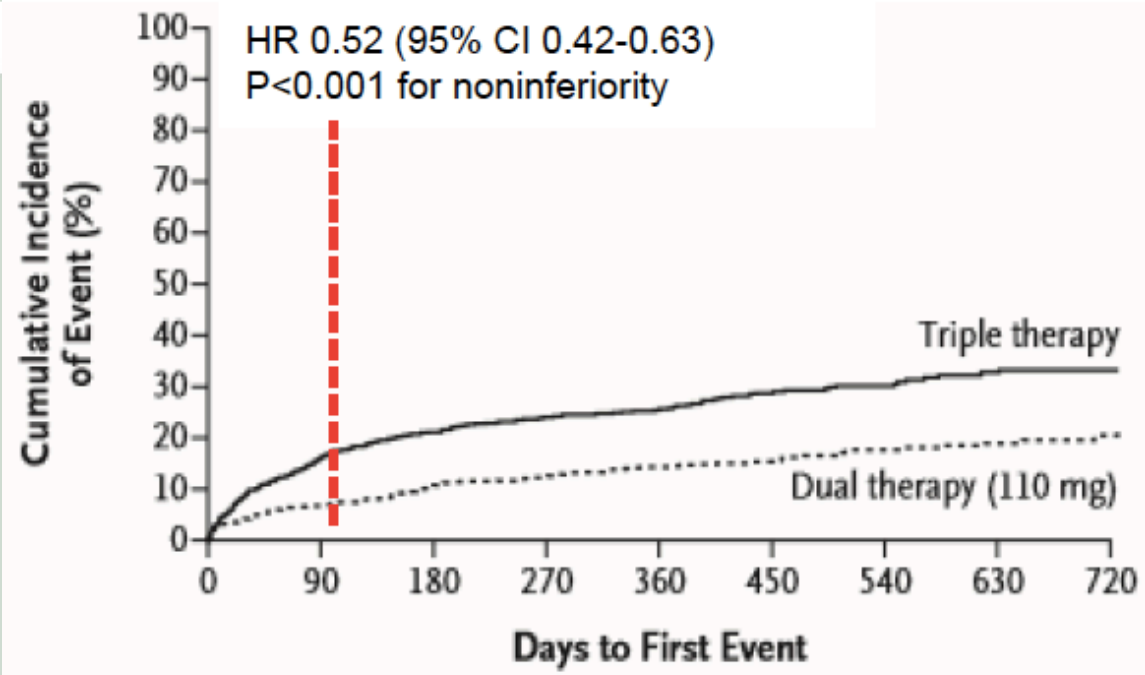
Minimum treatment 6 months

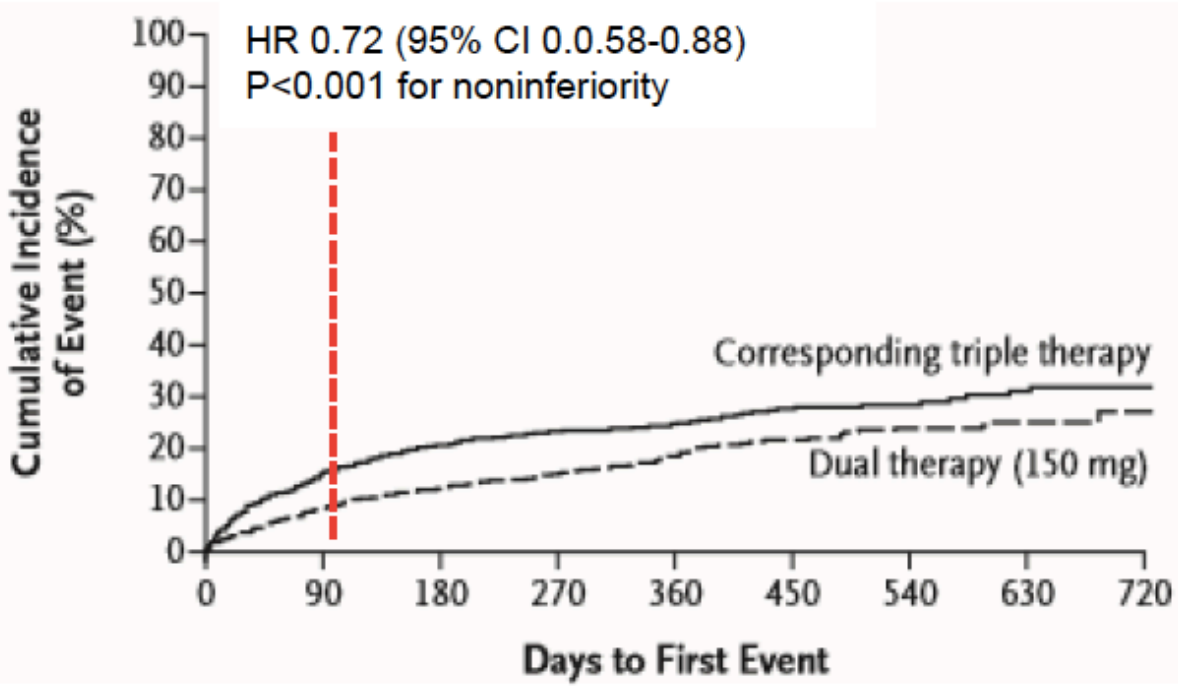
*1 mo. with BMS, 3 mos. with DES

Cannon CP et al. Clin Cardiol 2016;39:555-64

RE-DUAL PCI trial: primary end-point

Major or CRNM bleeding





Cannon CP et al. Clin Cardiol 2016;39:555-64

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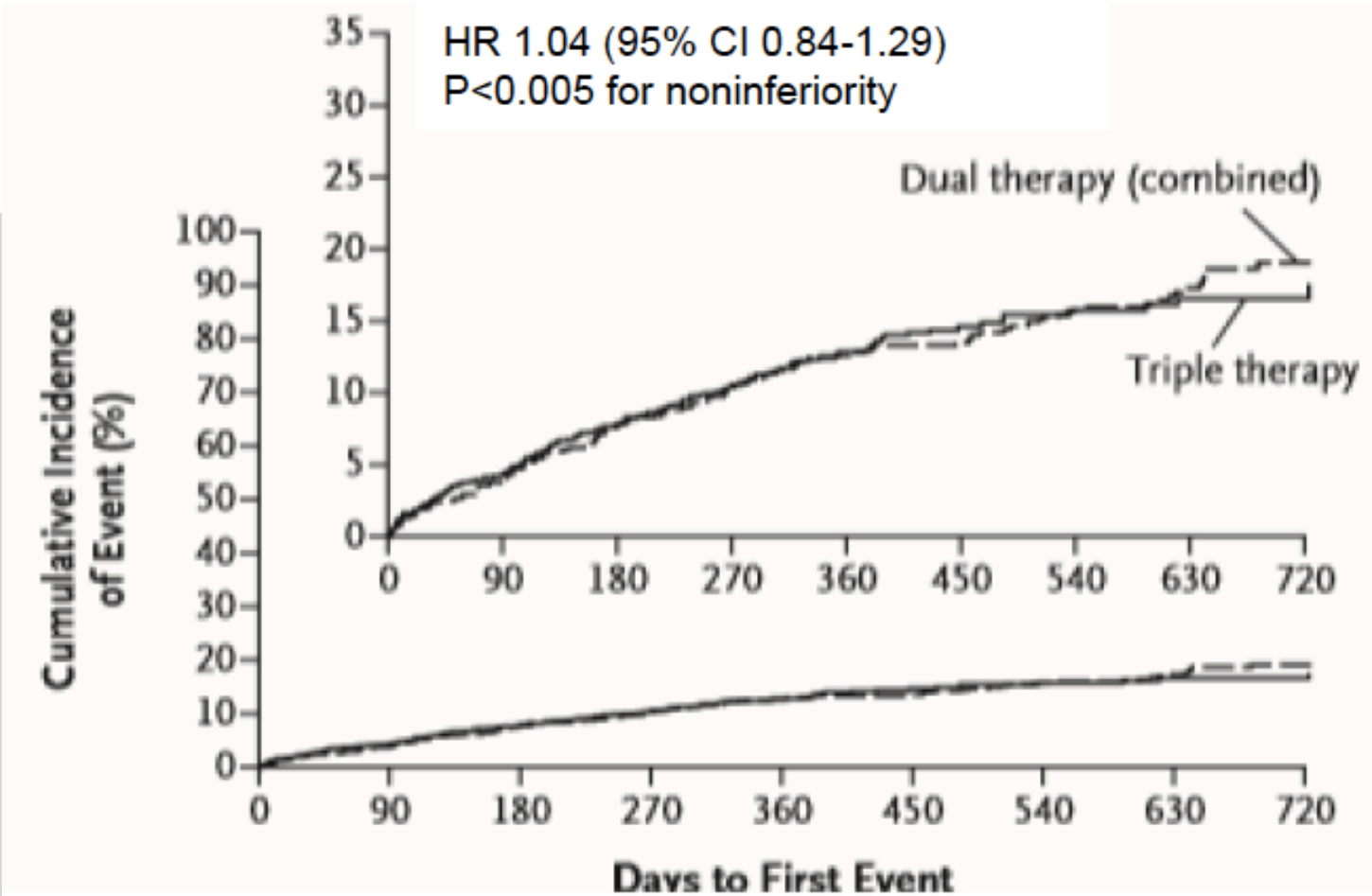
RE-DUAL PCI trial: secondary efficacy end-point



Composite of TE events (MI, stroke, systemic embolism), death or unplanned revascularization

Cannon CP et al. Clin Cardiol 2016;39:555-64

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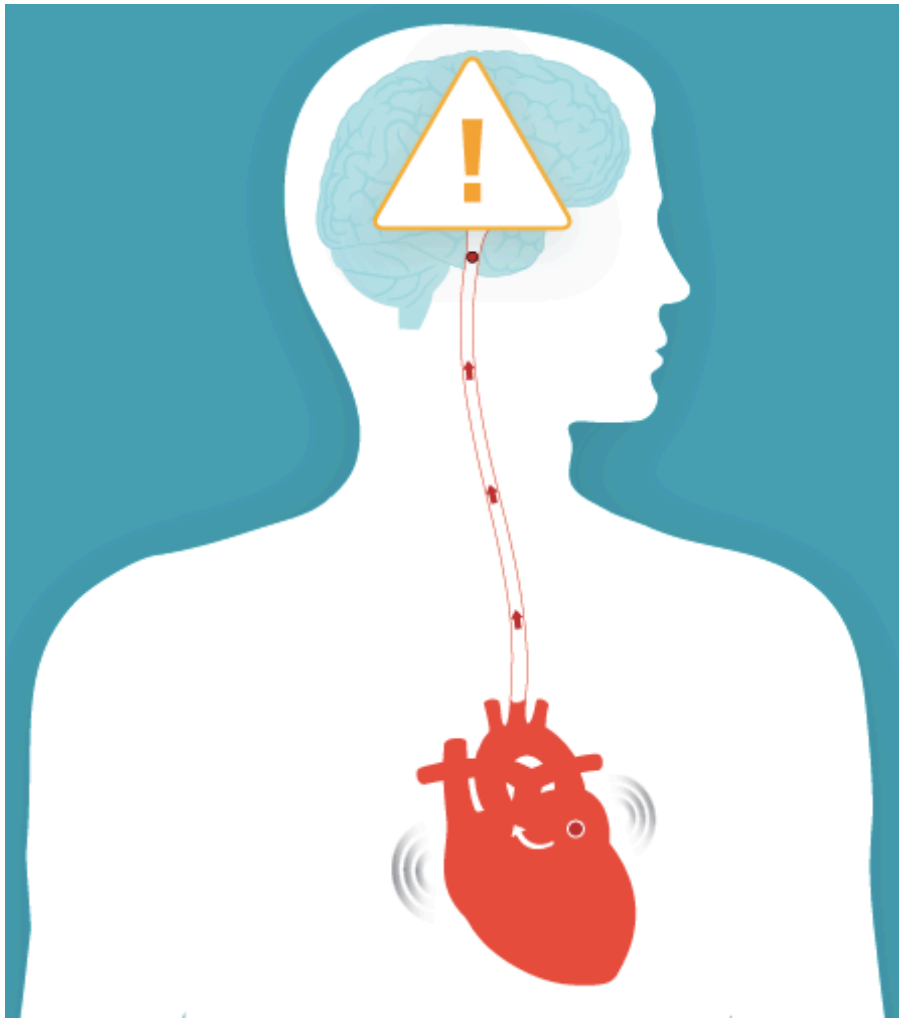
Overview

1. Real-world evidence:
    1. Use of oral anticoagulants
    2. Effectiveness and safety of oral anticoagulants
2. Guidelines recommendations on thromboprofilaxis
3. Oral anticoagulation in special situations
    1. Cardioversion
    2. Ablation
    3. Percutaneous coronary interventions
    4. Fragile patients
4. Conclusions



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Conclusiones

1. Manejo subóptimo de la anticoagulación en FA (sobre- e infra-untilización)
2. Se está experimentando un cambio de perfil en el tipo de anticoagulante. España se encuentra por debajo de la media europea en el grado de prescripción de ACOD.
3. Los datos de vida real confirman la efectividad y seguridad de los ACOD.
4. Baja capacidad predictiva de la “intuición médica” en la predicción de riesgo embólico.
5. La anticoagulación oral está indicada en individuos con CHA2DS2-Vasc ≥2 y se debería considerar en varones con CHA2DS2-Vasc 1.
6. Los ensayos randomizados demuestran que los ACOD son igual de eficaces y seguros que los antivitamina-K en cardioversión y ablación
7. La triple terapia tras revascularización disminuye los eventos embólicos pero aumenta el riesgo de sangrado. Los ACOD podrían ser una buena alternativa.

FIBRIL·LACIÓ AURICULAR

Indicacions d'anticoagulació

FA VALVULAR (pròtesis valvulars mecàniques i amb malaltia valvular mitral)

Risc tromboembòlic és molt elevat → anticoagulants orals antivitamina K (AVK).

- ✓ INR recomanat: entre 2-3
- ✓ INR en pròtesis mecàniques mitrals: entre 2.5-3.5.
- ✓ **No s'ha aprovat l'ús dels nous anticoagulants en aquesta situació.**

FA NO VALVULAR

Cal estratificar el risc embolígen per decidir:

- ✓ El risc embolígen s'avalua amb la escala CHA2DS2-VASC.
- ✓ El risc de sagnat s'avalua amb la escala HAS-BLED.

*Els pacients a qui es programa una **cardioversió elèctrica electiva** han de rebre anticoagulació oral des d'almenys 3 setmanes abans fins a un mínim de 4 setmanes després de la mateixa.*

Elecció del fàrmac anticoagulant oral

- **Pacients amb FA i malaltia valvular**: Acenocumarol o Warfarina.

- **Pacients amb FA no valvular i indicació d'anticoagulació** (CHA2DS2VASc >1):
  - ***Acenocumarol o Warfarina*** com a primera elecció, excepte:
  - ***Nou anticoagulant oral*** *(dabigatran, rivaroxaban o apixaban):*
    - Mal control de l'INR tot i una bona evidència de compliment.
    - Al·lèrgia o intolerància als efectes adversos dels AVK.
    - Seguiment de l'INR dificultós o poc pràctic.
    - Antecedent d'AVC hemorràgic o risc elevat d'hemorràgia intracranial (després de consulta o indicació per neuròleg).
    - Presentació d'AVC embòlic malgrat tractament correcte amb acenocumarol.

Thank you

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Algoritmo de elección de ACOD según perfil de pacientes

Choosing the oral anticoagulant drug to fit the patient profile	
Recurrent stroke, systemic embolic event, or transient ischaemic attack despite good anticoagulation control (TTR >70%)	Dabigatran 150 mg BID
Moderate-to-severe renal impairment (CrCl 15–49 mL/min)	Apixaban 5 mg BID*, rivaroxaban 15 mg once daily, dabigatran (if CrCl 30–49 mL/min)†, or edoxaban 30 mg once daily‡
High risk of gastrointestinal bleeding	Apixaban 5 mg BID* or dabigatran 110 mg BID§
Gastrointestinal symptoms or dyspepsia	Apixaban 5 mg BID*, rivaroxaban 20 mg once daily¶, or edoxaban 60 mg once daily‖
High risk of bleeding (HAS-BLED ≥3)	Dabigatran 110 mg BID§, apixaban 5 mg BID*, or edoxaban 60 mg once daily‖
Once daily dosing or preference to have a lower pill burden	VKA, rivaroxaban 20 mg once daily¶, or edoxaban 60 mg once daily‖
Asian patients (consider drugs with reduced risk of intracranial haemorrhage and major bleeding in Asian subgroups)	Apixaban 5 mg BID*, dabigatran†, or edoxaban 60 mg once daily‖
Less likely to do well on VKA with good TTR (SAMe-TT_2R_2 score >2)	VKA with additional education and more regular follow-up, dabigatran†, rivaroxaban 20 mg once daily¶, apixaban 5 mg BID*, or edoxaban 60 mg once daily‖

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