JOURNEE D'ACTUALITES THERAPEUTIQUES

Samedi 1er Avril 2017

Novotel Nice Arénas

Gestion des cas difficiles sous AOD

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2015 - Mr G… Christian 62 ans – FA Paroxystique

- HTA, atcd de coronaropathie avec thrombose de stent
- AIT en 2009
- 2010-2014 : Fluindione + Prasugrel + Pantoprazole
- A eu hémorragie digestive grave (choc hémorragique) en 2014 → embolisation artérielle + résection polypes coliques

Va mieux sur le plan rythmique --> souhaite surseoir à l'ablation.

Actuellement : isoptine lp 240 / Effient / Préviscan / Cortancyl 10 mg / urorec / Crestor

ressent une crise /15 jours de durée 15 mn à 2 h

--> ablation toujours d'actualité mais remise à plus tard selon les souhaits du patient

Auriez-vous repris les anticoagulants après cette hémorragie digestive?

2015 - Mr G… Christian 62 ans : après l'hémorragie digestive

Reinitiation of OAC after a bleeding event should be considered in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke prevention interventions, improved management of factors that contributed to bleeding, and stroke risk.	**IIa**	**B**
In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the cause of bleeding is resolved.	**I**	**C**

ESC guidelines for the management of atrial fibrillation, 2016

Quels anticoagulants après cette hémorragie digestive?

2015 - Mr G… Christian 62 ans : après l'hémorragie digestive

In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.	**IIa**	**B**

ESC guidelines for the management of atrial fibrillation, 2016

2015 – Ablation de FA programmée

Il est actuellement traité par une bithérapie anti-thrombotique associant des AVK à l''Efient. Cette bithérapie anti-thrombotique efficace l'expose également à un risque hémorragique. En effet, le traitement par Efient avait été motivé dans les suites de la réalisation d'un VASP ayant objectivé une mauvaise réponse au Plavix avec un VASP sous Efient réalisé en septembre 2011 tout à fait satisfaisant à 18 % (plutôt en faveur d'une hyper-réponse). Une stratégie satisfaisante me semblerait d'associer au traitement anticoagulant, une bithérapie anti-plaquettaire par Duoplavin.

Je ne modifie toutefois pas ce jour le traitement anti-thrombotique du patient et te propose Franck, comme tu le voulais, de réaliser un contrôle coronarograhique et de prendre cette décision au décours de cet examen.
Celui-ci sera programmé en fonction de la date de l'ablation retenue

2016 : Ablation programmée
Quelle stratégie d'anticoagulation?

Catheter ablation of atrial fibrillation and atrial fibrillation surgery (1)

Recommendations	Class	Level
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre.	I	A
Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF ablation procedure if flutter has been documented or occurs during the AF ablation.	IIa	B
Catheter ablation of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk.	IIa	B
All patients should receive oral anticoagulation for at least 8 weeks after catheter (IIaB) or surgical (IIaC) ablation.	IIa	B C
Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high-risk of stroke.	IIa	C
When catheter ablation of AF is planned, continuation of oral anticoagulation with a VKA (IIaB) or NOAC (IIaC) should be considered during the procedure, maintaining effective anticoagulation.	IIb	B C
Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryothermy balloon catheters.	IIa	B

European Heart Journal - doi:10.1093/eurheartj/ehw210

Biologie d'entrée
Creatinine 140µmol/l kaliémie 4.73 mmol/l Hb 13.5 g/dl INR : **2.12**

Antithrombotic management in patients undergoing atrial fibrillation catheter ablation for the maintenance of sinus rhythm: consensus recommendations

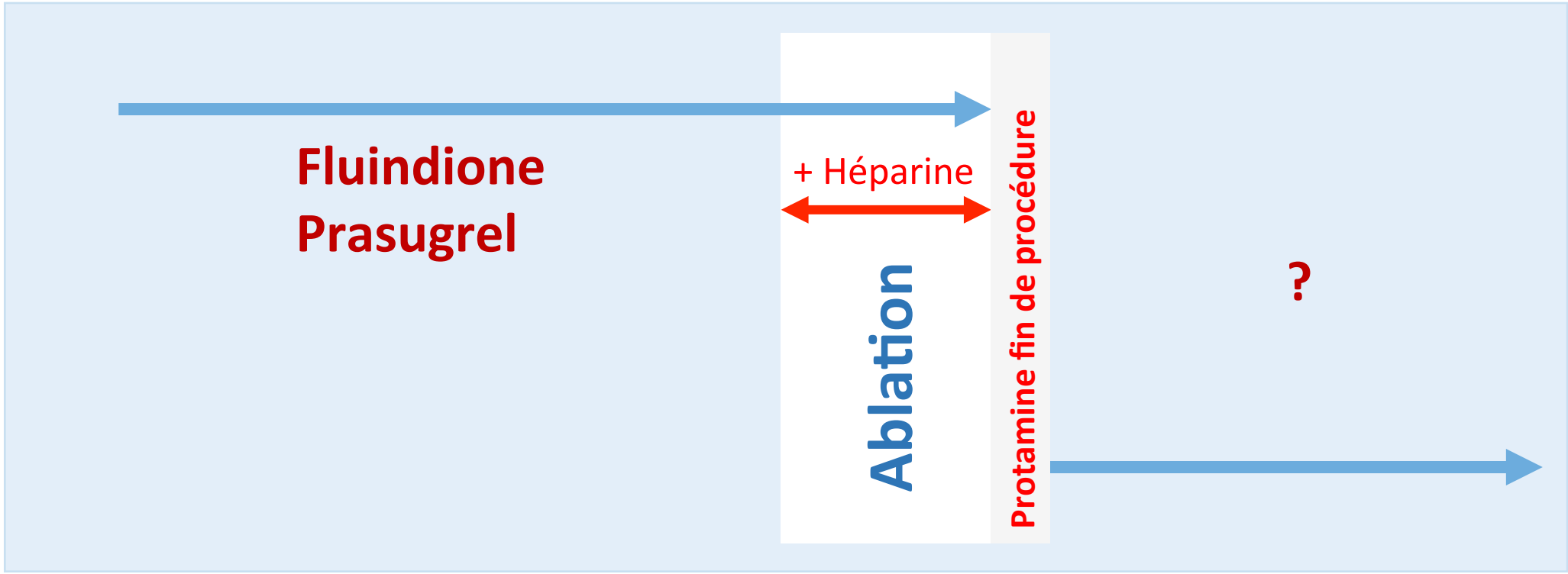
All patients undergoing AF catheter ablation who present for the procedure in AF should be anticoagulated with a NOAC, or a VKA with a therapeutic INR of 2.0–3.0 for 3 weeks prior to the procedure; or undergo a TEE to screen for thrombi prior to the procedure; post procedure, patients should receive anticoagulation for at least 2 months.

In patients receiving a VKA, the ablation should be performed without interruption of VKA therapy.

During the ablation procedure, patients should receive unfractionated heparin with an ACT of >300 s.

Sticherling et al., Europace 2015

Mr G… Christian - Traitement anticoagulant et ablation de FA



Quel traitement antithrombotique après l'ablation ?

Date de l'examen : 23/11/2015

N° d'examen : 151123120525
Signataire(s) :

Edition du 23/11/2015

Angiographie Coronaire

Synthèse

Contexte

Coronarographie de contrôle

Résultats

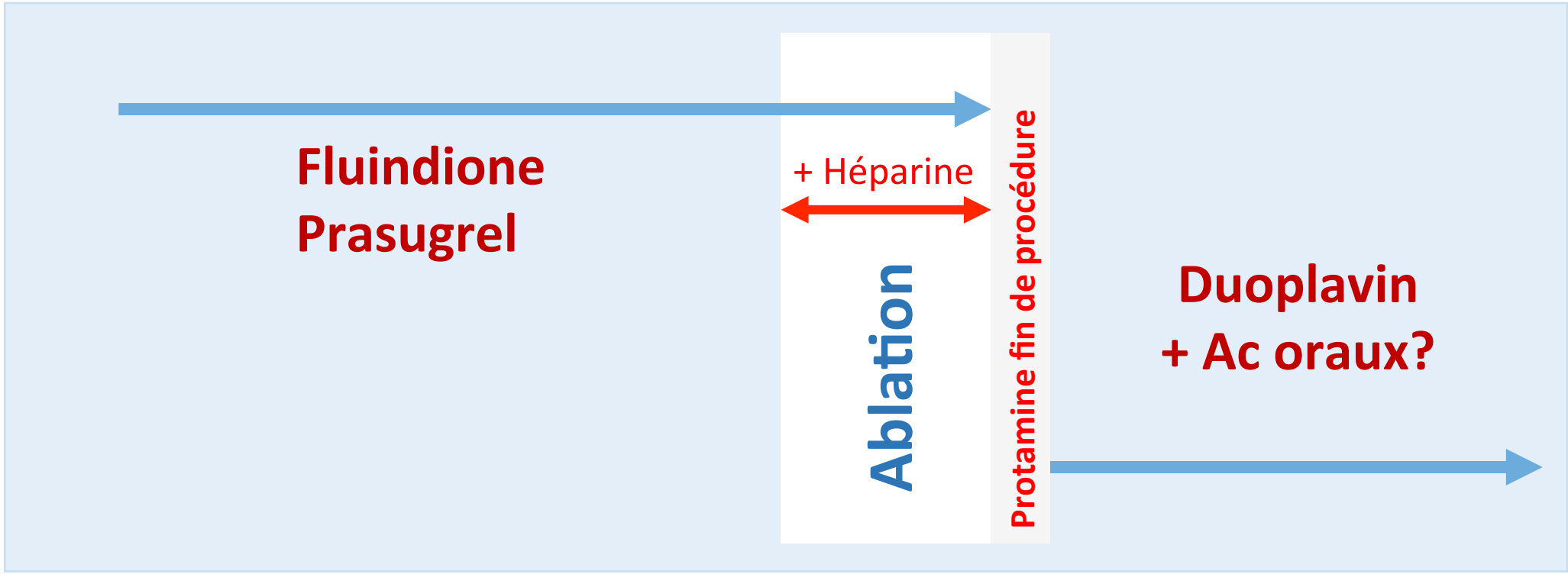
Coronarographie

Radiale droite /

Absence de resténose intrastnet Cx, plaque Mg non significative
IVA et CD indemnes de lésion significaive

Absence d'indication à geste de revascularisation
Arrêt Efient possible à remplacer par Duoplavin compte tenu anticogulation orale

Mr G… Christian - Traitement anticoagulant après ablation de FA

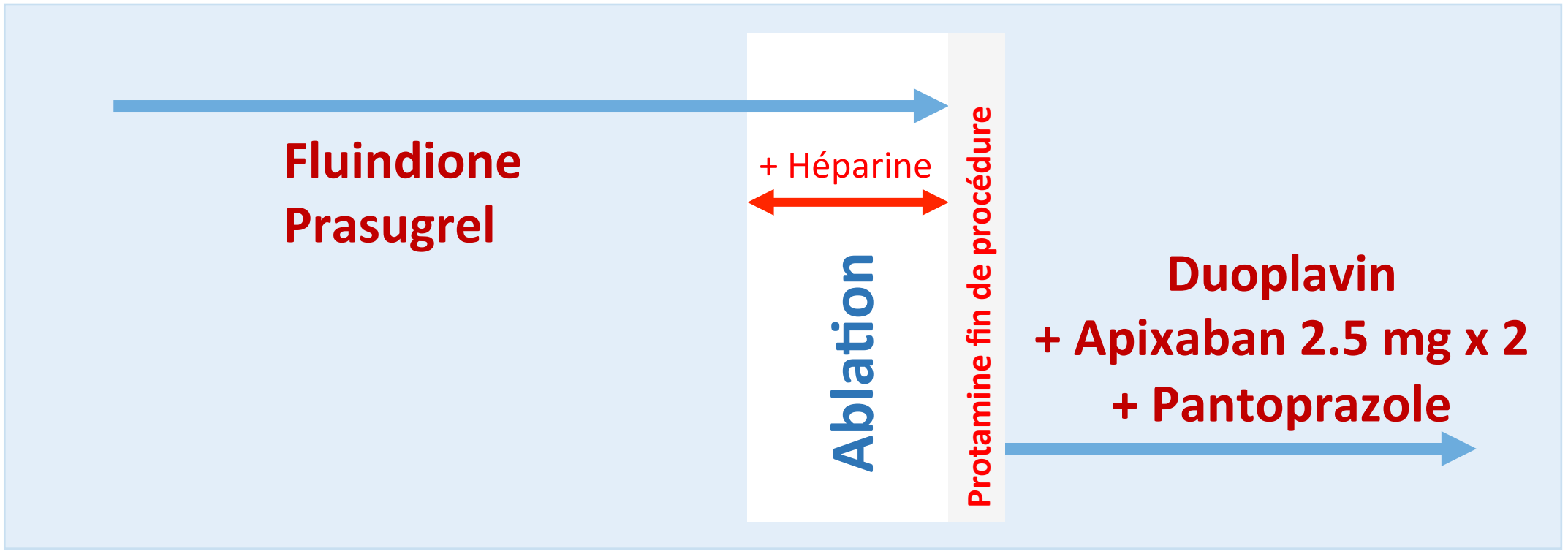


Traitement antithrombotique après l' ablation de FA

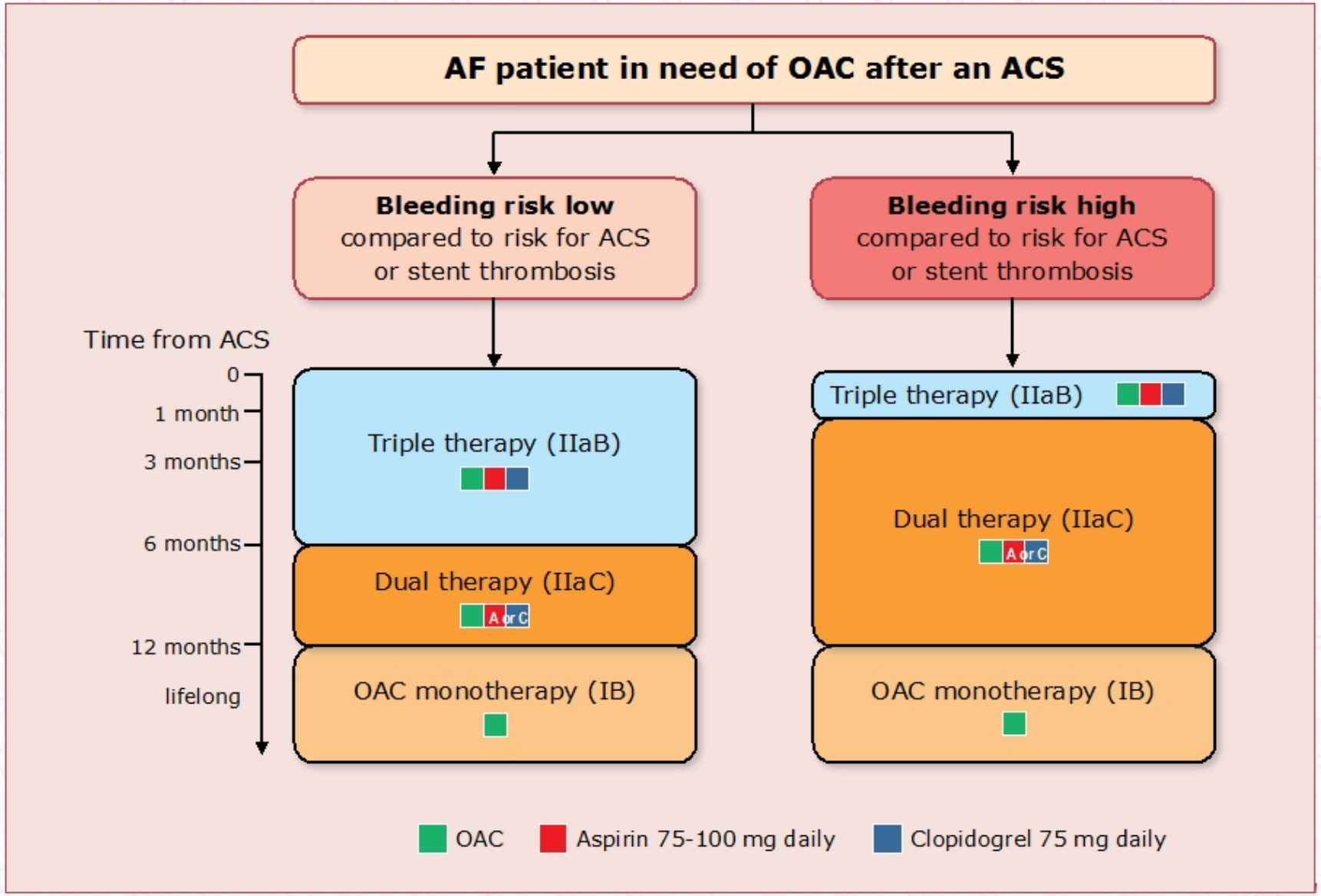
Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high-risk of stroke.	**IIa**	**C**
In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.	**IIa**	**B**

ESC guidelines for the management of atrial fibrillation, 2016

Mr G… Christian - Traitement anticoagulant après ablation de FA



Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation



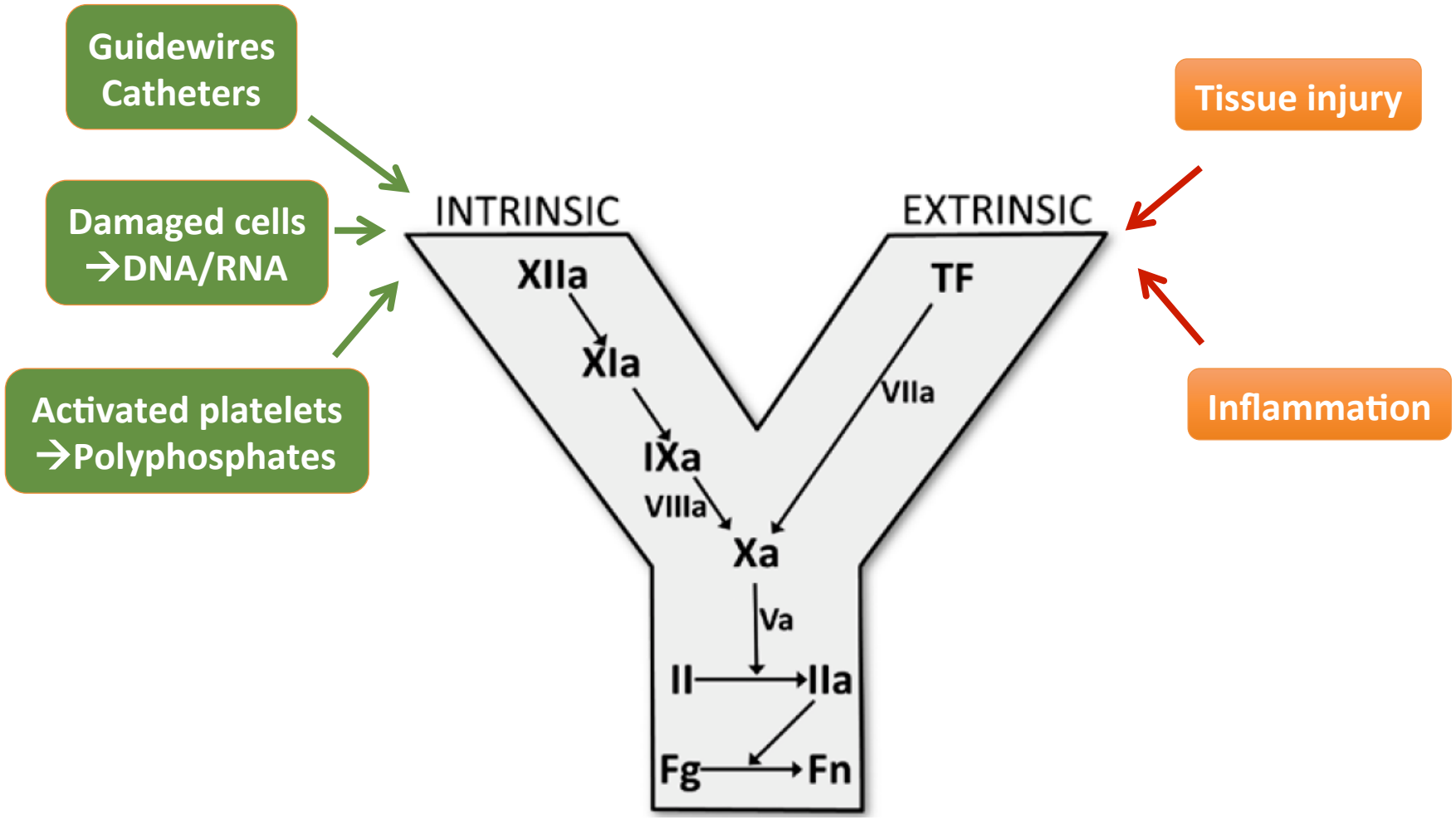
European Heart Journal - doi:10.1093/eurheartj/ehw210

Après une hémorragie grave sous anticoagulants pour de la fibrillation atriale : toujours se poser la question de la réinitiation des anticoagulants

Après ablation de la FA les anticoagulants doivent être maintenus (quel que soit le résultat de l'ablation) s'ils sont indiqués par le score CHA_2DS_2VASc du patient

A distance de l'angioplastie ou du SCA, discuter un traitement anticoagulant seul chez le coronarien ayant des antécédents de fibrillation atriale

Stimuli for activation of coagulation during AF ablation



from Weitz et al., Circulation 2014

Stroke/TIA and Tamponade during AF ablation

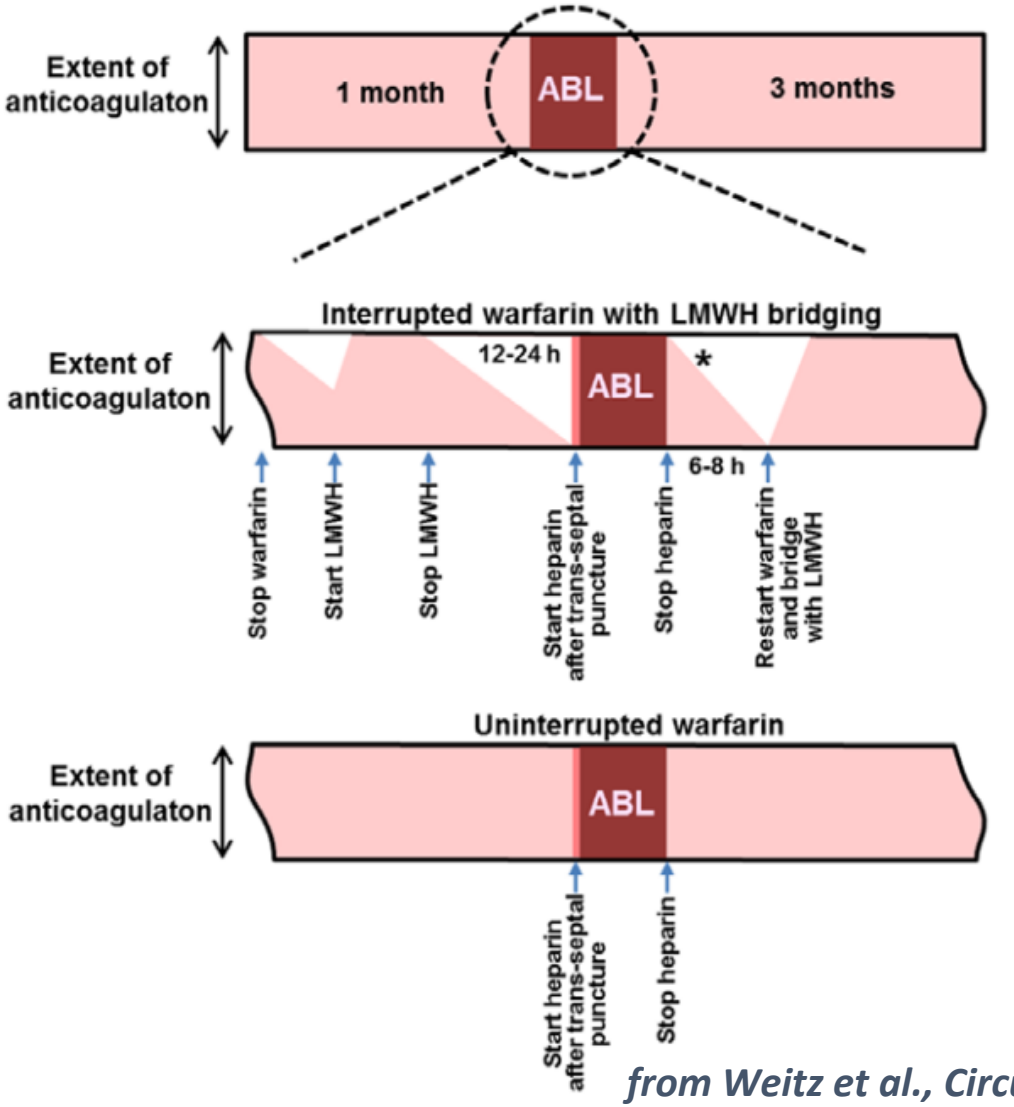
Author/year	Study design	Size (patients)	Stroke/TIA (%)	Tamponade (%)	References
Stabile (CACAF) 2006	RCT	68	1.5	1.5	8
Wazni (RAAFT) 2005	RCT	33	0	0	9
Oral 2006	RCT	130	0	0	10
Pappone 2006	RCT	99	1	0	11
Jais (A4) 2008	RCT	155	0	1.2	12
Wilber (Thermocool-AF) 2010	RCT	106	0	0.9	13
Nielsen (MANTRA PAF) 2012	RCT	146	1.3	2.1	3
Packer (STOP AF) 2013	RCT	163	4.2	0.6	14
Cappato 2010	Survey	16'309	0.9	1.3	15
Deshmukh 2013	Survey	93'801	1.0	1.5	16

Sticherling et al. Europace 2015

Periprocedural anticoagulation strategies for AF ablation

Interrupted Warfarin + Bridging

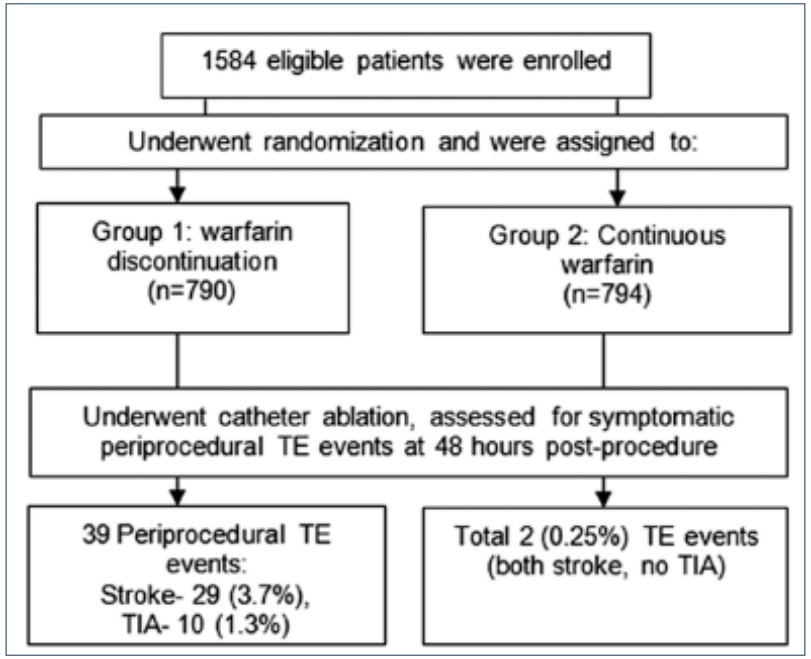
Uninterrupted Warfarin

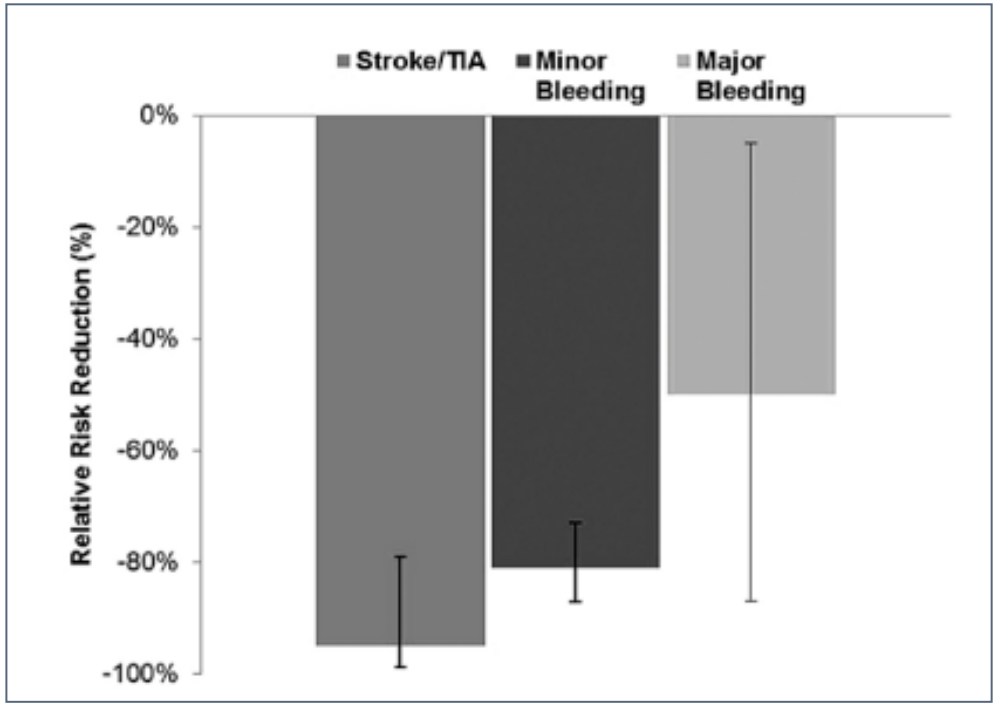


from Weitz et al., Circulation 2014

Periprocedural Stroke and Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation With Different Anticoagulation Management

Results From the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) Randomized Trial

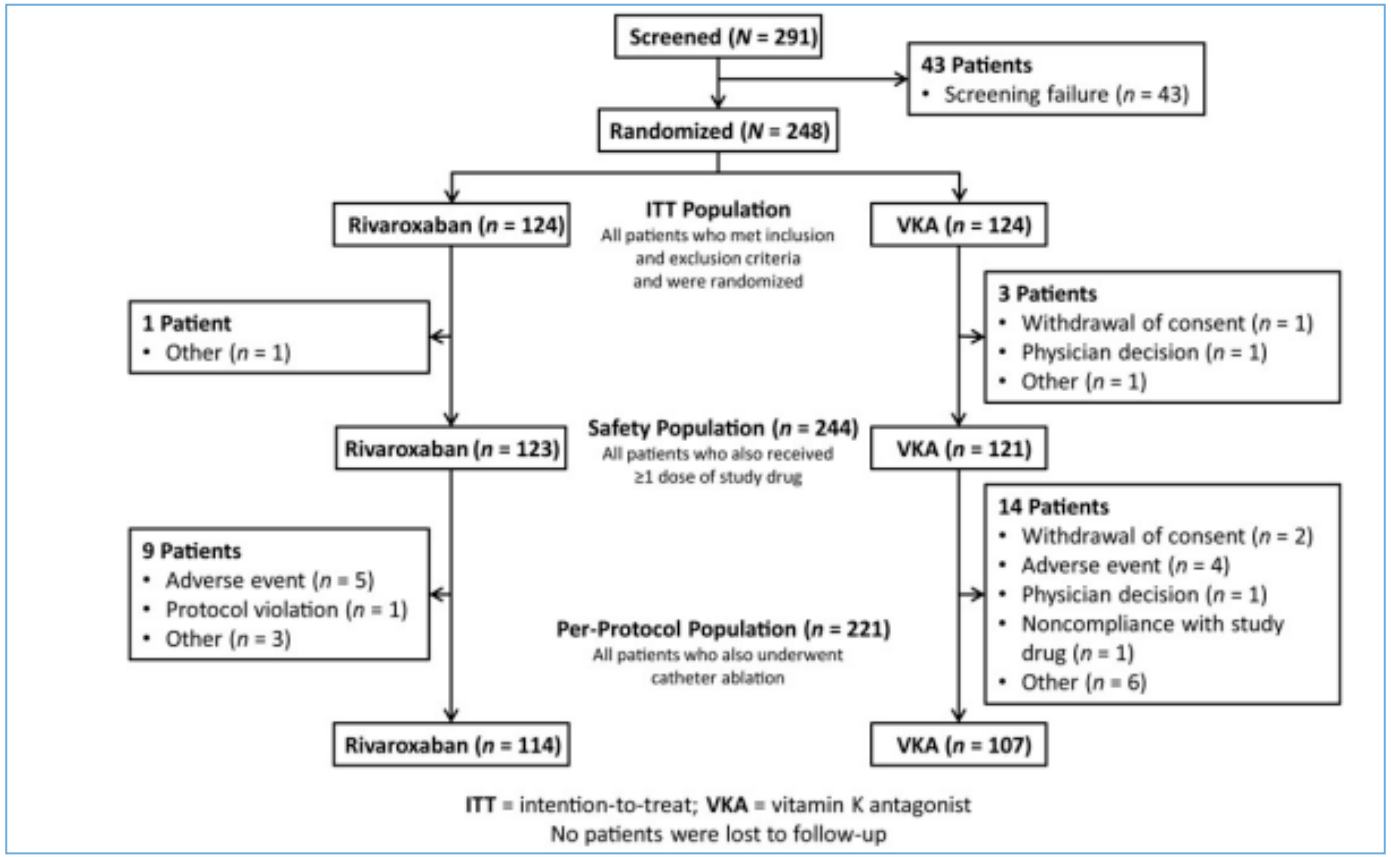




Di Biase et al. Circulation 2014

Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation

Riccardo Cappato[1,2], Francis E. Marchlinski[3], Stefan H. Hohnloser[4],



Eur Heart J 2015

Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation

Riccardo Cappato[1,2], Francis E. Marchlinski[3], Stefan H. Hohnloser[4],

Table I Baseline demographic characteristics of the ITT population

	Rivaroxaban (*N* = 124)	VKA (*N* = 124)	Total (*N* = 248)	*P* Value
Mean age, years (SD)	58.6 (9.9)	60.5 (10.5)	59.6 (10.2)	0.211
Age ≥75, *n* (%)	5 (4.0)	10 (8.1)	15 (6.0)	0.183
Age 65–75	34 (27.4)	41 (33.1)	75 (30.2)	0.183
Male	86 (69.4)	90 (72.6)	176 (71.0)	0.576
Caucasian	112 (90.3)	116 (93.5)	228 (91.9)	0.351
Non-Hispanic/Latino	90 (72.6)	94 (75.8)	184 (74.2)	0.562
Paroxysmal AF	95 (76.6)	87 (70.2)	182 (73.4)	0.250
Prior cardioversion	47 (37.9)	54 (43.5)	101 (40.7)	0.366
Prior catheter ablation	11 (8.9)	11 (8.9	22 (8.9)	0.563
Mean BMI, kg/m^2 (SD)	29.8 (5.7)	28.9 (5.5)	29.4 (5.6)	0.231
CHF	12 (9.7)	9 (7.3)	21 (8.5)	0.494
Hypertension	59 (47.6)	57 (46.0)	116 (46.8)	0.799
Mean systolic BP, mmHg (SD)	133 (16)	131 (18)	132 (17)	0.325
Mean diastolic BP, mmHg (SD)	81 (10)	79 (11)	80 (10)	0.233
Diabetes mellitus	8 (6.5)	14 (11.3)	22 (8.9)	0.180
Prior Stroke/TIA/embolism	0	3 (2.4)	3 (1.2)	0.081
Vascular disease	22 (17.7)	25 (20.2)	47 (19.0)	0.627
Mean CHADS2 Score (SD)	0.7 (0.7)	0.8 (0.9)	0.7 (0.8)	0.179
Mean CHA2DS2-VASc Score (SD)	1.5 (1.3)	1.7 (1.4)	1.6 (1.3)	0.277
Beta blocker, selective	65 (52.4)	61 (49.2)	126 (50.8)	0.611
Antiarrhythmic, class IC	51 (41.1)	49 (39.5)	100 (40.3)	0.796
Antiarrhythmic, class III	30 (24.2)	39 (31.5)	69 (27.8)	0.202
Vitamin K antagonist	36 (29.0)	37 (29.8)	73 (29.4)	0.889
Rivaroxaban	23 (18.5)	29 (23.4)	52 (21.0)	0.349
Dabigatran	12 (9.7)	10 (8.1)	22 (8.9)	0.655
Antiplatelet agent	37 (29.8)	29 (23.4)	66 (26.6)	0.250
Proton pump inhibitor	26 (21.0)	18 (14.5)	44 (17.7)	0.184

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Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation

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Table 3 The number of CEC-adjudicated outcomes reported during the study period (the number of patients is also shown)

	Rivaroxaban	VKA	Total
Any CEC-adjudicated event	26	25	51
	$n = 124$	$n = 124$	$n = 248$
Any thromboembolic events (Composite)[a]	0	2	2
Ischemic stroke	0	1	1
Vascular death	0	1	1
	$n = 123$	$n = 121$	$n = 244$
Any bleeding events[b]	21	18	39
Major bleeding event			
Vascular pseudoaneurysm	0	1	1
Non-major bleeding events			
Arteriovenous fistula	0	1	1
Catheter/puncture site haemorrhage	1	1	2
Contusion	1	1	2
Ecchymosis	0	1	1
Epistaxis	2	1	3
Eye haemorrhage (non-intraocular)	1	0	1
Gingival bleeding	1	0	1
Haematoma/vessel puncture site haematoma	8	10	18
Haematuria	2	0	2
Haemorrhagic stomatitis	0	1	1
Mouth haemorrhage	1	0	1
Urinary tract infection	1	0	1
Vascular pseudoaneurysm	3	1	4

Eur Heart J 2015

RE-CIRCUIT®
Study of peri-procedural anticoagulation in AF ablation

Safety and Efficacy of Uninterrupted Anticoagulation with Dabigatran Etexilate versus Warfarin in Patients Undergoing Catheter Ablation of Atrial Fibrillation: The RE-CIRCUIT™ Study

Hugh Calkins, M.D.,[1] Stephan Willems, M.D., Atul Verma, M.D., Richard Schilling, M.D., Stefan H. Hohnloser, M.D., Ken Okumura, M.D., Ph.D., Kelly Guiver, M.Sc., Branislav Biss, M.D., M.B.A, Matias Nordaby, M.D., Edward P. Gerstenfeld, M.D.

On behalf of the RE-CIRCUIT™ Investigators

March 19, 2017
10:45 am – 10:55 am

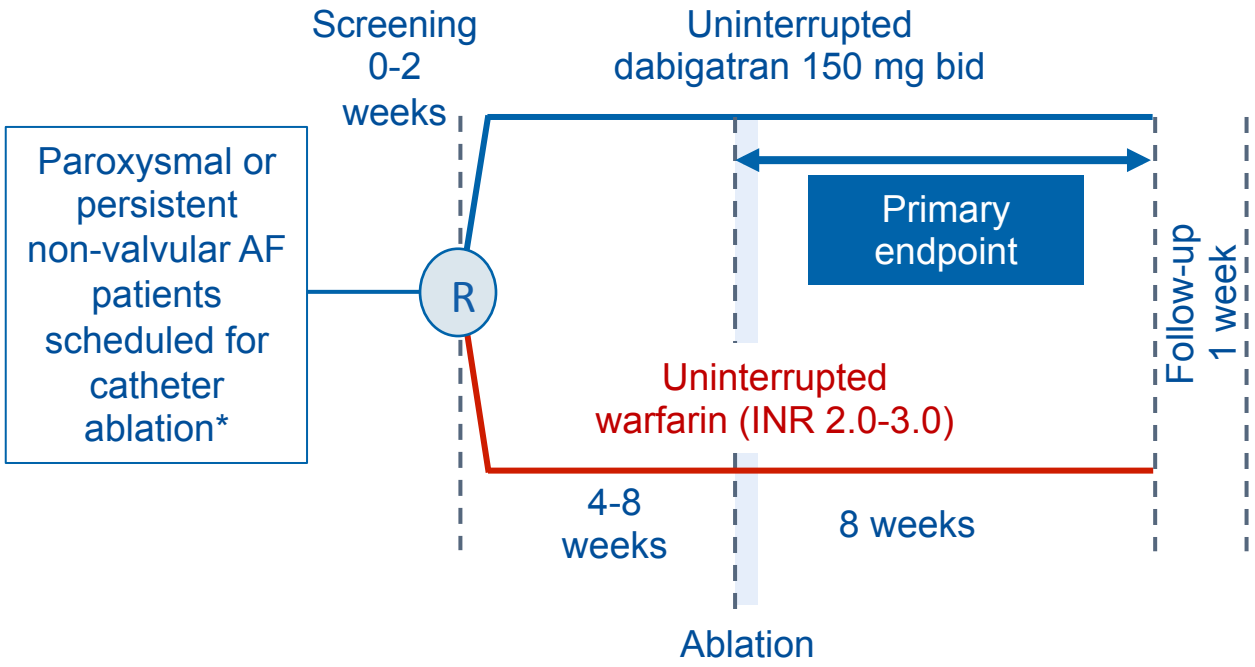
[1]Johns Hopkins Medical Institutions, Baltimore, MD, USA.

RE-CIRCUIT™: objective

Exploratory study to assess the safety and efficacy of uninterrupted peri-procedural regimens of dabigatran and warfarin in nonvalvular atrial fibrillation (NVAF) patients undergoing AF ablation

Boehringer Ingelheim Clinical Trial Protocol, Trial No. 1160.204

Study Design

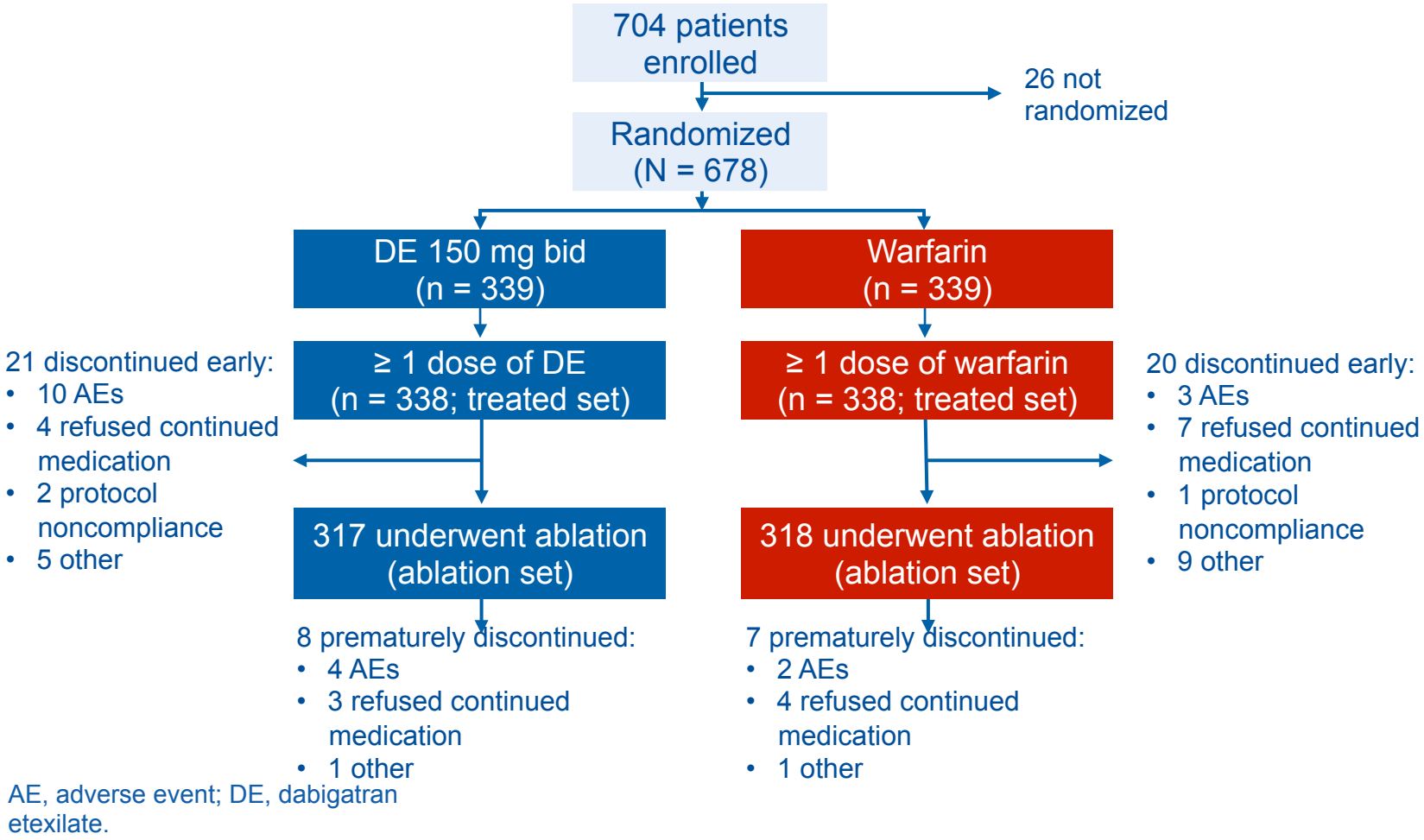


- **Primary endpoint:** incidence of adjudicated ISTH MBEs from venous access up to 8 weeks post-ablation†
- **Secondary endpoints** included adjudicated thromboembolic events from venous access to 8 weeks post-ablation†

*And eligible for dabigatran 150 mg bid according to local prescribing information.

†Primary end point assessed from the start of the ablation procedure and up to 8 weeks post-ablation.

Patient Disposition



AE, adverse event; DE, dabigatran etexilate.

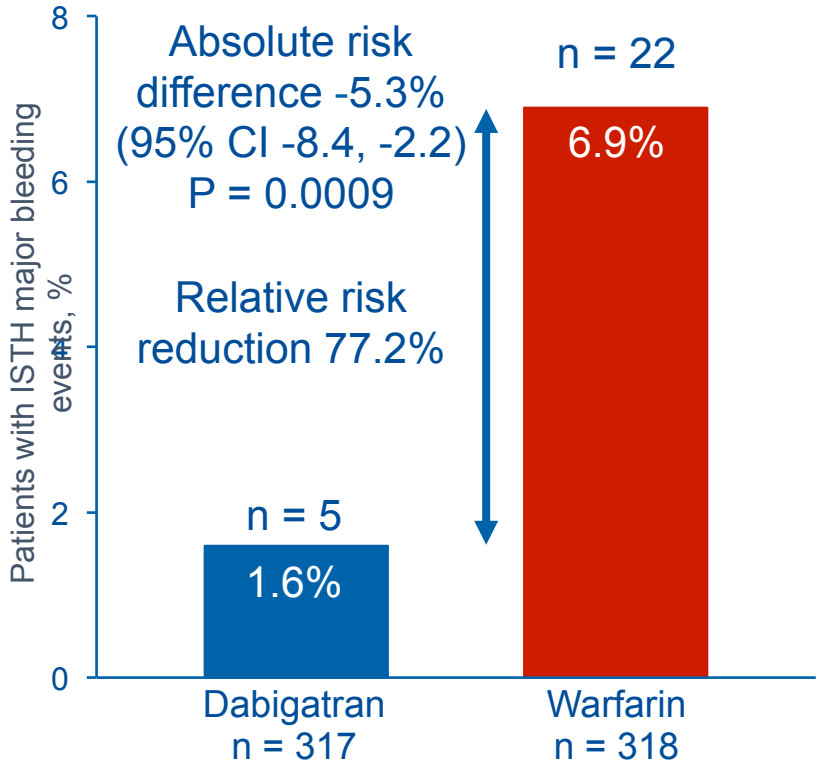
Baseline Demographics

Characteristics	Dabigatran 150 mg bid (n = 317)	Warfarin (n = 318)
Mean age (standard deviation), years	59.1 (10.4)	59.3 (10.3)
Atrial fibrillation, n (%)		
Paroxysmal	213 (67.2)	219 (68.9)
Persistent	86 (27.1)	81 (25.5)
Longstanding persistent	18 (5.7)	18 (5.7)
CHA_2DS_2-VASc score, mean	2.0	2.2
Medical history, n (%)		
Congestive heart failure	31 (9.8)	34 (10.7)
Hypertension	166 (52.4)	177 (55.7)
Diabetes mellitus	30 (9.5)	34 (10.7)
Previous stroke	10 (3.2)	9 (2.8)
Coronary artery disease	32 (10.1)	48 (15.1)
Previous myocardial infarction	10 (3.2)	15 (4.7)
Prior major bleeding or predisposition	3 (0.9)	4 (1.3)
TTR during study, mean %*	–	66.4

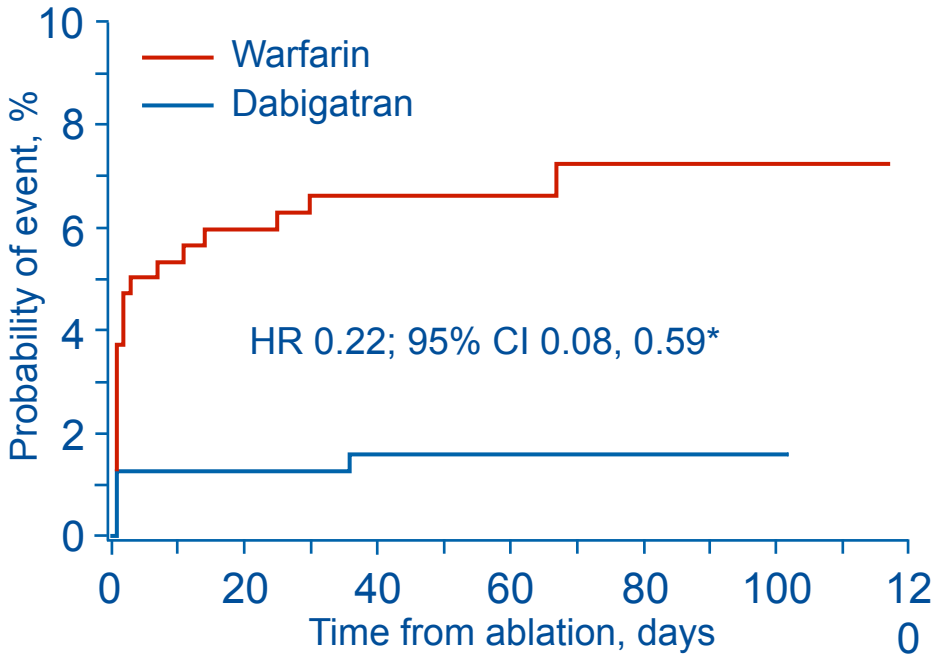
TTR, time in therapeutic range of INR 2.0-3.0. *Based on treated set, n = 330.

Results

- Patients on uninterupted dabigatran had significantly fewer MBEs as compared with
  patients on warfarin



Fewer MBEs from the Time of Ablation



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

*Cox proportional hazard model and Wald confidence limits.

Sites and Management of ISTH MBEs

	Dabigatran	Warfarin
ISTH MBEs, n*	5	23†
Pericardial tamponade	1	6
Pericardial effusion	1	0
Groin bleed	2	2
Groin hematoma	0	8
Gastrointestinal bleed	1	2
Intracranial bleed	0	2
Pseudoaneurysm	0	1
Hematoma	0	2
Required medical action	4	21
Intervention/procedure	1	11

*Based on number of events rather than number of patients.

†One patient had two adjudicated ISTH MBEs.

Results: Secondary Endpoints

Low Rate of Thromboembolic Events

- Stroke: no events
- Systemic embolism: no events
- Transient ischemic attack: dabigatran 0 vs warfarin 1

Minor Bleeding Events Similar Between Treatments

- Dabigatran 59 (18.6%) vs warfarin 54 (17.0%)

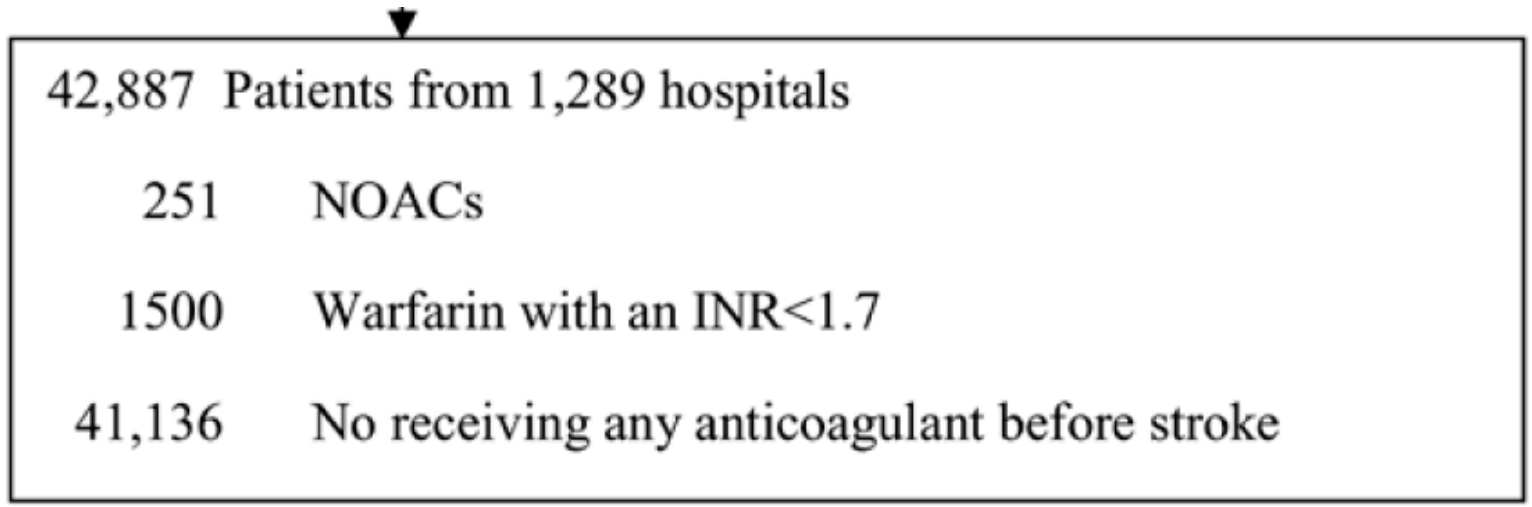
Conclusion

- In conclusion, the results of the RE-CIRCUIT study demonstrate that performance of AF ablation on uninterrupted dabigatran is a better anticoagulation strategy
  as compared with performance of AF ablation on uninterrupted warfarin

- The availability of the specific reversal agent idarucizumab, while not needed in any patient in this trial, further supports the adoption of uninterrupted dabigatran as the preferred anticoagulation strategy over uninterrupted warfarin in patients undergoing AF ablation

Cas difficile : thrombolyse pour AVC

Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before Stroke



Xian Y et al., Circulation 2017

Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before Stroke

	No. Events/Total No. of Patients (%)				
	NOACs (n=245)	Warfarin with INR<1.7 (n=245)	No Oral Anticoagulant (n=245)	Odds Ratio NOACs vs No (95% CI)	Odds Ratio Warfarin vs No (95% CI)
Primary outcomes					
Symptomatic intracranial hemorrhage <36 h	12/245 (4.9)	12/245 (4.9)	15/245 (6.1)	0.79 (0.36–1.72)	0.79 (0.36–1.72)
Life-threatening or serious systemic hemorrhage <36 h	1/245 (0.4)	1/245 (0.4)	1/245 (0.4)	1.00 (0.06–16.1)	1.00 (0.06–16.1)
Any rt-PA complication*	16/245 (6.5)	23/245 (9.4)	24/245 (9.8)	0.64 (0.33–1.24)	0.95 (0.53–1.74)
Secondary outcomes					
In-hospital mortality	23/245 (9.4)	21/245 (8.6)	24/245 (9.8)	0.95 (0.52–1.74)	0.86 (0.47–1.60)
Discharge to home	101/245 (41.2)	88/245 (35.9)	86/245 (35.1)	1.30 (0.90–1.87)	1.04 (0.72–1.50)
Discharge to hospice	19/245 (7.8)	26/245 (10.6)	24/245 (9.8)	0.77 (0.41–1.45)	1.09 (0.61–1.96)
Discharge to skilling nursing facility	34/245 (13.9)	43/245 (17.6)	45/245 (18.4)	0.72 (0.44–1.16)	0.95 (0.60–1.50)
Discharge inpatient rehabilitation facility	62/245 (25.3)	61/245 (24.9)	59/245 (24.8)	1.07 (0.71–1.61)	1.05 (0.69–1.58)
Able to ambulate independently at discharge†	102/226 (45.1)	80/225 (35.6)	89/225 (39.6)	1.26 (0.86–1.83)	0.84 (0.58–1.24)
Modified Rankin Scale at discharge†					
mRS 0–1	34/149 (22.8)	23/151 (15.2)	38/143 (26.6)	0.82 (0.48–1.39)	0.50 (0.28–0.89)
mRS 0–2	44/149 (29.5)	44/151 (29.1)	47/143 (32.9)	0.86 (0.52–1.41)	0.84 (0.51–1.38)

Xian Y et al., Circulation 2017

Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before Stroke

What Is New?

- Non–vitamin K antagonist oral anticoagulants (NOACs) have been increasingly used as alternatives to warfarin for stroke prevention in patients with atrial fibrillation.
- Despite the efficacy of NOACs, some patients may still experience an ischemic stroke.
- To date, the question of whether patients with ischemic stroke taking NOACs should be treated with intravenous rt-PA (recombinant tissue plasminogen activator) has been debated.
- We examined 42 887 patients with ischemic stroke treated with rt-PA at 1289 hospitals in the United States between 2012 and 2015.
- We found no statistically significant differences in the risk of symptomatic intracranial hemorrhage between patients who were taking NOACs, warfarin (international normalized ratio<1.7), or not taking any oral anticoagulant before stroke.

What Are the Clinical Implications?

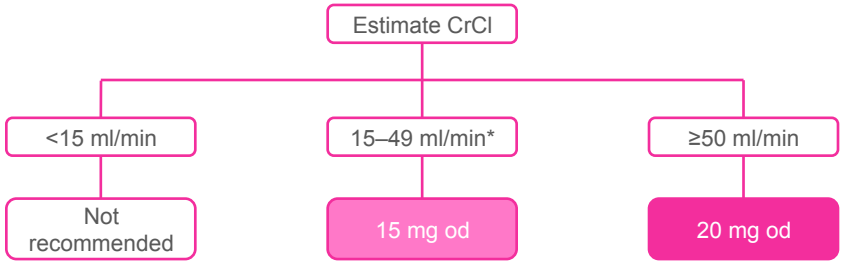
- This study represents the largest clinical experience of stroke thrombolysis in patients receiving NOACs before stroke.
- rt-PA appears to be reasonably well tolerated without prohibitive risks for adverse events among selected NOAC-treated patients.
- However, our observations must be considered as preliminary because of the absence of coagulation parameters, timing of the last NOAC intake, and whether nonspecific reversal strategies may have been applied.

Xian Y et al., Circulation 2017

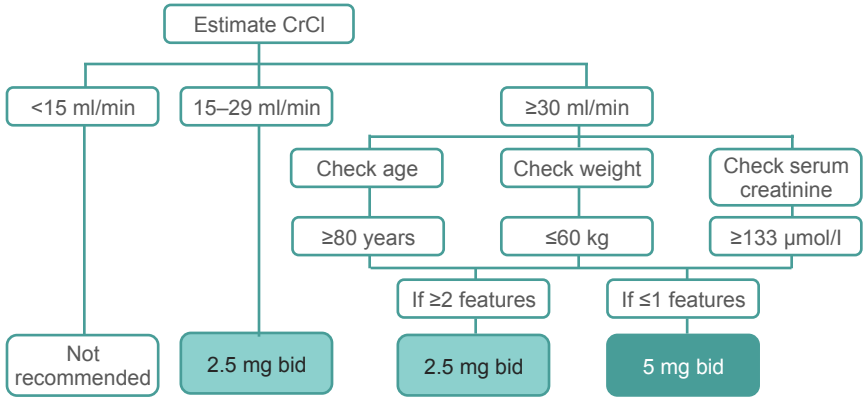
Cas difficile : la réduction de dose

Dose Adjustments in NVAF Patients with ≥1 Risk Factors for Stroke/Systemic Embolism

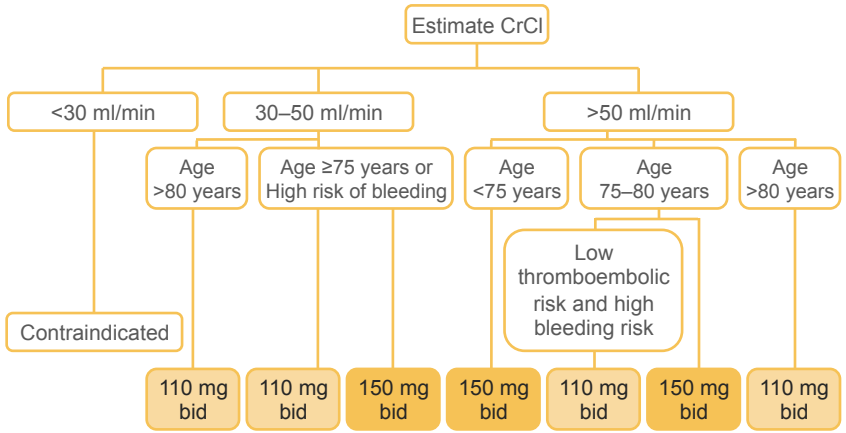
Rivaroxaban[1]



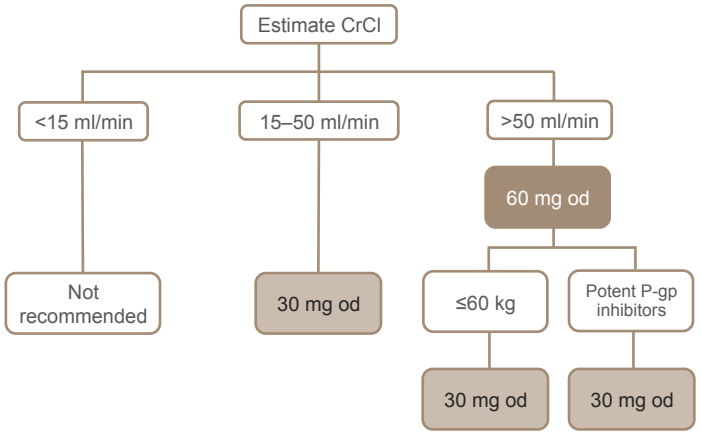
Apixaban[2]



Dabigatran[3]



Edoxaban[4]



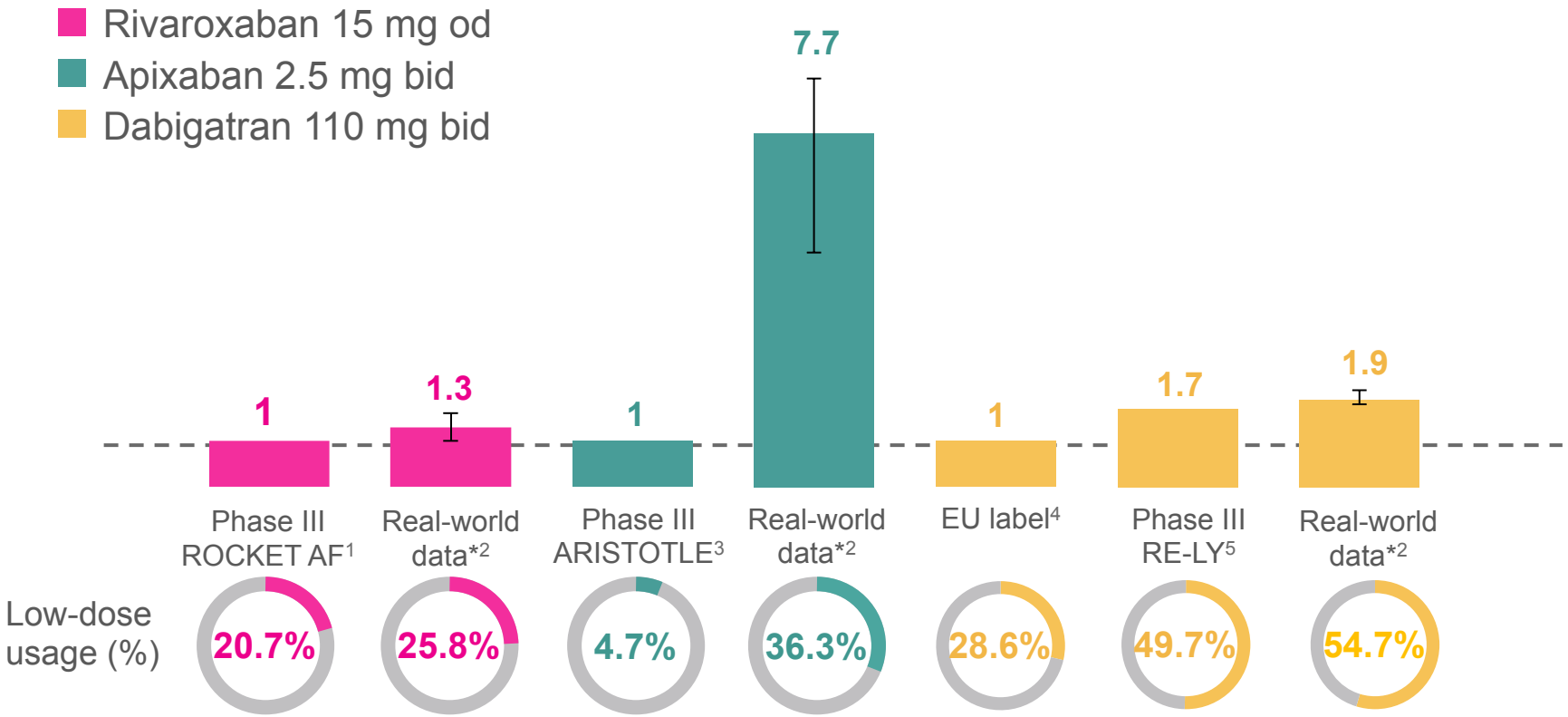
1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC

◄ Slide Index

Low-Dose Usage in the Real World Versus Clinical Trials

Use of low-dose rivaroxaban consistent with expectations from phase III

X-fold increase in use of low-dose versus phase III trial or EU label recommendation



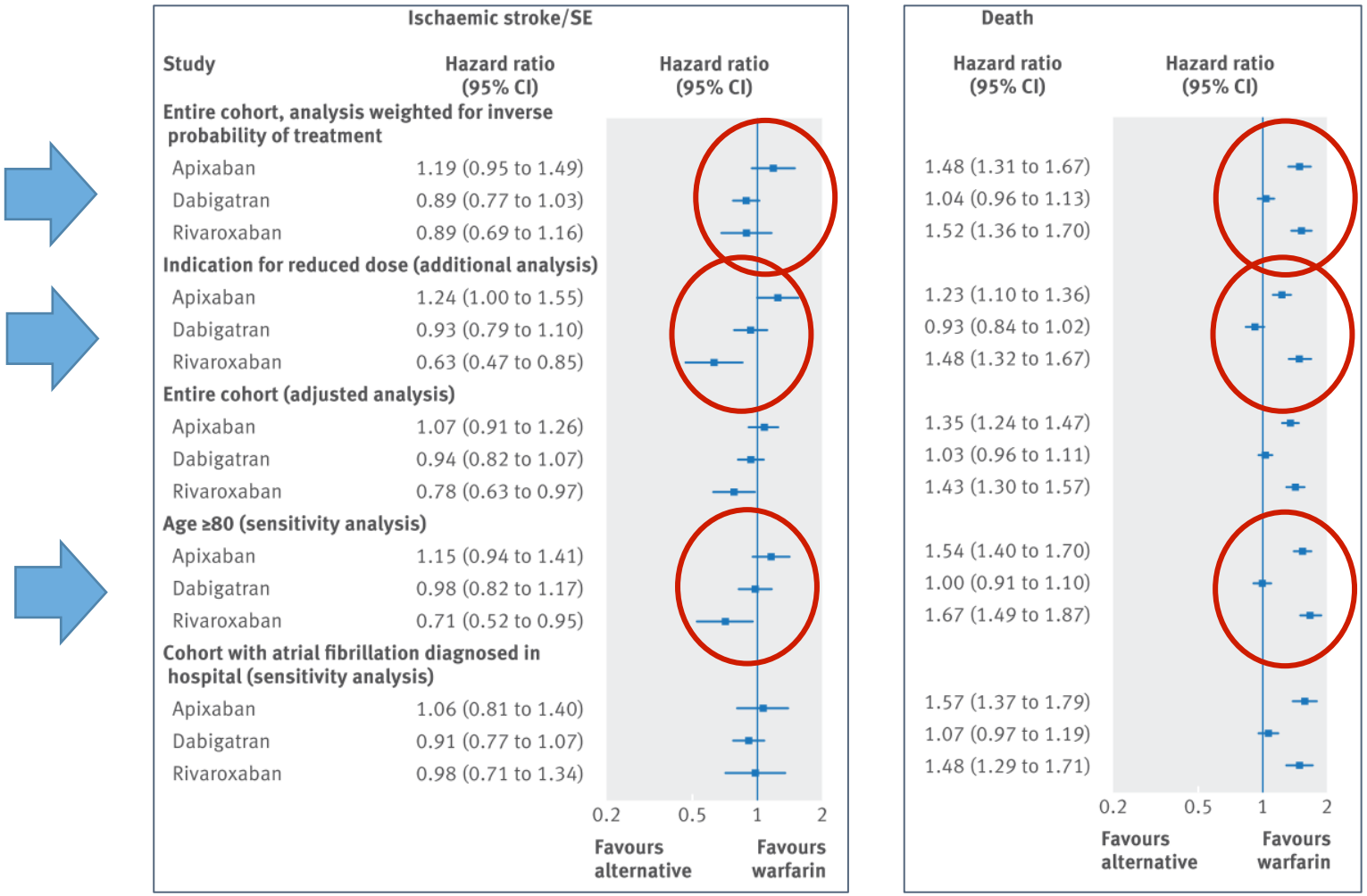
*Mean and range: data from the US, Germany, Canada and UK (US excluded for dabigatran because dabigatran 110 mg dose not approved)

1. Fox KA *et al*, *Eur Heart J* 2011;32:2387–2394; 2.IMS MIDAS. Q4 2014; 3. Granger GB *et al*, *N Engl J Med* 2011;365:981–992;
4. Lip GYH *et al, Thromb Haemost* 2014;111:933–942; 5. Connolly SJ *et al*, *N Engl J Med* 2009;361:1139–1151

◄ Slide Index

Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

Peter Brønnum Nielsen,[1] Flemming Skjøth,[1,2] Mette Søgaard,[1,3] Jette Nordstrøm Kjældgaard,[1,3] Gregory Y H Lip,[1,4] Torben Bjerregaard Larsen[1,3]



BMJ 2017

Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

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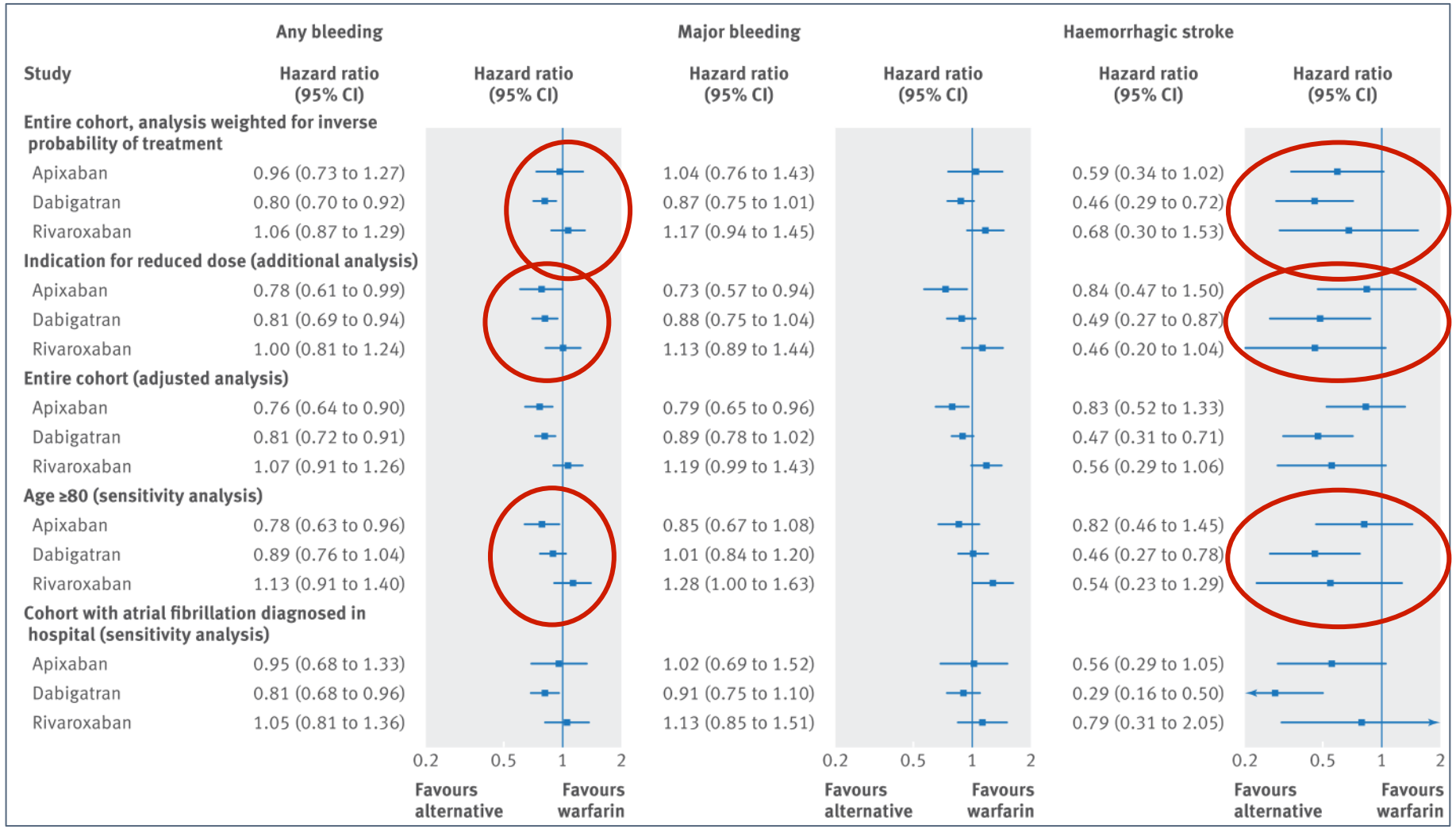

BMJ 2017

Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of reduced dose non-vitamin K antagonist oral anticoagulants (NOAC) has been increasing since their introduction

Limited evidence exists relating to effectiveness and safety of reduced doses compared with warfarin based on data from clinical practice

WHAT THIS STUDY ADDS

Rates of ischaemic stroke or systemic embolism with apixaban 2.5 mg were higher but not significantly so compared with warfarin

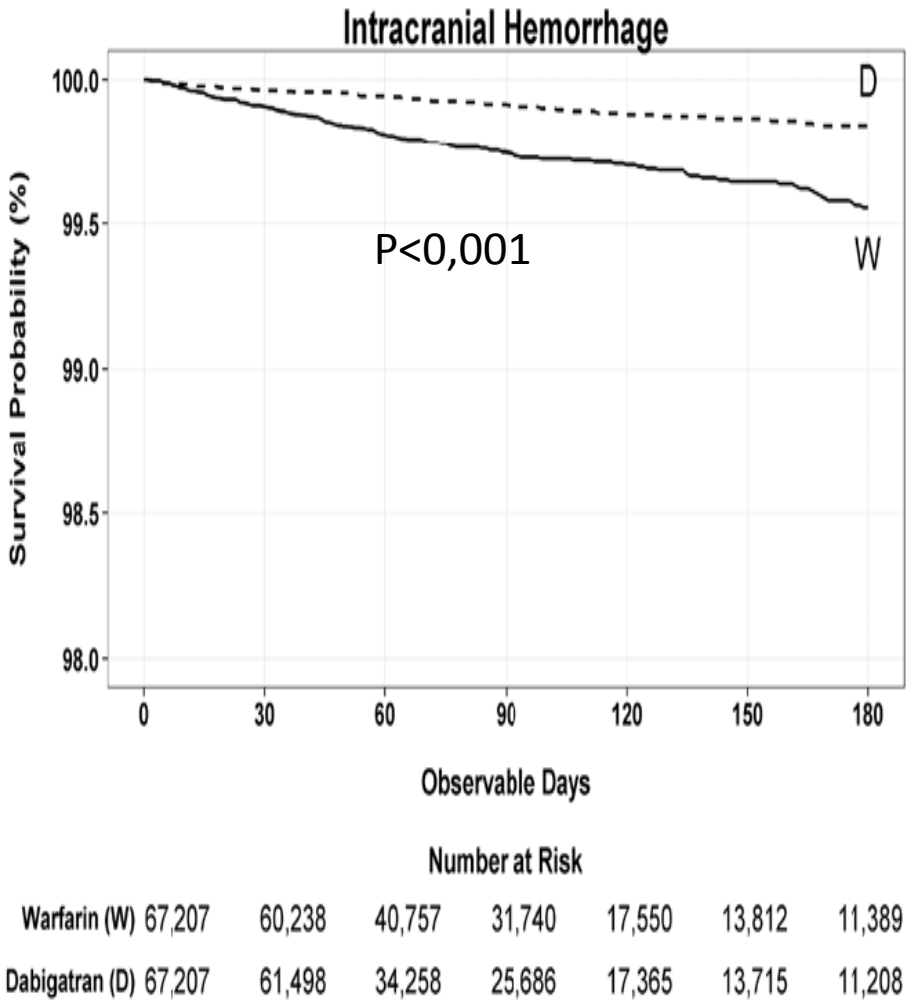
Dabigatran 110 mg and rivaroxaban 15 mg both showed a trend towards lower thromboembolic rates, but rates were not significantly different to rates with warfarin

Rates of bleeding, the principal safety outcome, were not significantly different for apixaban and rivaroxaban compared with warfarin but were lower for dabigatran

BMJ 2017

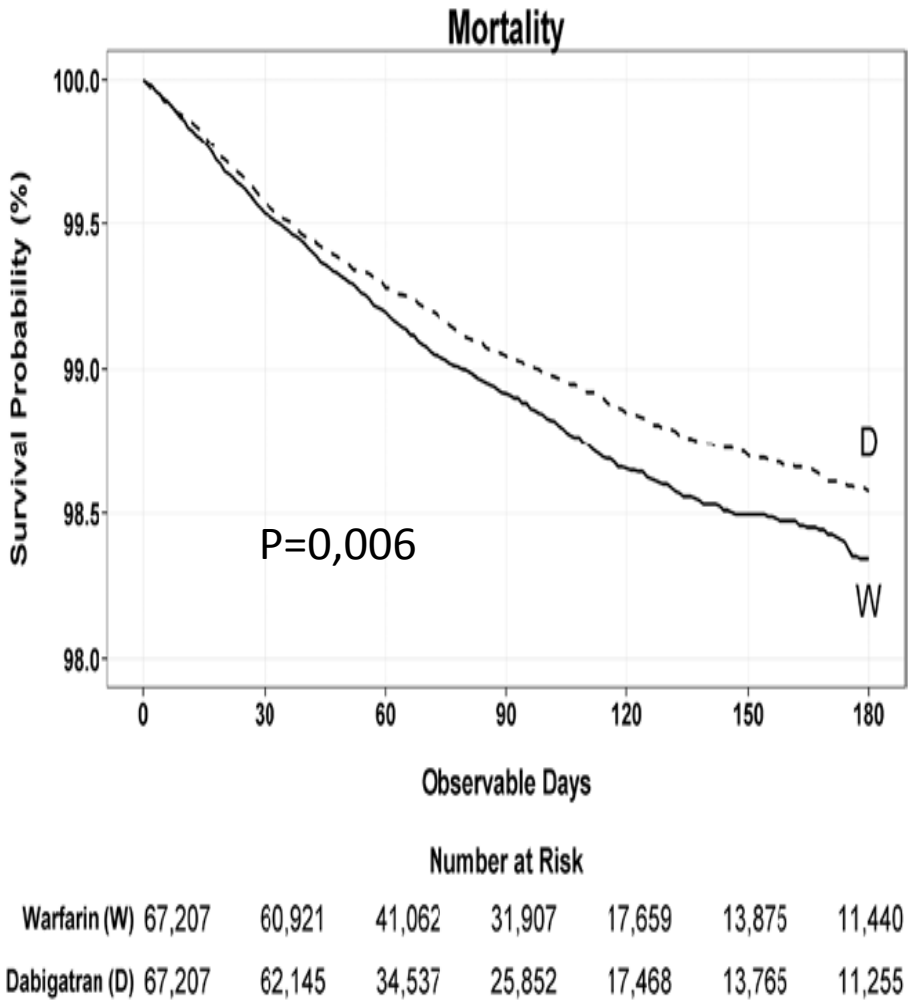
Cas difficile : les sujets âgés

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation



Number at Risk

Warfarin (W)	67,207	60,238	40,757	31,740	17,550	13,812	11,389
Dabigatran (D)	67,207	61,498	34,258	25,686	17,365	13,715	11,208

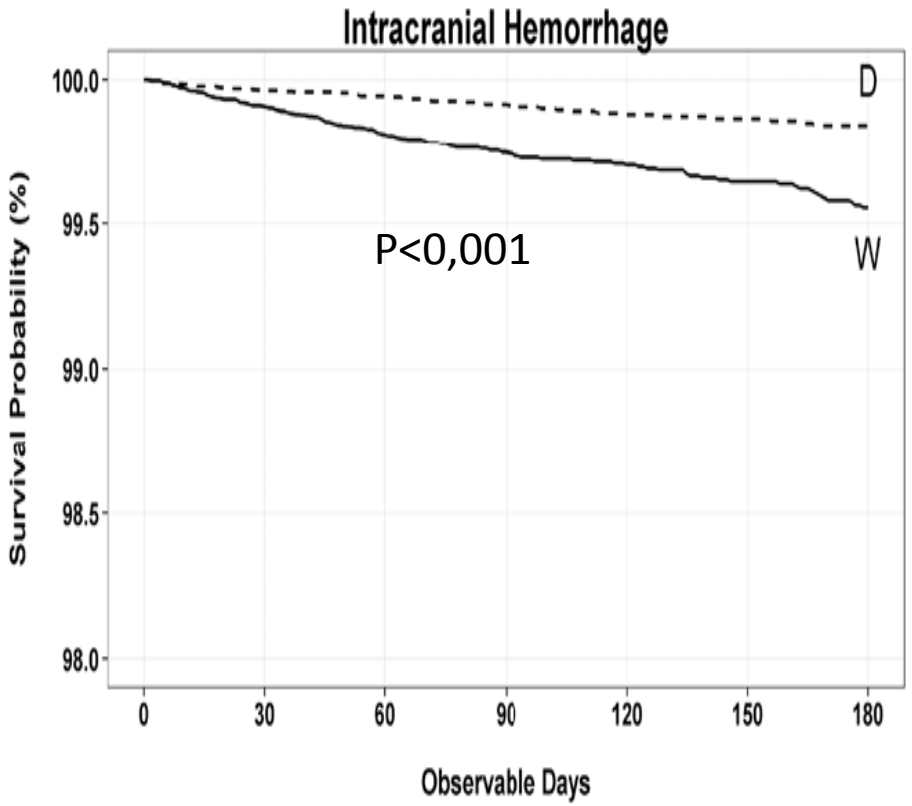


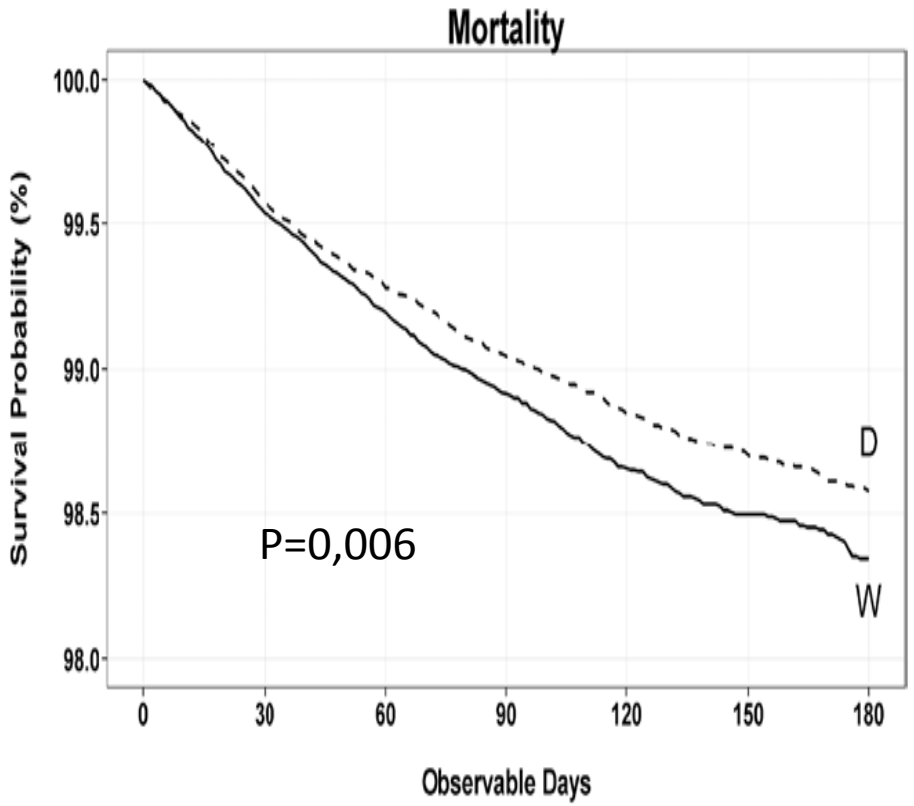
Number at Risk

Warfarin (W)	67,207	60,921	41,062	31,907	17,659	13,875	11,440
Dabigatran (D)	67,207	62,145	34,537	25,852	17,468	13,765	11,255

Graham DJ, et al. Circulation. 2015;131:157-164.

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation





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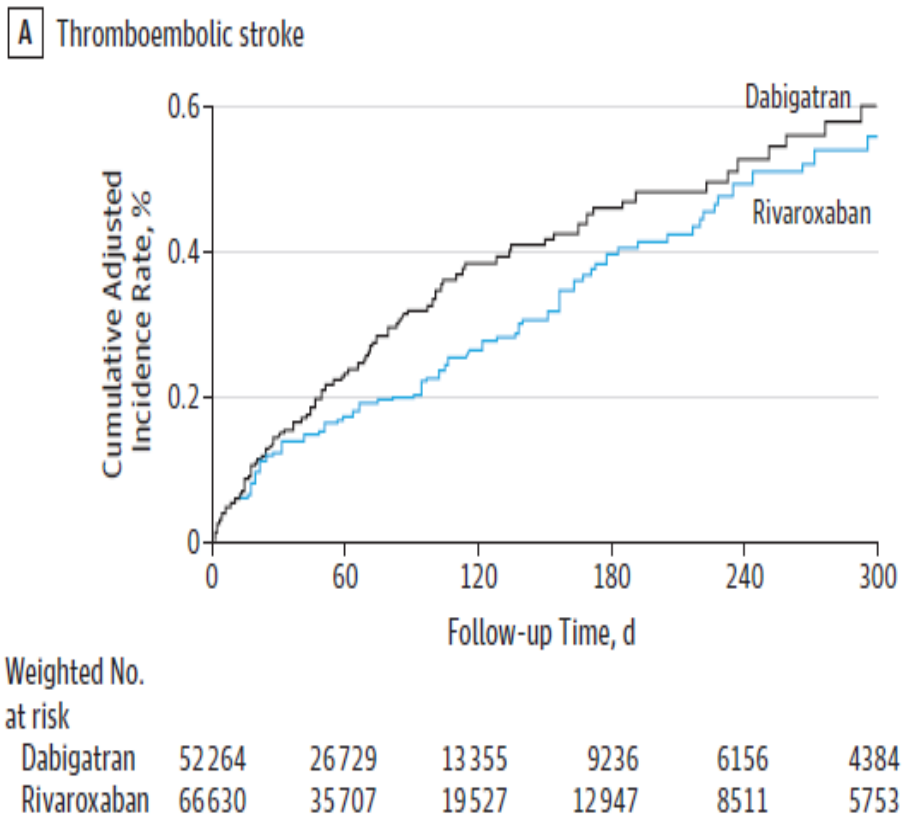
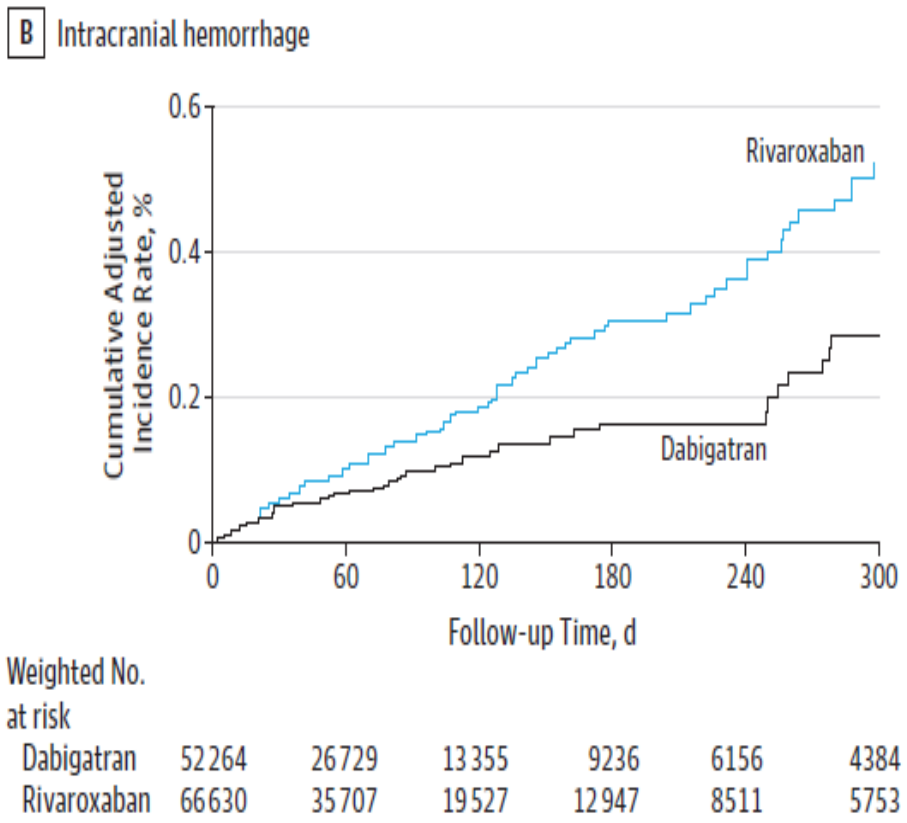
Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

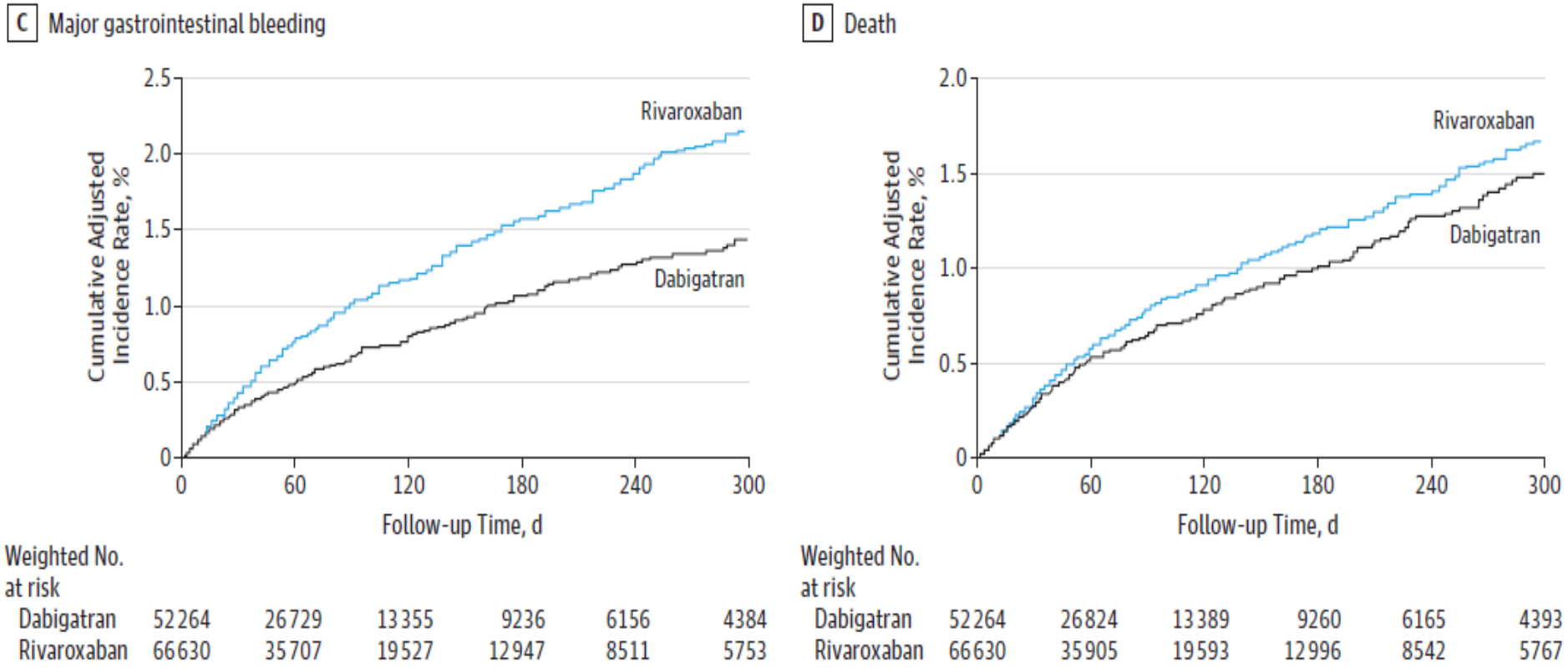




Graham DJ, et .JAMA Internal Medicine, 2016.

Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation

118 891 patients with nonvalvular AF who were 65 years or more who initiated treatment with dabigatran or rivaroxaban



Graham DJ, et .JAMA Internal Medicine, 2016.

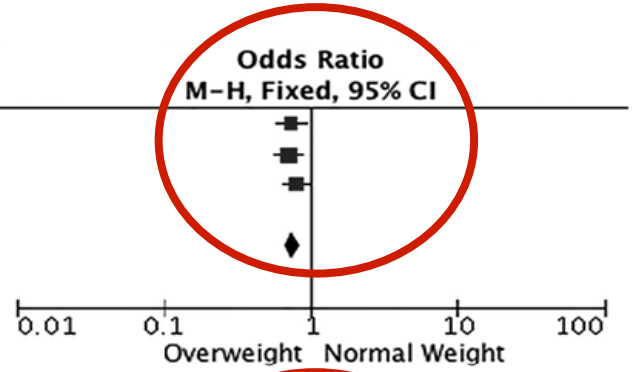
Cas difficile : les grands obèses

Is There an Obesity Paradox for Outcomes in Atrial Fibrillation? A Systematic Review and Meta-Analysis of Non–Vitamin K Antagonist Oral Anticoagulant Trials

A Stroke/SEE

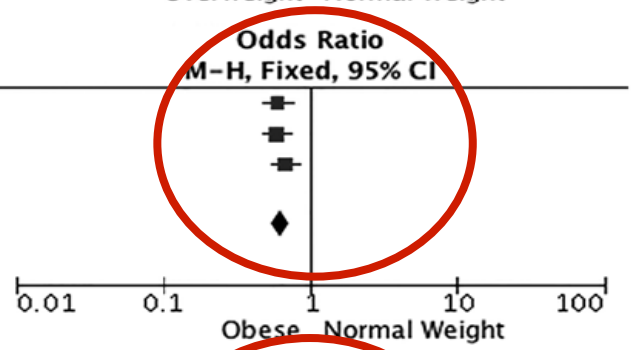
Study or Subgroup	Overweight Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	174	6702	142	4052	29.4%	0.73 [0.59, 0.92]
RE-LY	196	7111	182	4697	36.4%	0.70 [0.57, 0.86]
ROCKET AF	225	5523	167	3314	34.2%	0.80 [0.65, 0.98]
Total (95% CI)		**19336**		**12063**	**100.0%**	**0.75 [0.66, 0.84]**
Total events	595		491			

Heterogeneity: $Chi^2 = 0.79$, $df = 2$ ($P = 0.67$); $I^2 = 0\%$
Test for overall effect: $Z = 4.73$ ($P < 0.00001$)



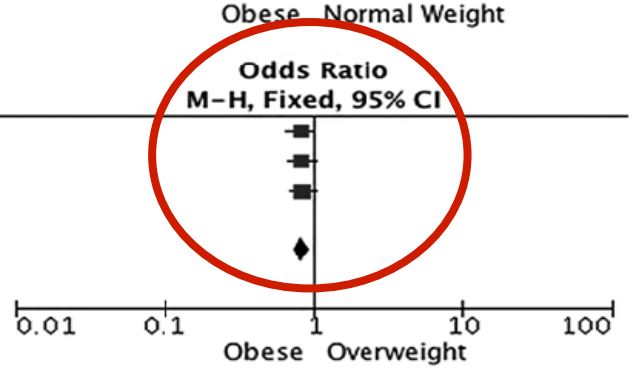
Study or Subgroup	Obese Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	152	7159	142	4052	30.7%	0.60 [0.47, 0.75]
RE-LY	145	6279	182	4697	35.2%	0.59 [0.47, 0.73]
ROCKET AF	179	5194	167	3314	34.1%	0.67 [0.54, 0.83]
Total (95% CI)		**18632**		**12063**	**100.0%**	**0.62 [0.54, 0.70]**
Total events	476		491			

Heterogeneity: $Chi^2 = 0.89$, $df = 2$ ($P = 0.64$); $I^2 = 0\%$
Test for overall effect: $Z = 7.31$ ($P < 0.00001$)



Study or Subgroup	Obese Events	Total	Overweight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	152	7159	174	6702	31.1%	0.81 [0.65, 1.01]
RE-LY	145	6279	196	7111	31.7%	0.83 [0.67, 1.04]
ROCKET AF	179	5194	225	5523	37.2%	0.84 [0.69, 1.03]
Total (95% CI)		**18632**		**19336**	**100.0%**	**0.83 [0.73, 0.94]**
Total events	476		595			

Heterogeneity: $Chi^2 = 0.05$, $df = 2$ ($P = 0.98$); $I^2 = 0\%$
Test for overall effect: $Z = 2.98$ ($P = 0.003$)



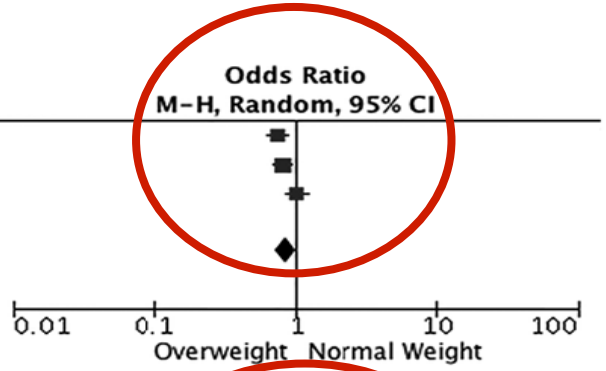
Proietti M, el al. Stroke. 2017, in press.

Is There an Obesity Paradox for Outcomes in Atrial Fibrillation? A Systematic Review and Meta-Analysis of Non–Vitamin K Antagonist Oral Anticoagulant Trials

B **Major Bleeding**

Study or Subgroup	Overweight Events	Overweight Total	Normal Weight Events	Normal Weight Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	271	6687	219	4035	32.1%	0.74 [0.61, 0.88]
RE-LY	424	7111	344	4697	36.3%	0.80 [0.69, 0.93]
ROCKET AF	312	5555	183	3327	31.5%	1.02 [0.85, 1.23]
Total (95% CI)		**19353**		**12059**	**100.0%**	**0.84 [0.70, 1.01]**
Total events	1007		746			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.58$, df = 2 (P = 0.04); $I^2 = 70\%$
Test for overall effect: Z = 1.87 (P = 0.06)

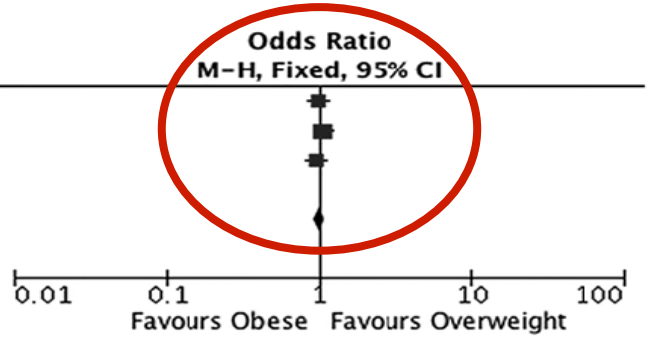


Study or Subgroup	Obese Events	Obese Total	Normal Weight Events	Normal Weight Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	285	7134	219	4035	32.2%	0.73 [0.61, 0.87]
RE-LY	394	6279	344	4697	37.3%	0.85 [0.73, 0.98]
ROCKET AF	279	5214	183	3327	30.5%	0.97 [0.80, 1.18]
Total (95% CI)		**18627**		**12059**	**100.0%**	**0.84 [0.72, 0.98]**
Total events	958		746			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.77$, df = 2 (P = 0.09); $I^2 = 58\%$
Test for overall effect: Z = 2.21 (P = 0.03)

Study or Subgroup	Obese Events	Obese Total	Overweight Events	Overweight Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	285	7134	271	6687	29.0%	0.99 [0.83, 1.17]
RE-LY	394	6279	424	7111	40.2%	1.06 [0.92, 1.22]
ROCKET AF	279	5214	312	5555	30.8%	0.95 [0.80, 1.12]
Total (95% CI)		**18627**		**19353**	**100.0%**	**1.00 [0.92, 1.10]**
Total events	958		1007			

Heterogeneity: $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0\%$
Test for overall effect: Z = 0.06 (P = 0.95)

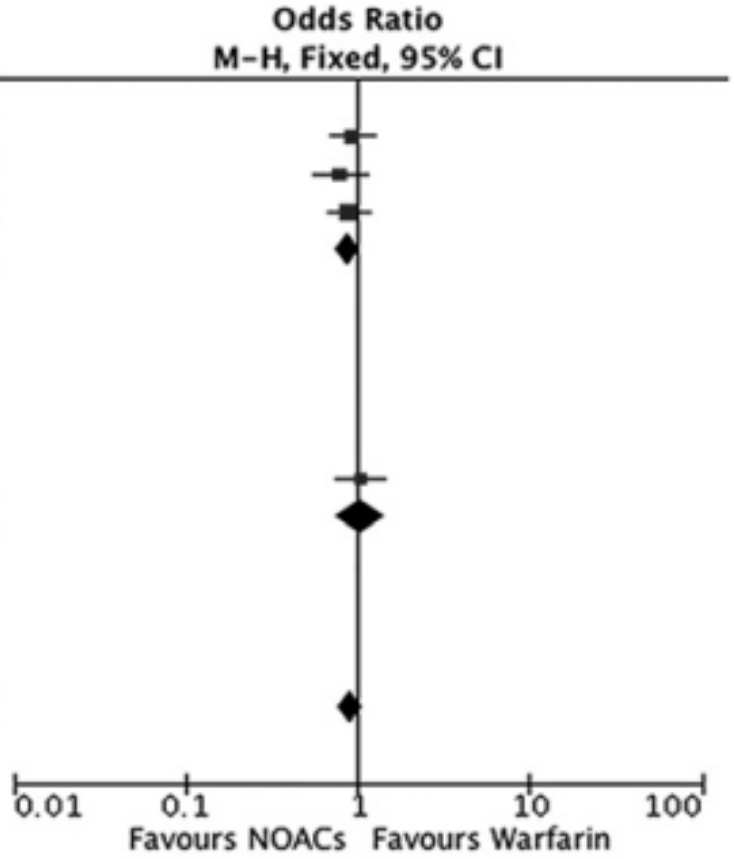


Proietti M, el al. Stroke. 2017, in press.

Is There an Obesity Paradox for Outcomes in Atrial Fibrillation? A Systematic Review and Meta-Analysis of Non–Vitamin K Antagonist Oral Anticoagulant Trials

B Overweight

Study or Subgroup	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.1.1 Single/High Dose						
ARISTOTLE	84	3351	90	3351	26.1%	0.93 [0.69, 1.26]
RE-LY	55	2358	69	2338	20.1%	0.79 [0.55, 1.12]
ROCKET AF	105	2730	120	2793	33.9%	0.89 [0.68, 1.16]
Subtotal (95% CI)		**8439**		**8482**	**80.0%**	**0.88 [0.74, 1.05]**
Total events	244		279			
Heterogeneity: $Chi^2 = 0.53$, df = 2 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 1.46 (P = 0.14)						
5.1.2 Low Dose						
RE-LY	72	2358	69	2338	20.0%	1.04 [0.74, 1.45]
Subtotal (95% CI)		**2358**		**2338**	**20.0%**	**1.04 [0.74, 1.45]**
Total events	72		69			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
Total (95% CI)		**10797**		**10820**	**100.0%**	**0.91 [0.78, 1.06]**
Total events	316		348			
Heterogeneity: $Chi^2 = 1.27$, df = 3 (P = 0.74); $I^2 = 0\%$						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: $Chi^2 = 0.74$, df = 1 (P = 0.39), $I^2 = 0\%$						

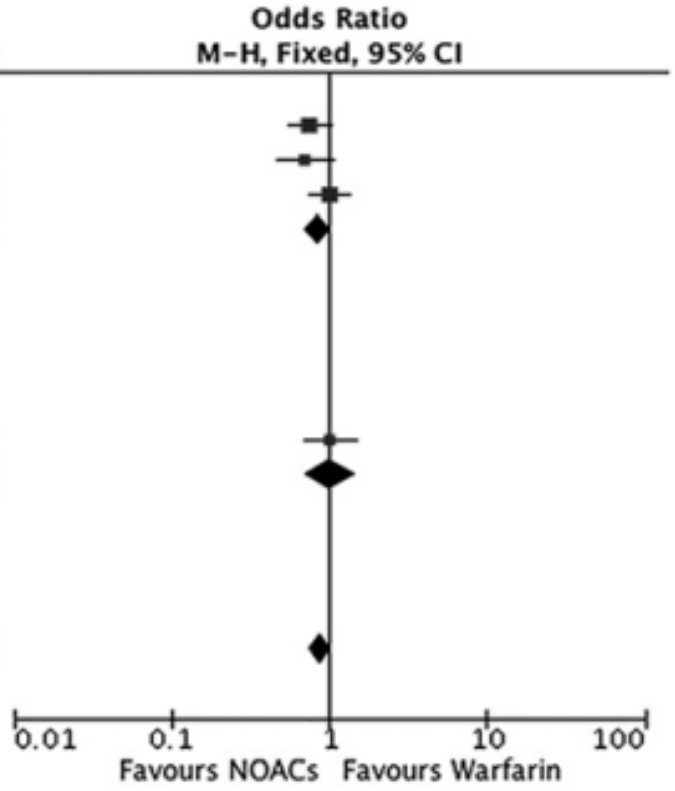


Proietti M, el al. Stroke. 2017, in press.

Is There an Obesity Paradox for Outcomes in Atrial Fibrillation? A Systematic Review and Meta-Analysis of Non–Vitamin K Antagonist Oral Anticoagulant Trials

C Obese

Study or Subgroup	NOACs Events	Total	Warfarin Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.1.1 Single/High Dose						
ARISTOTLE	66	3594	86	3565	30.8%	0.76 [0.55, 1.05]
RE-LY	38	2088	54	2118	19.1%	0.71 [0.47, 1.08]
ROCKET AF	92	2651	87	2543	31.2%	1.01 [0.75, 1.37]
Subtotal (95% CI)		**8333**		**8226**	**81.1%**	**0.84 [0.70, 1.03]**
Total events	196		227			
Heterogeneity: $Chi^2 = 2.57$, df = 2 (P = 0.28); $I^2 = 22\%$						
Test for overall effect: Z = 1.71 (P = 0.09)						
6.1.2 Low Dose						
RE-LY	53	2073	54	2118	18.9%	1.00 [0.68, 1.47]
Subtotal (95% CI)		**2073**		**2118**	**18.9%**	**1.00 [0.68, 1.47]**
Total events	53		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**10406**		**10344**	**100.0%**	**0.87 [0.74, 1.04]**
Total events	249		281			
Heterogeneity: $Chi^2 = 3.18$, df = 3 (P = 0.37); $I^2 = 6\%$						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.43), $I^2 = 0\%$						



Proietti M, el al. Stroke. 2017, in press.


SO FAR
SO GOOD