AOD dans la FANV

Dr. Folco Frattini
CH Antibes

Study design of phase III trials of NOACs in NVAF

	Apixaban ARISTOTLE[1]	**Apixaban** AVERROES[2]	**Dabigatran** RE-LY[3]	**Edoxaban** ENGAGE AF-TIMI 48[4]	**Rivaroxaban** ROCKET AF[5]
N	18 201	5 599	18 113	21 105	14 264
Design	Double-blind, double-dummy	Double-blind, double-dummy	Blinded (dabigatran) Open-label (warfarin)	Double-blind, double-dummy	Double-blind, double-dummy
Treatments	• Apixaban 5 mg twice-daily (2.5 mg twice-daily in selected patients*) • Warfarin (INR target: 2–3)	• Apixaban 5 mg twice-daily (2.5 mg twice-daily in selected patients*) • ASA (81–324 mg per day)	• Dabigatran 110 mg twice-daily • Dabigatran 150 mg twice-daily • Warfarin (INR target: 2–3)	• Edoxaban high-dose (60 mg)† • Edoxaban low-dose (30 mg)† • Warfarin (INR target: 2–3)	• Rivaroxaban 20 mg once-daily (15 mg once-daily in selected patients‡) • Warfarin (INR target: 2–3)
Objective	Non-inferiority	Superiority	Non-inferiority	Non-inferiority	Non-inferiority

*Patients with ≥ 2 of the following criteria: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 µmol/L).

Note: Per the SmPC, patients with the exclusive criterion of severe renal impairment (CrCl 15–29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice-daily. This criterion differs from the trial conduct.

† Dose was halved in selected patients

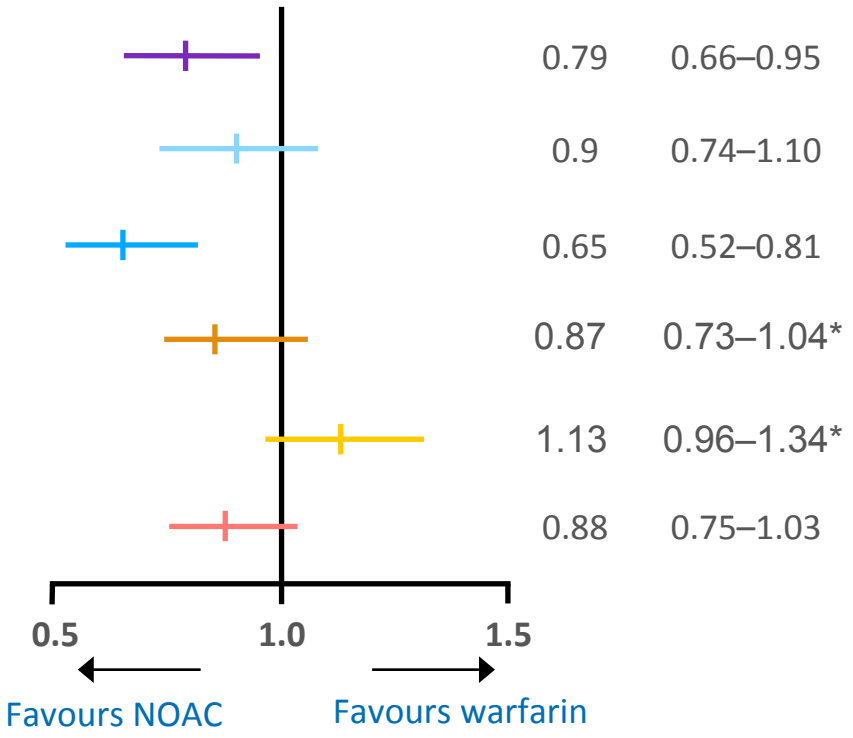
‡ If CrCl between 30–49 ml/min

NVAF, non-valvular atrial fibrillation; INR, international normalised ratio; ASA: acetylsalicylic acid; CrCl, creatinine clearance

1. Granger *et al. New Engl J Med* 2011;365:981-92; 2. Connolly *et al. N Engl J Med* 2011;364:806-17; 3. Connolly *et al. New Engl J Med* 2009;361:1139-51; 4. Giugliano *et al. N Engl J Med* 2013;369:2093-104. 5. Patel *et al. New Engl J Med* 2011;365:883-91

NOACs vs. warfarin: Stroke or systemic embolism (primary efficacy outcome)

	NOAC	Warfarin	HR	95% CI
	No. of events (%/yr)			
Apixaban (ITT)[1]	212 (1.27)	265 (1.60)	0.79	0.66–0.95
Dabigatran 110 mg (ITT)[2]	183 (1.54)	202 (1.71)	0.9	0.74–1.10
Dabigatran 150 mg (ITT)[2]	134 (1.11)	202 (1.71)	0.65	0.52–0.81
Edoxaban high dose (ITT)[3]	296 (1.57)	337 (1.8)	0.87	0.73–1.04*
Edoxaban low dose (ITT)[3]	383 (2.04)	337 (1.8)	1.13	0.96–1.34*
Rivaroxaban (ITT)[4,5]	269 (2.12)	306 (2.42)	0.88	0.75–1.03



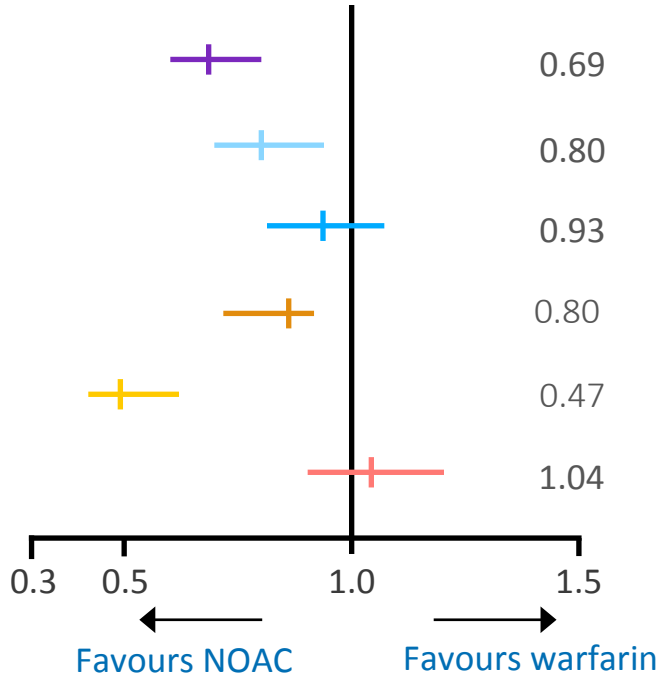
* A 97.5% confidence interval was used

HR, hazard ratio; ITT, intention-to-treat population

1. Granger *et al. N Engl J Med* 2011;365:981-92; 2. Connolly e*t al. N Engl J Med* 2010;363:1875-6; 3. Giugliano *et al. N Engl J Med* 2013;369:2093-104;
4. Patel *et al. N Engl J Med* 2011;365:883-91; 5. Rivaroxaban SmPC, 201

NOACs vs. warfarin: Major bleeding

	NOAC	Warfarin	HR	95% CI
	No. of events (%/yr)			
Apixaban[1]	327 (2.13)	462 (3.09)	0.69	0.60–0.80
Dabigatran 110 mg[2]	342 (2.87)	421 (3.57)	0.80	0.70–0.93
Dabigatran 150 mg[2]	399 (3.32)	421 (3.57)	0.93	0.81–1.07
Edoxaban high dose[3] *	418 (2.75)	524 (3.43)	0.80	0.71–0.91
Edoxaban low dose[3] *	254 (1.61)	524 (3.43)	0.47	0.41–0.55
Rivaroxaban[4,5]	395 (3.60)	386 (3.45)	1.04	0.90–1.20

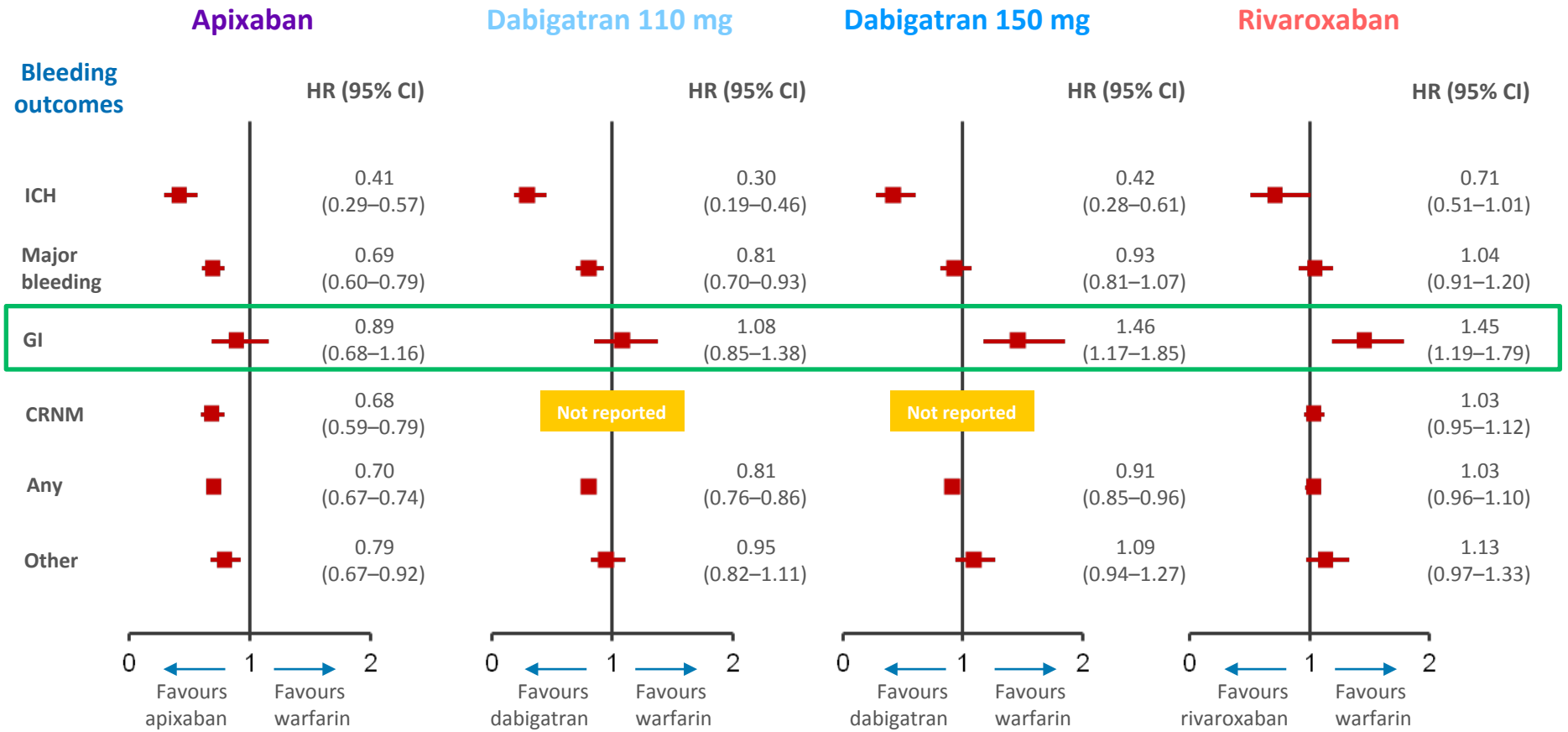


* Data are from the safety cohort during the treatment period (which began when the first dose of study drug was administered), with interval censoring of events during study-drug interruptions that lasted more than 3 days, except for net clinical outcomes, which are presented for the overall treatment period (which began at the time of randomisation).

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

1. Granger *et al. N Engl J Med* 2011;365:981-92; 2. Connolly e*t al. N Engl J Med* 2010;363:1875-6; 3. Giugliano *et al. N Engl J Med* 2013;369:2093-104; 4. Patel *et al. N Engl J Med* 2011;365:883-91; 5. Rivaroxaban SmPC, 2013.

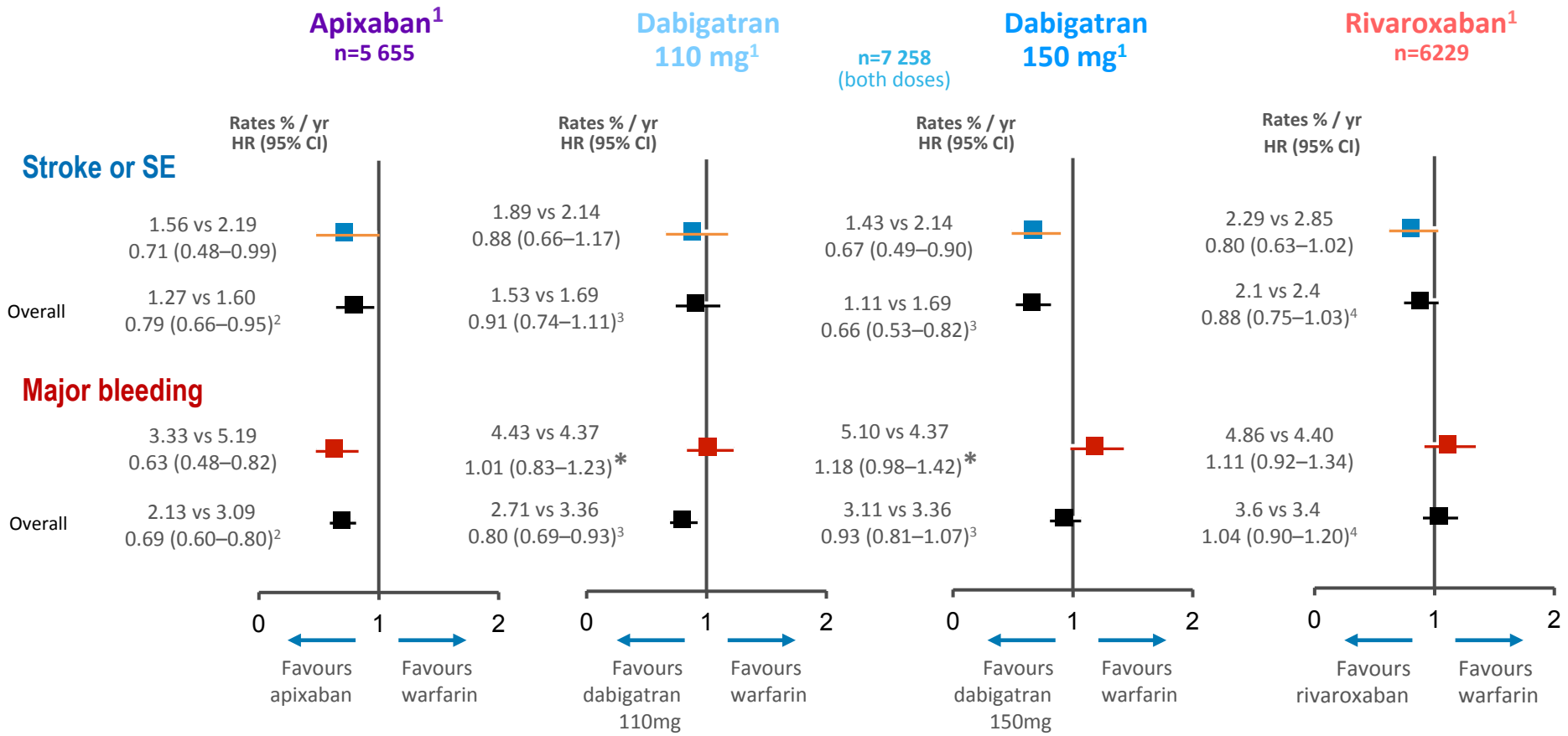
Accidents hémorragiques et AOD



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

Mitchell *et al. Clin Appl Thromb Haemost* 2013;19:619-31

Efficacy and safety data of NOACs in elderly patients (≥75 years)

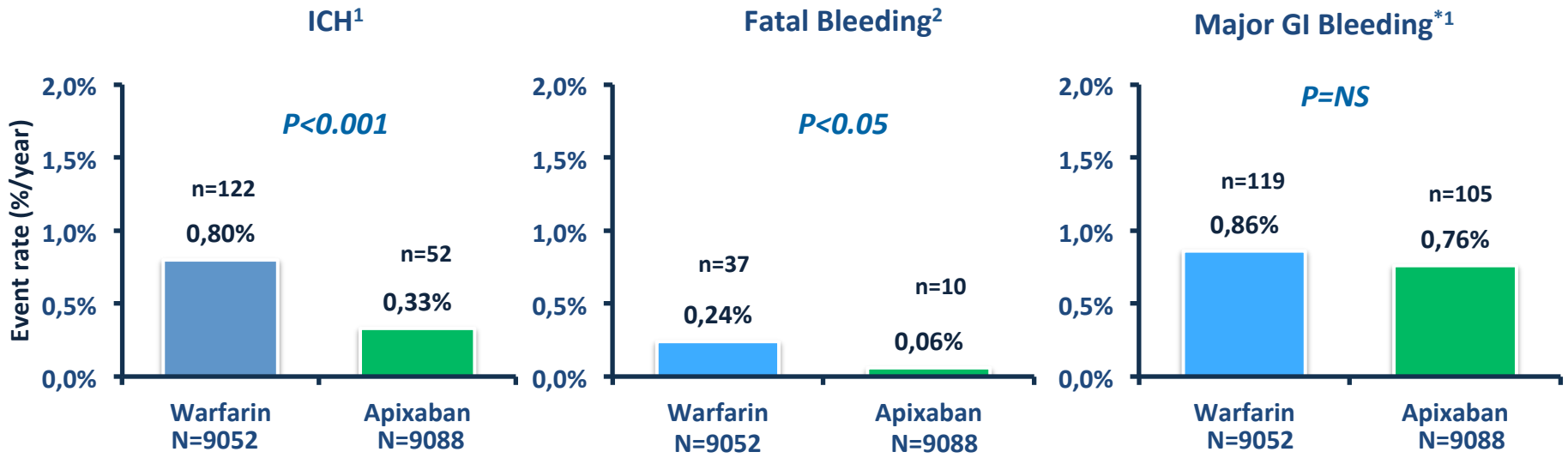


**p<0.001 for interaction between age and treatment*

Adapted from *Capranzano P et al. Expert Rev Cardiovasc Ther* 2013;11:959-73; Granger *et al. N Engl J Med* 2011;365:981-92; Connolly *et al. N Engl J Med* 2009;361:1139-51; and Patel *et al. N Engl J Med* 2011;365:883-91

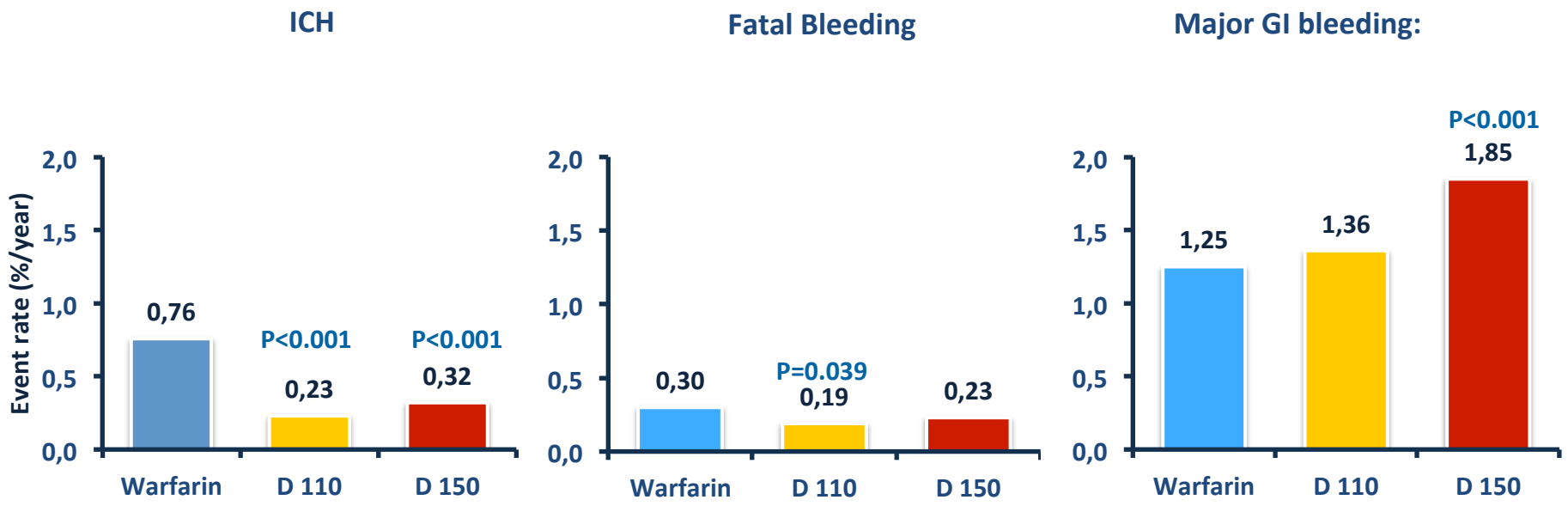
Head-to-head studies do not exist, and direct comparisons between agents may not be made

ARISTOTLE[1] Apixaban



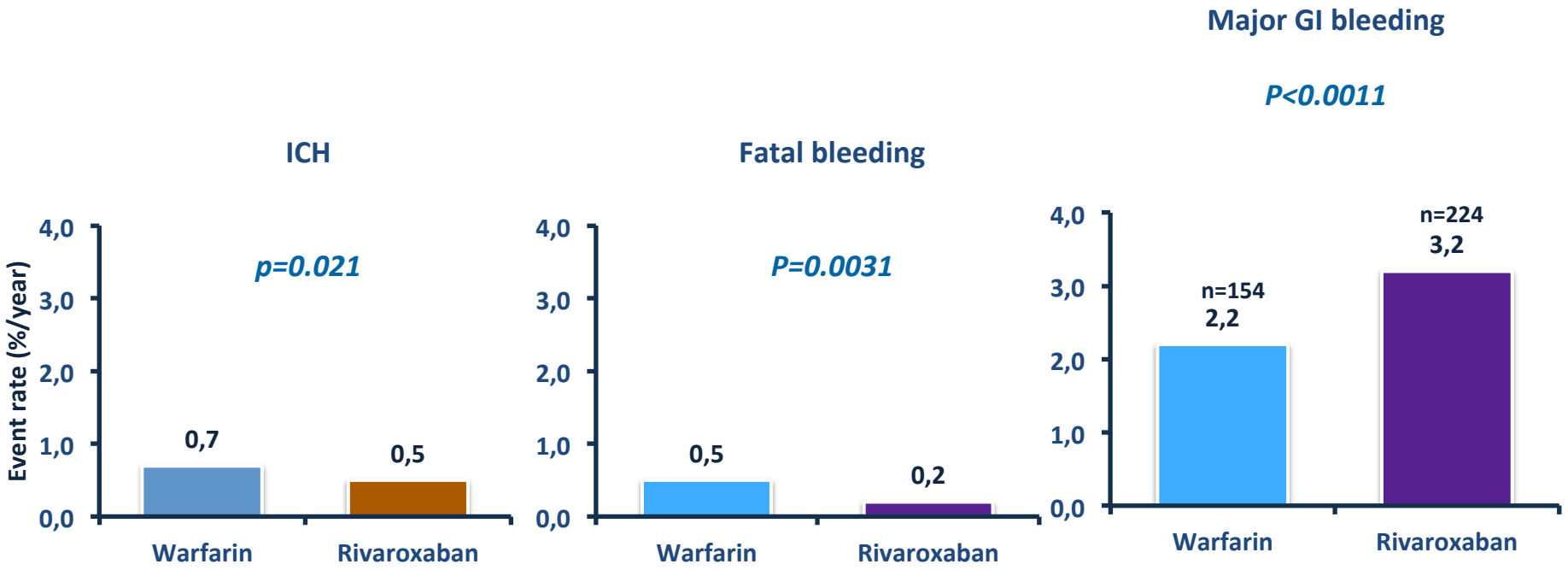
*Including upper GI, lower GI, and rectal bleeding. †As of January 2014.
GI, gastrointestinal; ICH, intracranial haemorrhage; NVAF, non-valvular atrial fibrillation; RRR, relative risk reduction.
1. Adapted from Granger CB et al. *N Engl J Med*. 2011;365:981-992; 2. SmPC Apixaban 2012;

RELY[1] Dabigatran



D 110, dabigatran 110 mg; D150, dabigatran 150 mg; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage; 1. Adapted from Eikelboom JW et al. *Circulation* 2011;123:2363-2372.

ROCKET[1] Rivaroxaban



CI, confidence interval; CRNM, clinically relevant non major; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage

1. Adapted from Patel MR et al. *N Engl J Med* 2011;365:383-91. 2. Adapted from Goodman SG et al. *J Am Coll Cardiol* 2013, doi.1016/j.jacc. 2013.11.013.

Efficacité et Sécurité

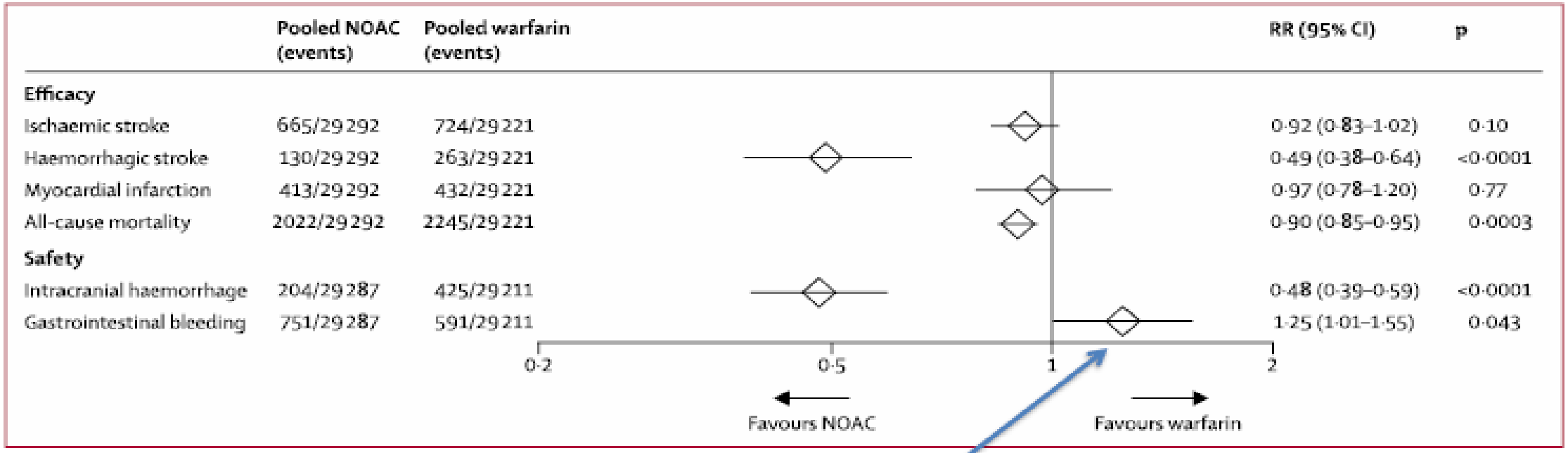


***Figure 2*: Secondary efficacy and safety outcomes**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

+25% saignements digestifs

AOD vs AVK

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

AVC
19% RRR

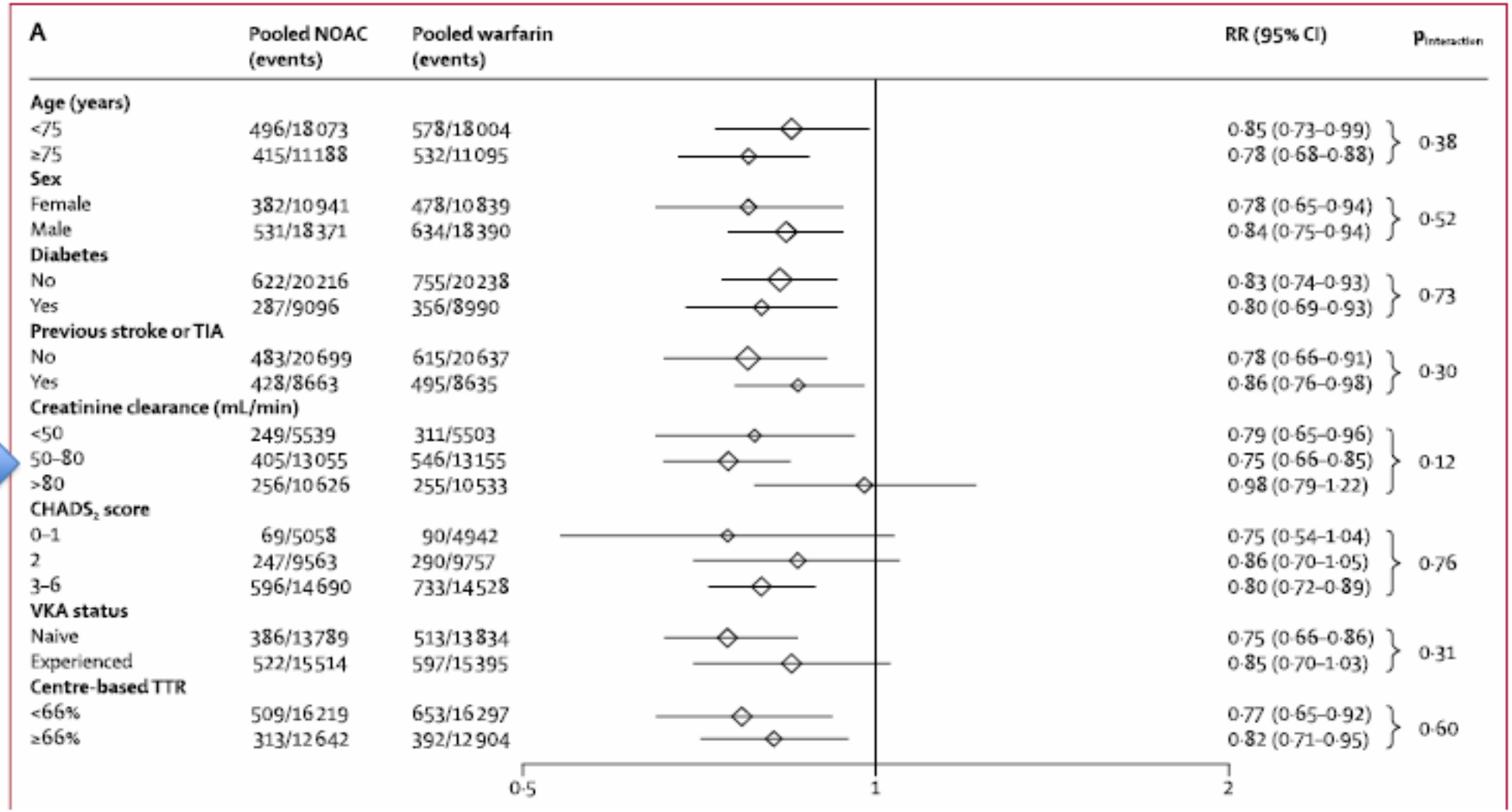
Saignts Graves
14% RRR

HIC
52% RRR

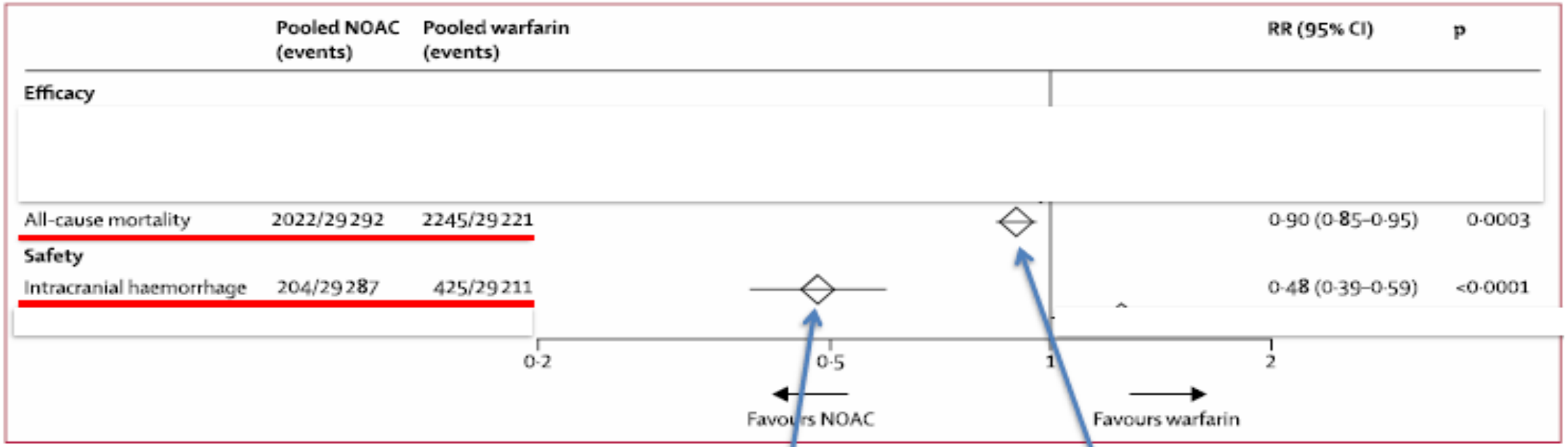
Mortalité globale
10% RRR

Impossible d'afficher l'image. Votre ordinateur manque peut-être de mémoire pour ouvrir l'image ou l'image est endommagée. Redémarrez l'ordinateur, puis ouvrez à nouveau le fichier. Si le x rouge est toujours affiché, vous devrez peut-être supprimer l'image avant de la réinsérer.

AVC en fonction des sous groupes



Efficacité et Sécurité



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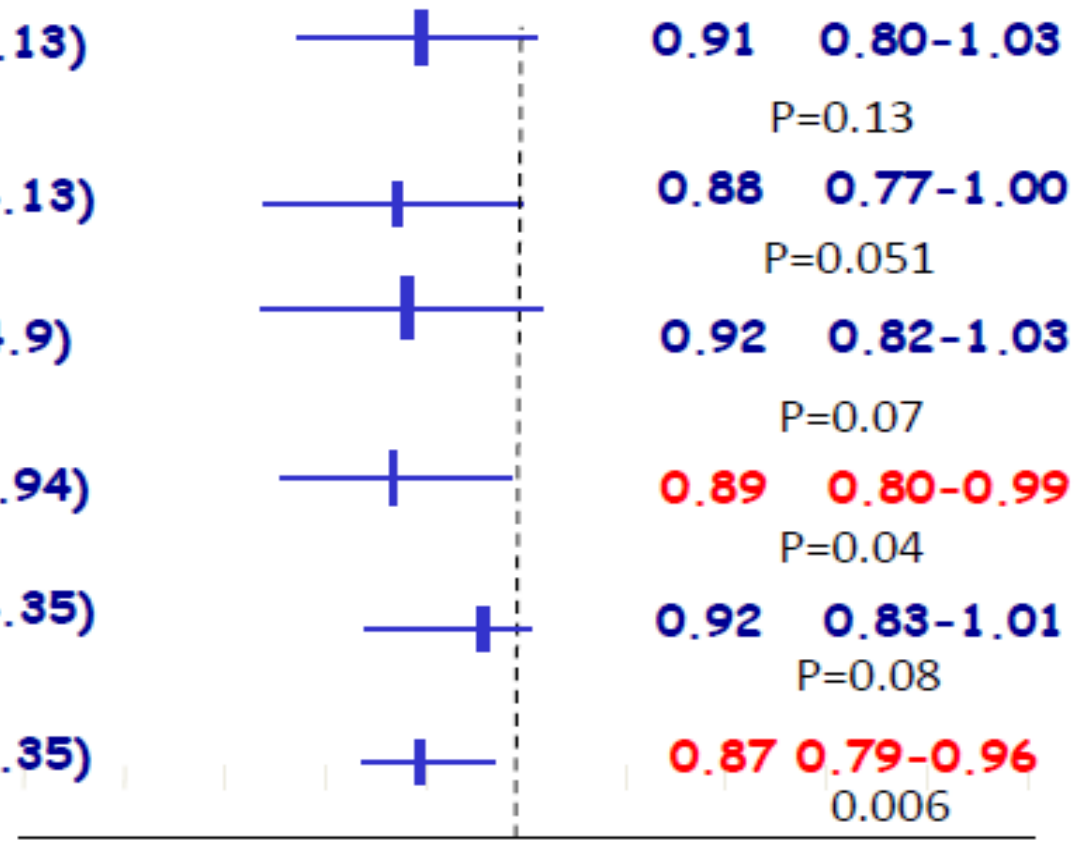
-52 % RRR HIC

-10% RRR Décès toutes causes

Mortalité globale dans les études NACO-FA

	NACO	WARFARIN	HR	IC 95%	
	Nb d'Event (%/an)				
RELY Dabigatran 110	446 (3.75)	487 (4.13)	0.91	0.80-1.03	P=0.13
RELY Dabigatran 150	438 (3.64)	487 (4.13)	0.88	0.77-1.00	P=0.051
ROCKET Rivaroxaban	582 (4.5)	632 (4.9)	0.92	0.82-1.03	P=0.07
ARISTOTLE Apixaban	603 (3.52)	669 (3.94)	0.89	0.80-0.99	P=0.04
ENGAGE Edoxaban High dose	773 (3.99)	839 (4.35)	0.92	0.83-1.01	P=0.08
ENGAGE Edoxaban Low dose	737 (3.80)	839 (4.35)	0.87	0.79-0.96	0.006



1-Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med, 2009; 361:1139–1151.
2-Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med, 2011; 365:883–891.
3-Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med, 2011;365:981–992.

Saignements graves

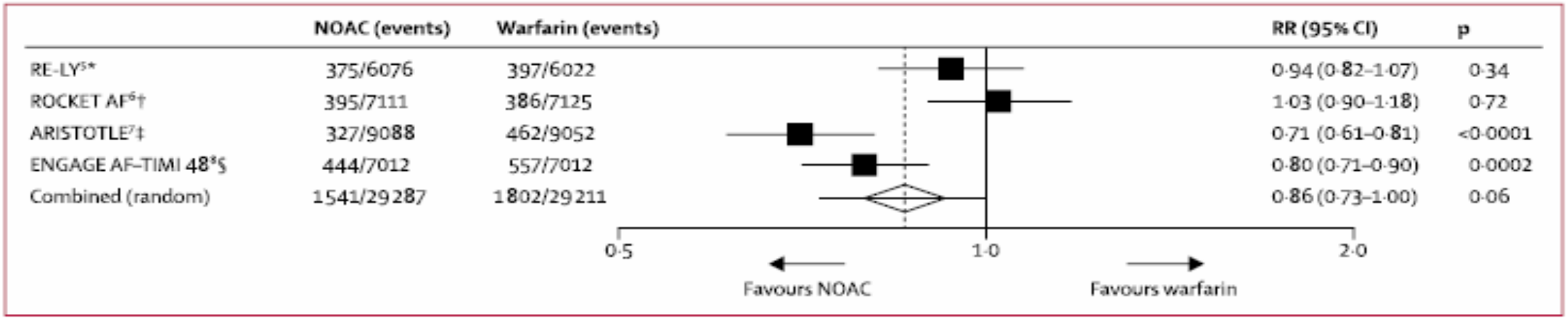


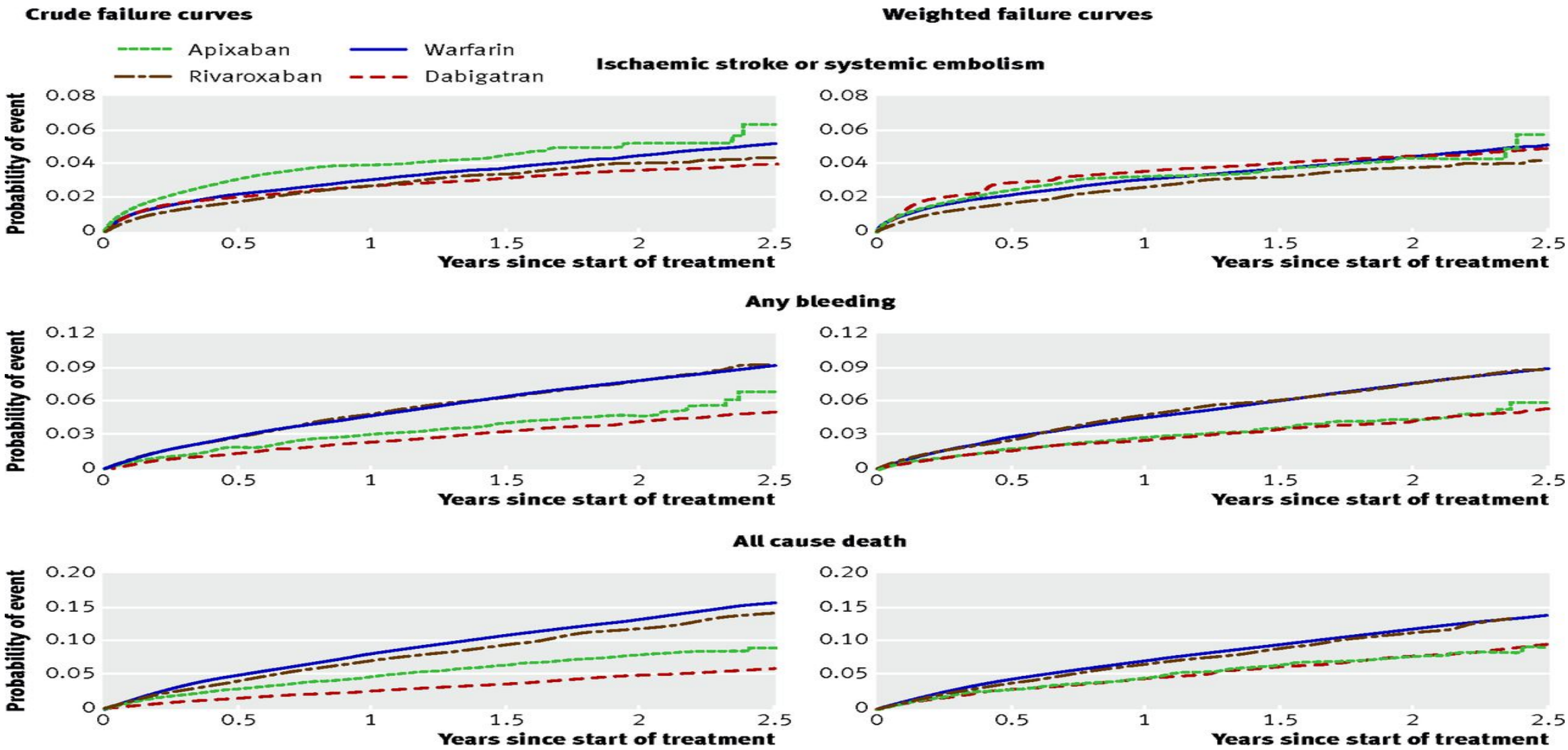
***Figure 3*: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

-14% saignements graves

On a aussi d’ importants registres de vraie vie sur les AOD.

Registre Danois (61678 pt, 4 ans, doses pleines)



Registre Danois (61678 pt, 4 ans)

1. Pas de différences entre AOD et AVK sur les AVC ischémiques.
2. Rivaroxaban supérieur pour AVC ischémiques + ES, avec sécurité équivalente aux AVK (mais évaluation sur 1 an!)
3. Dabigatran et apixaban ont efficacité équivalente aux AVK et sécurité supérieure.

Effectiveness and Safety of NOAC versus Warfarin in Nonvalvular Atrial Fibrillation (OptumLabs Database; Mayo Clinic 2016)

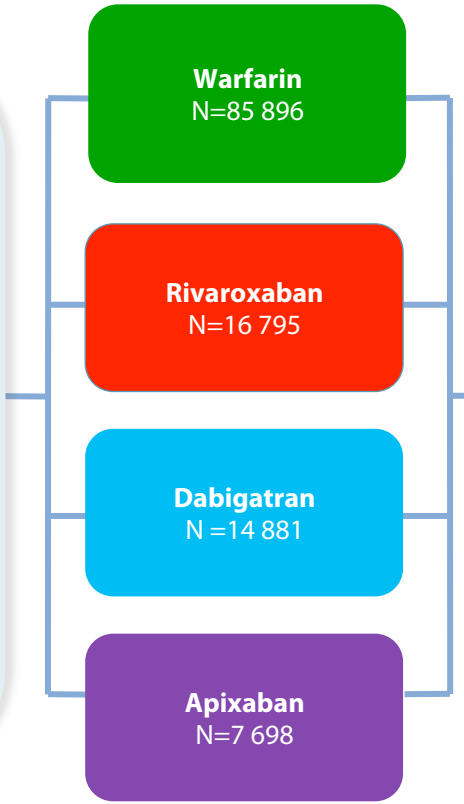
- **Objective : evaluate stroke/SE and bleeding outcomes associated with dabigatran, rivaroxaban, and apixaban use by comparing each agent with warfarin**
- **N= 125 243, 3 matched cohorts using 1:1 propensity score matching**

Retrospective analysis using administrative claims data from OptumLabs Data Warehouse .

- **Enrolment period:**
  Oct 1, 2010 – June 30, 2015 (dates of OAC use/ prescription filling)

- Statistical methods :

Patients were classified into 1:1 propensity score-matched cohorts (based on 48 dimensions)



Study Population

- Adult patients with NVAF diagnosis who used (filled a prescription for) OACs for at least 12 continuous months prior to the index date

Exclusion :

- valvular heart disease (ie, rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair), end-stage renal disease, kidney transplant, or on dialysis
- VTE at baseline (12 month before the index date), or knee/hip replacement within 6 weeks prior to the index date

Content is based on independent data

Yao et al. *J Am Heart Assoc*. 2016;5:e003725

Baseline Characteristics – 1/2
in Propensity Score-Matched NOAC or Warfarin Users

	Apixaban (n=7695)	Warfarin (n=7695)	Dabigatran (n=14 307)	Warfarin (n=14 307)	Rivaroxaban (n=16 175)	Warfarin (n=16 175)
Age, yr						
Median (IQR)	73 (66–81)	73 (66–81)	70 (62–78)	70 (61–78)	72 (64–79)	72 (64–80)
18–64	22.7	23.0	34.1	35.0	25.3	25.8
65–74	30.9	30.9	31.5	30.4	32.9	32.8
≥75	46.4	46.1	34.4	34.6	41.8	41.4
Female	46.9	46.8	39.7	40.4	43.2	43.7
Nonwhite race	20.2	20.4	18.9	19.3	19.9	20.4
Medical history						
Congestive heart failure	31.4	31.9	27.2	27.3	28.9	29.5
Hypertension	87.5	87.5	85.2	84.9	85.7	85.9
Diabetes mellitus	35.0	34.3	34.0	34.0	34.6	35.1
Stroke/TIA/SE	15.1	15.5	13.8	14.2	14.0	14.4
Vascular disease	28.3	28.4	23.1	23.4	26.9	27.5
Abnormal renal function	10.1	10.1	5.6	5.6	7.4	7.3
Abnormal liver function	4.0	4.1	3.5	3.6	3.7	3.8
Bleeding history or predisposition	31.4	31.8	29.4	30.1	30.7	31.5
Alcoholism	2.8	2.7	2.6	2.6	2.9	3.1
Pulmonary disease	33.1	33.7	28.2	28.4	31.2	32.1
Obesity	19.6	19.9	17.6	17.3	18.3	18.9
Smoking	19.8	20.0	16.1	16.0	18.5	19.4
Medication use						
Antiplatelets/NSAID	12.1	12.5	10.3	10.2	11.6	11.6
Amiodarone	9.6	10.1	8.4	8.4	8.3	8.8
Dronedarone	2.8	2.6	3.7	4.2	2.4	2.6
Other antiarrhythmic drugs	11.1	10.7	12.8	12.9	11.0	11.2
Digoxin	8.9	9.1	13.6	13.6	10.8	11.1
Diltiazem	16.9	17.0	17.5	17.3	17.5	17.9
Verapamil	1.3	1.3	1.9	1.9	1.7	1.7
Other calcium channel blockers	16.6	16.3	13.3	13.4	14.9	14.7
Statin	45.6	46.7	41.5	41.2	43.0	43.9

IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; SE, systemic stroke; TIA, transient ischemic attack; yr, year.

Yao et al. *J Am Heart Assoc*. 2016;5:e003725.

Baseline Characteristics – 2/2
in Propensity Score-Matched NOAC or Warfarin Users

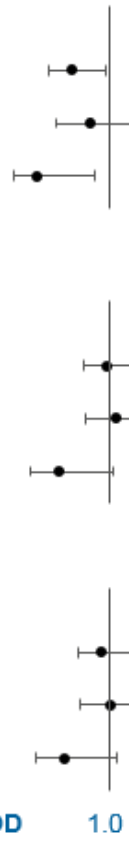
	Apixaban (n=7695)	Warfarin (n=7695)	Dabigatran (n=14 307)	Warfarin (n=14 307)	Rivaroxaban (n=16 175)	Warfarin (n=16 175)
Medication use (cont.)						
Other cholesterol reducers	5.9	5.9	7.3	7.6	5.7	5.7
ß-Blockers	47.5	47.8	44.6	44.5	45.6	45.0
Renin angiotensin system antagonists	47.1	47.2	45.4	45.0	45.5	46.0
Diuretics	32.3	31.8	28.5	28.5	29.6	29.6
Metformin	11.1	10.7	10.2	9.9	10.6	11.0
Sulfonylureas	6.0	6.0	6.0	5.9	6.0	5.9
Thiazolidinedione	0.8	0.8	1.5	1.3	0.9	0.9
Insulin	7.3	7.3	6.8	7.1	7.1	7.5
Other diabetes drugs	3.1	2.9	2.8	2.9	2.7	2.9
Antiulcer agents	21.9	21.4	18.4	18.4	20.3	21.2
Antidepressant	16.2	16.1	14.5	15.0	15.3	15.6
CHA_2DS_2-VASc						
Median (IQR)	4 (3–5)	4 (3–5)	3 (2–5)	3 (2–5)	4 (2–5)	4 (2–5)
0–1	9.9	10.0	15.9	16.6	12.2	12.1
2–3	33.2	33.0	38.2	36.9	35.6	35.6
≥4	56.8	57.0	45.9	46.5	52.2	52.3
HAS-BLED						
Median (IQR)	2 (2–3)	2 (2–3)	2 (1–3)	2 (1–3)	2 (2–3)	2 (2–3)
≥3	41.5	41.9	33.7	33.9	38.6	39.1
Charlson index						
Median (IQR)	2 (1–4)	2 (1–4)	2 (1–3)	2 (1–3)	2 (1–4)	2 (1–4)
0–1	37.7	37.9	45.5	45.3	41.3	40.6
2–3	32.0	32.1	30.4	30.4	30.8	30.5
≥4	30.3	30.0	24.1	24.3	27.9	28.9
SAMe-TT_2R_2						
Median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
≥3	30.7	31.1	26.1	26.4	28.8	30.5
Warfarin experienced	20.2	20.4	37.8	38.6	24.4	25.0
Reduced-dose NOAC	18.1	NA	8.8	NA	21.5	NA

Yao et al. *J Am Heart Assoc*. 2016;5:e003725.

IQR, interquartile range; NA, not available;
NOAC, non-vitamin K antagonist oral anticoagulant.

Résultats sur le critère primaire d'efficacité: AVC-ischémique/hémorragique ou embolie systémique (ES)

	Event Rate per 100 person-year		Hazard Ratio (95% CI)	*P* Value
Apixaban vs Warfarine				
	n=7695	n=7695		
AVC/ES	1.33	1.66	0.67 (0.46–0.98)	0.04
Ischémique	1.03	1.05	0.83 (0.53–1.29)	0.40
Hémorragique	0.19	0.46	0.35 (0.14–0.88)	0.03
Dabigatran vs Warfarine				
	n=14 307	n=14 307		
AVC/ES	1.18	1.22	0.98 (0.76–1.26)	0.88
Ischémique	0.92	0.88	1.06 (0.79–1.42)	0.70
Hémorragique	0.16	0.29	0.56 (0.30–1.04)	0.07
Rivaroxaban vs Warfarine				
	n=16 175	n=16 175		
AVC/ES	1.26	1.29	0.93 (0.72–1.19)	0.56
Ischémique	0.95	0.88	1.01 (0.75–1.36)	0.95
Hémorragique	0.21	0.32	0.61 (0.35–1.07)	0.08

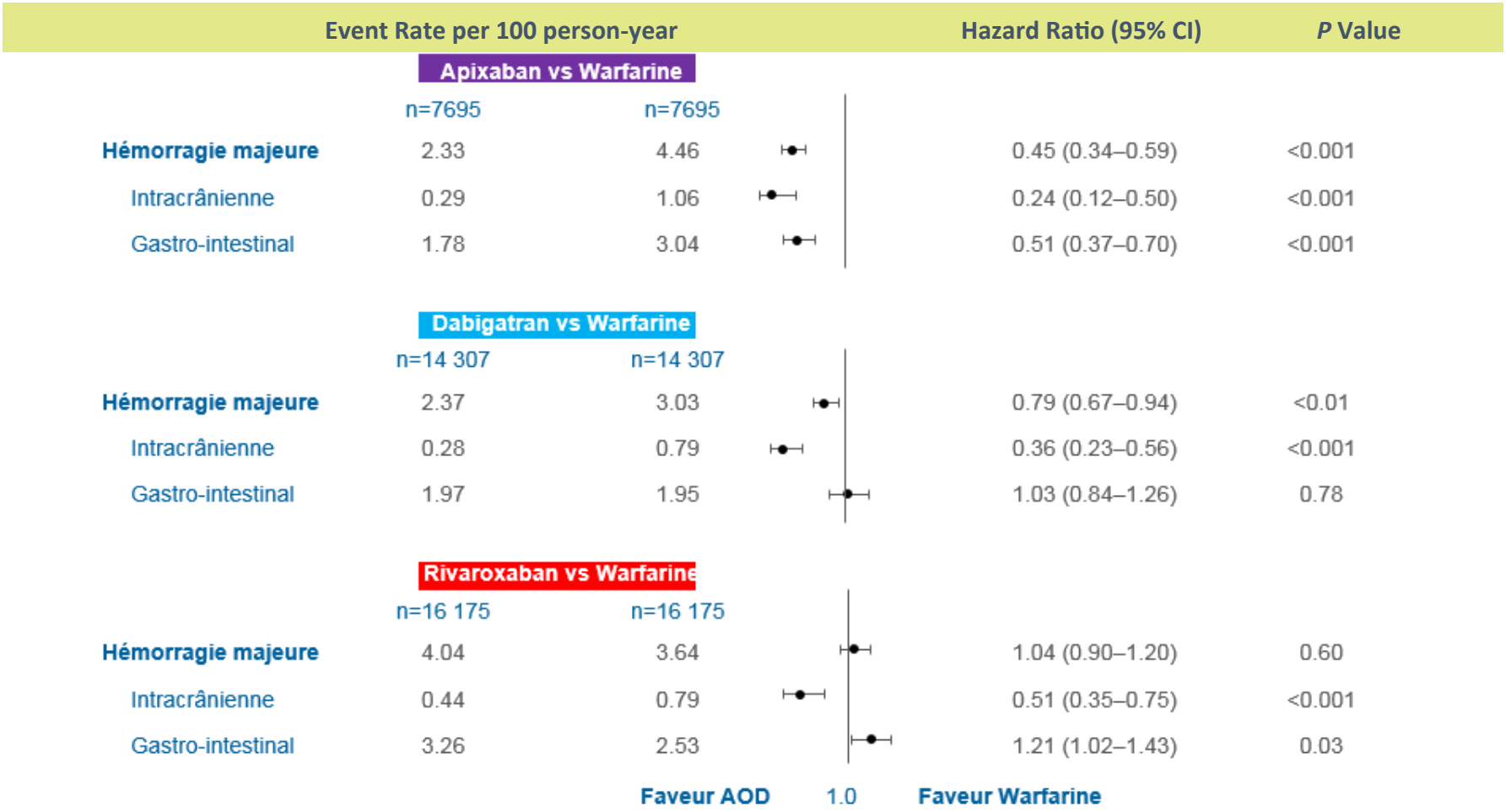


Faveur AOD 1.0 **Faveur Warfarine**

CI, confidence interval;
NOAC, non-vitamin K antagonist oral anticoagulant;
S, stroke; SE, systemic embolism.

Yao et al. *J Am Heart Assoc*. 2016;5:e003725.

Résultats sur le critère primaire de tolérance: hémorragies majeures (gastro-intestinale, intracrânienne et autres sites)



CI, confidence interval;
NOAC, non-vitamin K antagonist oral anticoagulant.

Yao et al. *J Am Heart Assoc*. 2016;5:e003725.

Registre de la Mayo Clinic (125000 pt, 5 ans)

1. Confirme l'efficacité et la sécurité de l'apixaban.
2. Confirme la neutralité du rivaroxaban (mais ↓ ICH !).
3. Dabigatran 150 mg: efficacité pas confirmée (9% de 75 mg), mais sécurité supérieure.
4. Important: les 3 AOD donnent une réduction des ICH.

A Nationwide Registry Study to Compare Bleeding Rates in Patients With Atrial Fibrillation Being Prescribed Oral Anticoagulants

Objective	• To evaluate bleeding risk in clinical practice in patients with non-valvular atrial fibrillation (NVAF) prescribed dabigatran, rivaroxaban or apixaban compared with warfarin
Study design	• Retrospective cohort study using data from the Norwegian Patient Registry (NPR) and Norwegian Prescription Database (NorPD)
Study period	• Jan 1, 2013 – 30 June, 2015
Study population	• Adult (≥18 years) patients with NVAF* diagnosis and at least one OAC (warfarin, dabigatran, rivaroxaban or apixaban) dispensation in the study period but being OAC naïve (no OAC exposure in the preceding 180 days before the index date#) before the start of the study • Patients with venous thromboembolism (VTE) during the last 180 days and those with a knee or hip replacement surgery during the last 35 days before starting OAC were excluded • Final sample included 32 675 patients; apixaban was dispensed in 6506 patients, dabigatran in 7925 patients, rivaroxaban in 6817 patients, and warfarin in 11 427 patients
Analyses	• Bleeding was defined as all bleeding events recorded in NPR between index date and 30 days after the calculated end of OAC supply and was categorized as major or clinically relevant non-major (CRNM) – Major bleeding was defined as any bleeding which occurred in a critical area or organ or any bleeding that was accompanied by blood transfusion ≤10 days after hospital admission date – CRNM bleeding was defined as any bleeding requiring medical intervention, leading to hospitalization or increased level of care or prompting a face to face evaluation, that did not fit the criteria for major bleeding • Primary endpoint was a composite of major or CRNM bleeding • Secondary endpoints were: 1) major bleeding, 2) CRNM bleeding, 3) gastrointestinal bleeding, 4) intracranial haemorrhage and 5) bleeds from other organ systems • Cox proportional hazard regression analyses were conducted to determine the risk of bleeding for the different NOACs vs warfarin, both unadjusted and adjusted for known patient characteristics (age, gender, previous bleeding, previous OAC use, co-morbidities and concomitant medications) at baseline • Post-hoc subgroup analyses for the primary endpoint were performed for elderly (≥ 75 years) as well as for OAC dose levels at index date (standard and reduced dose) in comparison with warfarin

**NVAF* = AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.
#*Index date* = the date of the first dispensed OAC (warfarin 2.5 mg, dabigatran 110 or 150 mg, rivaroxaban 15 or 20 mg and apixaban 2.5 or 5 mg) during the study period. Patients were followed until: 1) OAC discontinuation = next OAC dispensation >30 days after the calculated end of supply; 2) OAC switch = another OAC dispensed within 30 days after the calculated end of supply; 3) death; or 4) end of follow-up, whichever occurred first.

AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

Halvorsen et al. *Eur Heart J Cardiovasc Pharmacother*. 2016 September 27 [Epub ahead or print].

Baseline Characteristics of the Study Population According to OAC Treatment

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Number of patients	11 427	7925	6817	6506
Men	6737 (59.0)	4915 (62.0)	3711 (54.4)	3579 (55.0)
Age, years				
Mean (SE)	74.6 (11.9)	70.8 (11.3)	74.7 (10.7)	74.5 (11.1)
Median (25th -75th percentile)	76 (67-84)	71 (64-79)	75 (68-83)	75 (68-83)
≥75 years	6248 (54.7)	2967 (37.4)	3524 (51.7)	3295 (50.6)
Medical history				
Chronic Kidney Disease	569 (5.0)	58 (0.73)	135 (2.0)	163 (2.5)
Chronic Heart Failure	3316 (29.0)	1250 (15.8)	1388 (20.4)	1341 (20.6)
Diabetes	1674 (14.7)	822 (10.4)	794 (11.7)	797 (12.3)
Stroke, TIA and thromboembolism	1329 (11.6)	745 (9.4)	1096 (16.1)	905 (13.9)
Ischemic Heart Disease	4102 (35.9)	1699 (21.4)	1736 (25.5)	1795 (27.6)
Previous bleeding hospitalization	1922 (16.8)	890 (11.2)	1009 (14.8)	982 (15.1)
Previous OAC (>180 days prior to index)	2910 (25.5)	900 (11.4)	748 (11.0)	527 (8.1)
Active cancer (last year)	1145 (10.0)	589 (7.4)	625 (9.2)	562 (8.6)
COPD	1064 (9.3)	518 (6.5)	580 (8.5)	567 (8.7)
Hypertension	7654 (67.0)	4677 (59.0)	4500 (66.0)	.4254 (65.4)
Anemia (last year)	553 (4.8)	155 (2.0)	203 (3.0)	201 (3.1)
Viral hepatitis	25 (0.22)	16 (0.20)	7 (0.10)	11 (0.17)
Hospital admission last year	7734 (67.7)	4422 (55.8)	4460 (65.4)	4412 (67.8)
Co-medication				
Low-dose aspirin (last year)	5420 (47.4)	3687 (46.5)	3621 (53.1)	3304 (50.8)
NSAID (last year)	2264 (19.8)	1937 (24.4)	1583 (23.2)	1498 (23.0)
Non-aspirin anti-platelet inhibitors (last year)	278 (2.4)	185 (2.3)	231 (3.4)	189 (2.9)
Risk scores				
Modified HAS-BLED score ≥3	4894 (42.8)	2934 (37.0)	3206 (47.0)	3029 (46.6)
CHA_2DS_2VASc score Mean ≥2	 3.09 9449 (82.7)	 2.46 5785 (73.0)	 2.94 5709 (83.7)	 2.93 5411 (83.2)
Co-morbidity score ≥1	7527 (65.6)	3851 (48.6)	4124 (60.5)	3916 (60.2)
Reduced NOAC dose at index date	NA	2758 (34.8)	1824 (26.8)	1901 (29.2)

Values are numbers (percentages) unless otherwise stated.

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke/transient ischemic attack (doubled), vascular disease, age 65–74, and sex (female); COPD, chronic obstructive pulmonary disease; HAS-BLED, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding, history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol (1 point each); NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant; NOAC, non-vitamin K antagonist oral anticoagulant; SE, standard error; TIA, transient ischemic attack.

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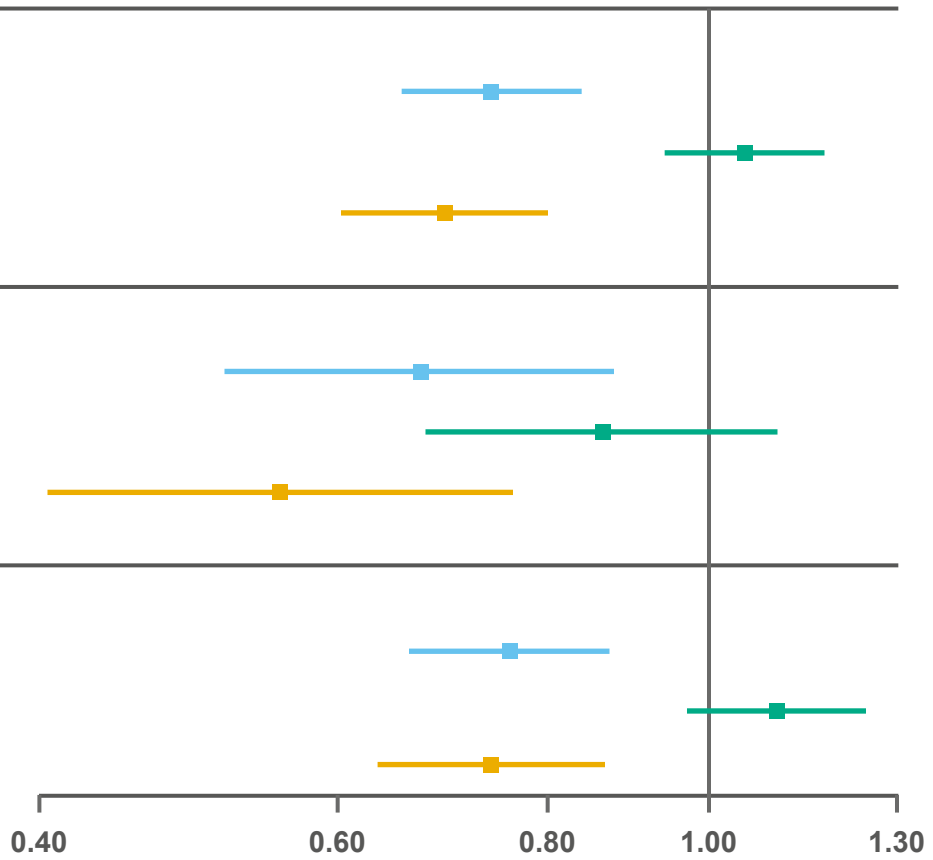
Risk of Bleeding for Dabigatran, Rivaroxaban and Apixaban Compared to Warfarin

A) Major or clinically relevant non-major bleeding

OAC	IR	HR (95% CI)	*P* value
Major or CRNM			
Warfarin	11.44	1 (ref.)	
Dabigatran	6.74	0.74 (0.66, 0.84)	<0.001
Rivaroxaban	11.43	1.05 (0.94, 1.17)	0.400
Apixaban	8.58	0.70 (0.61, 0.80)	<0.001
Major			
Warfarin	2.42	1 (ref.)	
Dabigatran	1.29	0.67 (0.52, 0.88)	0.004
Rivaroxaban	2.07	0.86 (0.68, 1.10)	0.231
Apixaban	1.51	0.56 (0.40, 0.76)	0.001
CRNM			
Warfarin	8.85	1 (ref.)	
Dabigatran	5.38	0.76 (0.66, 0.87)	<0.001
Rivaroxaban	9.20	1.10 (0.97, 1.24)	0.133
Apixaban	7.00	0.74 (0.64, 0.87)	<0.001



Crude IRs for first bleeding episode are given as events per 100 person-years.

CI, confidence interval; CRNM, clinically relevant non-major; HR, adjusted hazard ratio; IR, incidence rate; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

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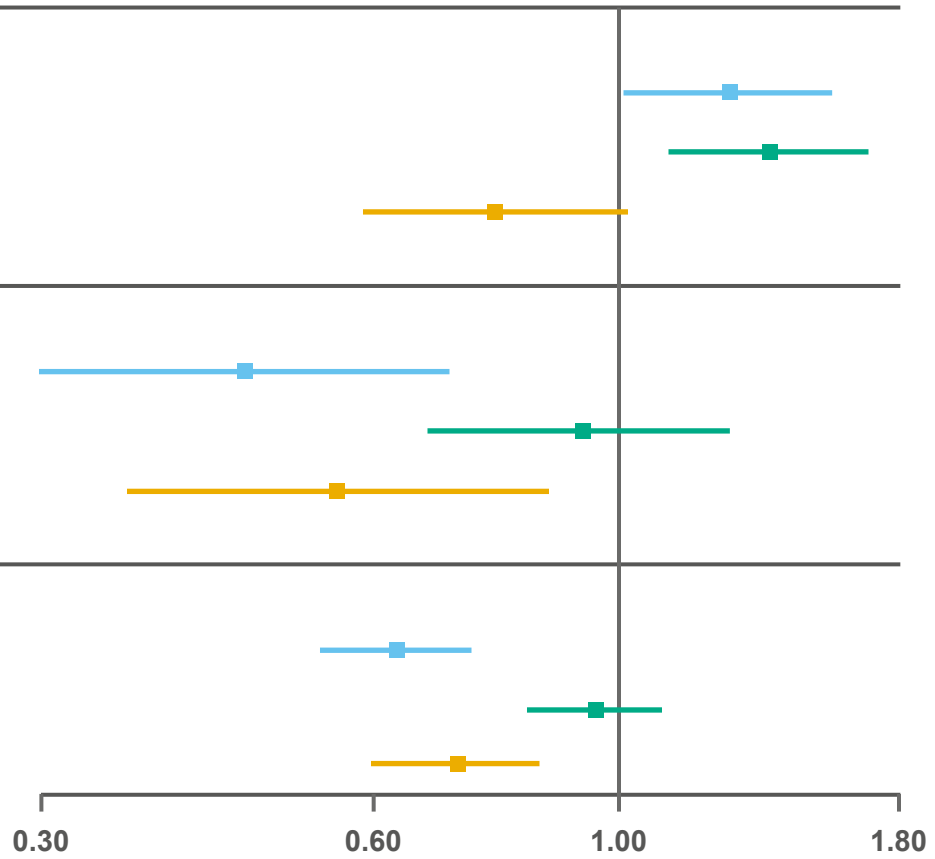
Risk of Bleeding for Dabigatran, Rivaroxaban and Apixaban Compared to Warfarin

B) GI bleeding, ICH and bleeding from other sites

OAC	IR	HR (95% CI)	*P* value
GI			
Warfarin	2.67	1 (ref.)	
Dabigatran	2.43	1.26 (1.01, 1.57)	0.037
Rivaroxaban	3.33	1.37 (1.12, 1.69)	0.003
Apixaban	2.16	0.77 (0.59, 1.02)	0.068
ICH			
Warfarin	1.20	1 (ref.)	
Dabigatran	0.45	0.46 (0.30, 0.70)	<0.001
Rivaroxaban	1.19	0.93 (0.67, 1.29)	0.656
Apixaban	0.80	0.56 (0.36, 0.86)	0.009
Other			
Warfarin	7.33	1 (ref.)	
Dabigatran	3.75	0.63 (0.54, 0.74)	<0.001
Rivaroxaban	6.60	0.95 (0.83, 1.10)	0.505
Apixaban	5.51	0.71 (0.60, 0.85)	<0.001



Crude IRs for first bleeding episode are given as events per 100 person-years.

CI, confidence interval; GI, gastrointestinal; ICH, intracranial hemorrhage; HR, adjusted hazard ratio; IR, incidence rate; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

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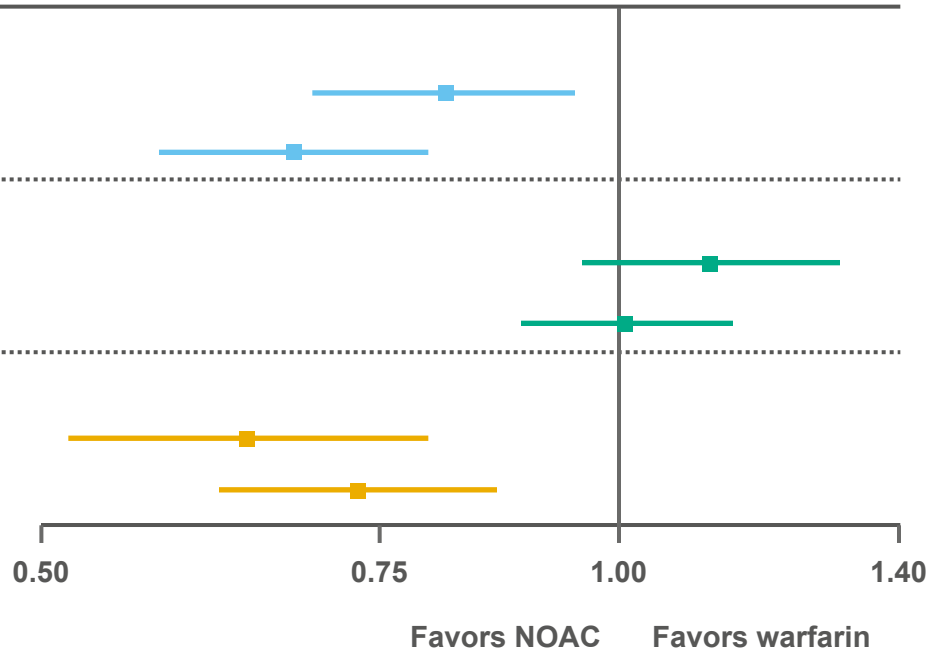
Risk of Major or CRNM Bleeding for the Reduced and Standard Dose of Dabigatran, Rivaroxaban and Apixaban Compared to Warfarin

OAC	IR	HR (95% CI)	*P* value
Major or CRNM			
Warfarin	11.44	1 (ref.)	
Dabigatran 110	9.76	0.81 (0.69, 0.95)	0.009
Dabigatran 150	5.12	0.68 (0.58, 0.80)	<0.001
Warfarin	11.44	1 (ref.)	
Rivaroxaban 15	15.86	1.12 (0.96, 1.31)	0.158
Rivaroxaban 20	9.84	1.01 (0.89, 1.15)	0.853
Warfarin	11.44	1 (ref.)	
Apixaban 2.5	10.60	0.64 (0.52, 0.80)	<0.001
Apixaban 5	7.78	0.73 (0.62, 0.86)	<0.001



Crude IRs for first bleeding episode are given as events per 100 person-years.

CI, confidence interval; CRNM, clinically relevant non-major; HR, adjusted hazard ratio; IR, incidence rate; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

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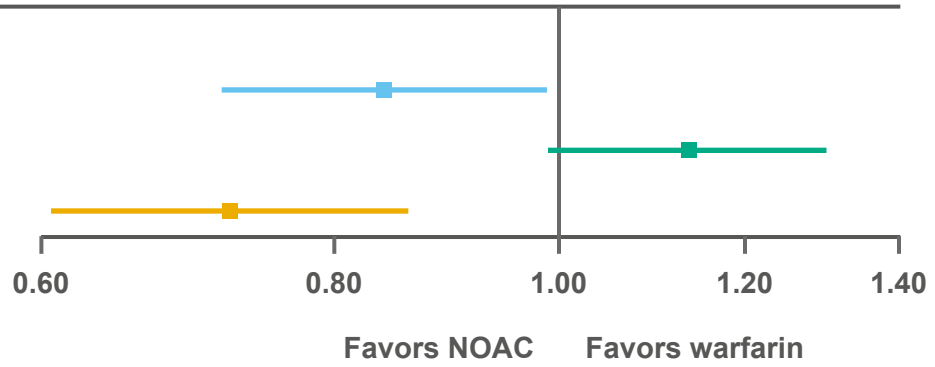
Risk of Major or CRNM Bleeding for Dabigatran, Rivaroxaban and Apixaban Compared to Warfarin in the Subgroup of Patients ≥ 75 years

OAC	IR	HR (95% CI)	*P* value
Major or CRNM			
Warfarin	14.64	1 (ref.)	
Dabigatran	10.00	0.84 (0.72, 0.99)	0.036
Rivaroxaban	14.68	1.14 (0.99, 1.30)	0.067
Apixaban	10.82	0.72 (0.61, 0.86)	<0.001



Crude IRs for first bleeding episode are given as events per 100 person-years.

CI, confidence interval; CRNM, clinically relevant non-major; HR, adjusted hazard ratio; IR, incidence rate; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

Halvorsen et al. *Eur Heart J Cardiovasc Pharmacother*. 2016 September 27 [Epub ahead or print].

Registre Norvégien (32600 pt, 2,5 ans, sécurité seule)

1. Confirme la sécurité de l'apixaban et du dabigatran, à toutes les doses.
2. Confirme la neutralité du rivaroxaban, à toutes les doses.
3. Dans ce registre le rivaroxaban n'a pas diminué les ICH.
4. Sécurité confirmée aussi chez les patients ≥ 75 ans.

Synthèse finale (jusqu'ici)

1. L'efficacité supérieure des AOD en général dépend surtout de la réduction des AVC hémorragiques.
2. Leur efficacité est au moins équivalente à celle des AVK.
3. L'avantage plus important des AOD est la sécurité, et surtout la réduction des hémorragies intracrâniennes.
4. L'augmentation des hémorragies GI semble un prix acceptable à payer.
5. Bons résultats aussi dans l'IR modérée (Cl.Cr 30-49 ml/min)

Synthèse finale (jusqu'ici)

1. Apixaban (5 mg 2/J) semble avoir le meilleur profil sur l'efficacité (générale) et sur la sécurité (il est le seul qui n'augmente pas les hémorragies GI).
2. Données insuffisantes pour l'efficacité d'apixaban 2.5 mg.
3. Dabigatran 150 mg a une efficacité supérieure ou équivalente aux AVK, et probablement une sécurité supérieure (↓ ICH).
4. Dabigatran 110 mg a une efficacité similaire aux AVK et une sécurité supérieure.
5. Dabigatran est le seul AOD qui a un antidote disponible.

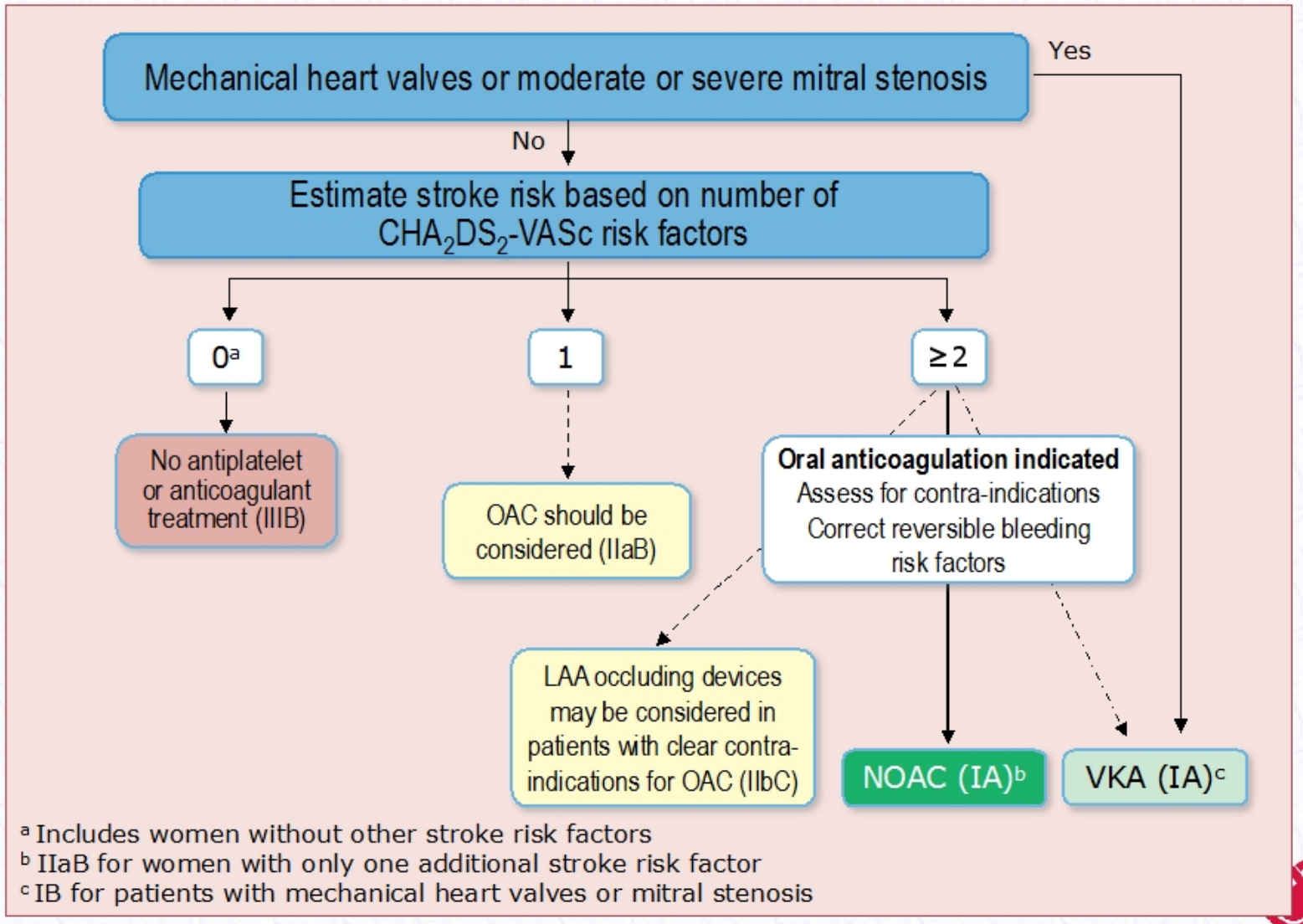
Synthèse finale (jusqu'ici)

1. Rivaroxaban (20 mg/J) a une efficacité équivalente aux AVK, et probablement une sécurité supérieure (réduction des ICH).
2. Données insuffisantes pour l'efficacité du rivaroxaban 15 mg.

Synthèse finale (jusqu'ici)

1. Edoxaban 60 mg/J a une efficacité équivalente aux AVK et une sécurité supérieure (réduction des ICH).
2. Edoxaban 30 mg/J a montré une efficacité inférieure aux AVK sur les AVC ischémiques: non approuvé.
3. Puisque tous les 3 AOD (rivaroxaban à confirmer?) donnent une réduction des ICH, vue l'efficacité > ou = aux AVK, le bénéfice clinique net des AOD est supérieur.

Stroke prevention in patients with atrial fibrillation



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