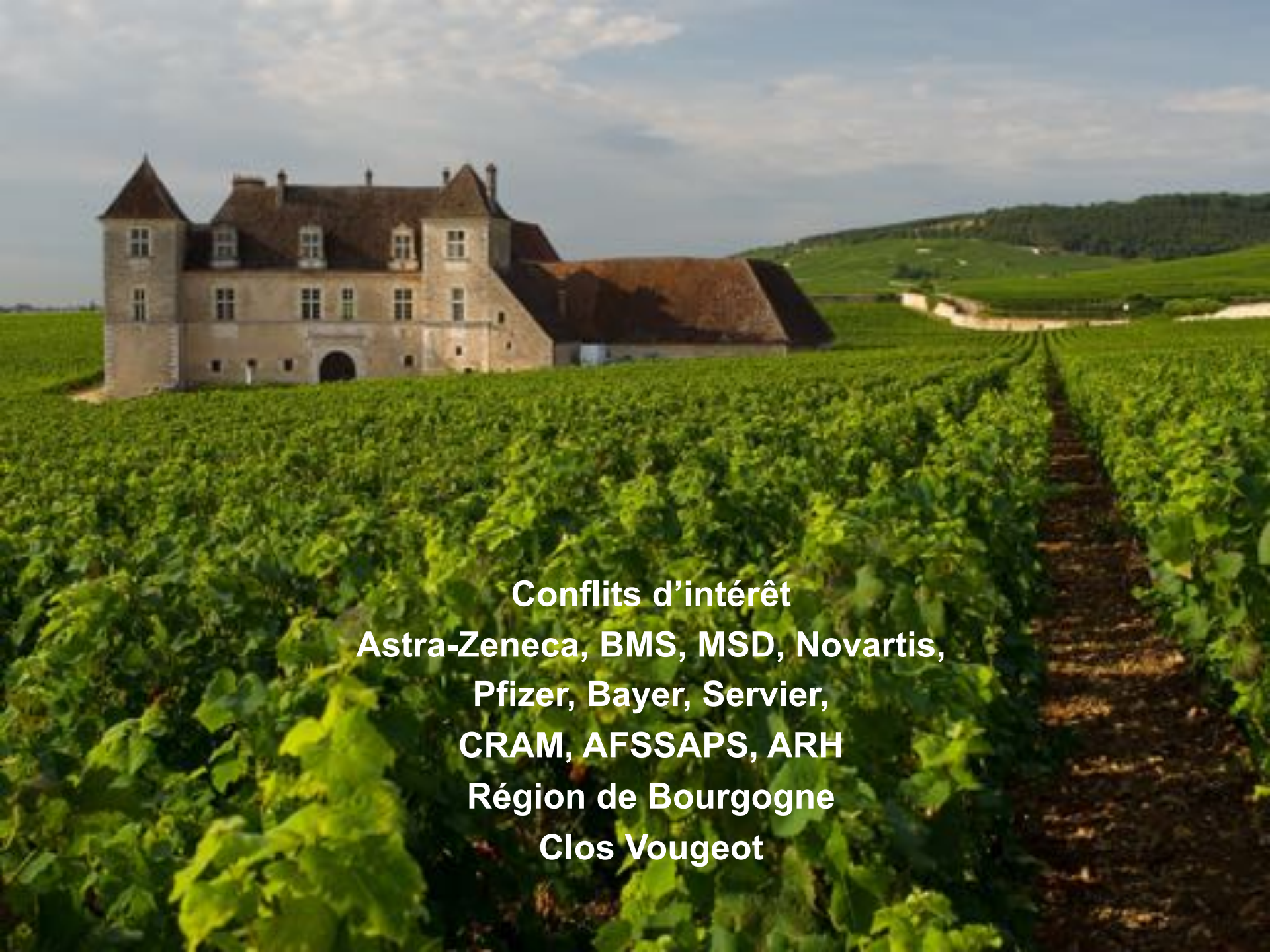
APPAC

PALAIS DES CONGRES BIARRITZ

7/8/9 JUIN 2017

La fin des AVK dans la fibrillation atriale non valvulaire

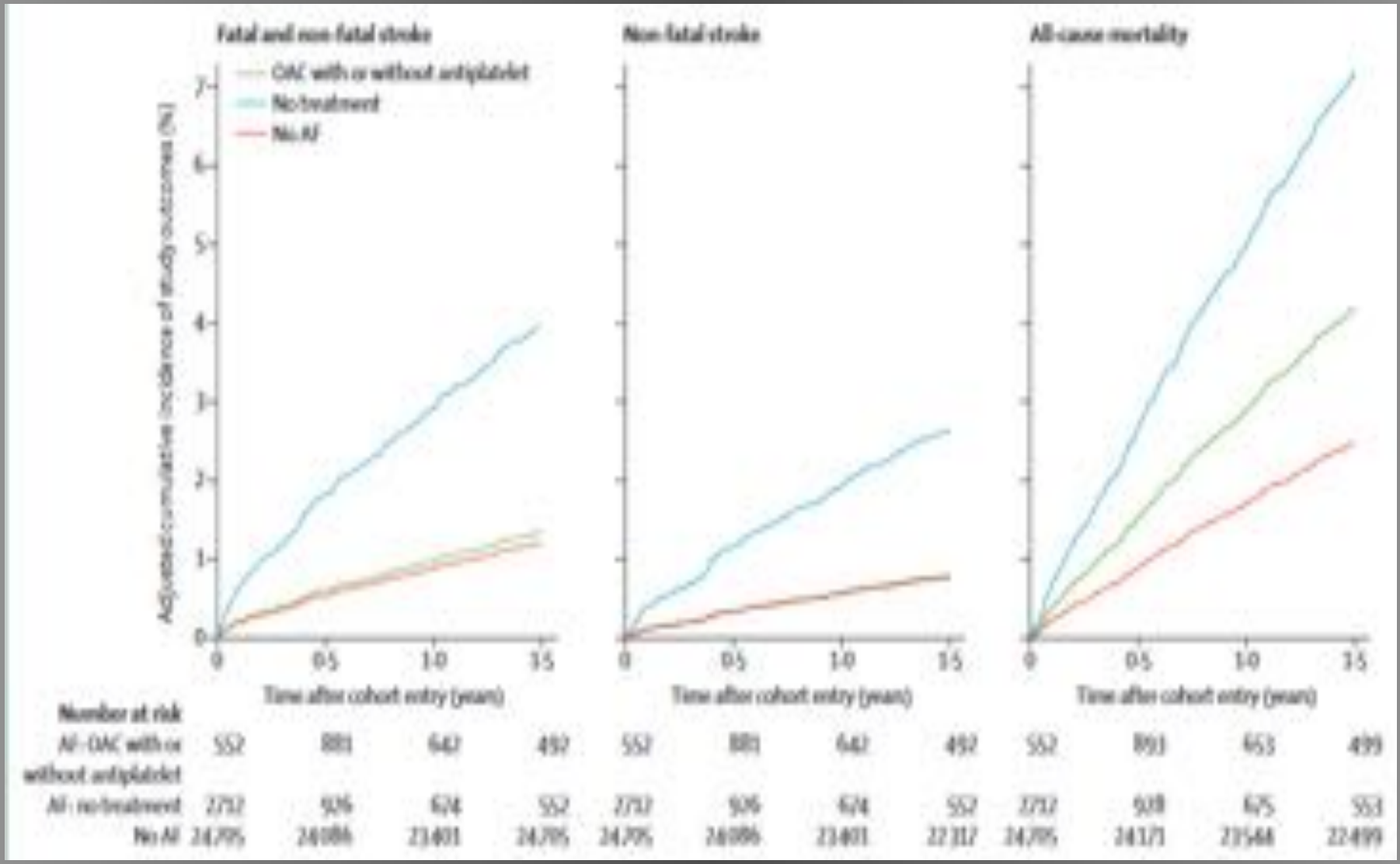
Dr Y Cottin
Dijon


Conflits d'intérêt
Astra-Zeneca, BMS, MSD, Novartis,
Pfizer, Bayer, Servier,
CRAM, AFSSAPS, ARH
Région de Bourgogne
Clos Vougeot

« Dans la vie, rien n’est à craindre, tout est à comprendre »

Marie Curie

Residual risk of stroke and death in anticaogulant-treated patients with atrial fibrillation.



Freedman B et al. JAMA Cardiol. 2016;1:66–68.

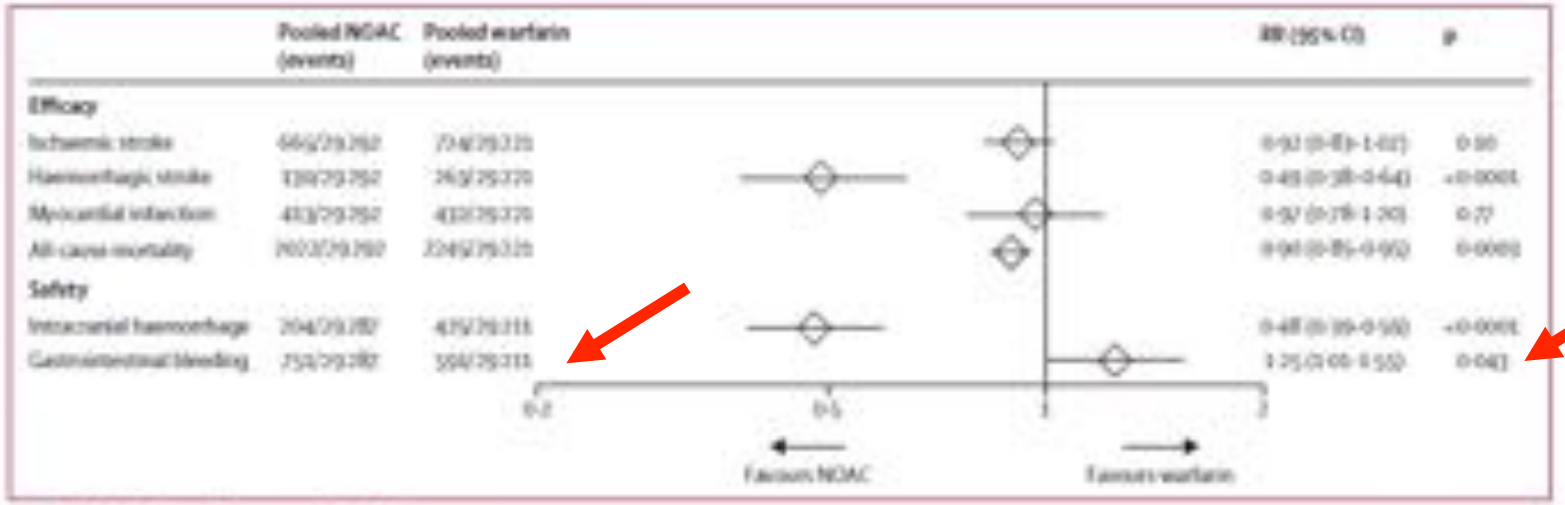


Figure 2: Secondary efficacy and safety outcomes

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=0·11; 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.

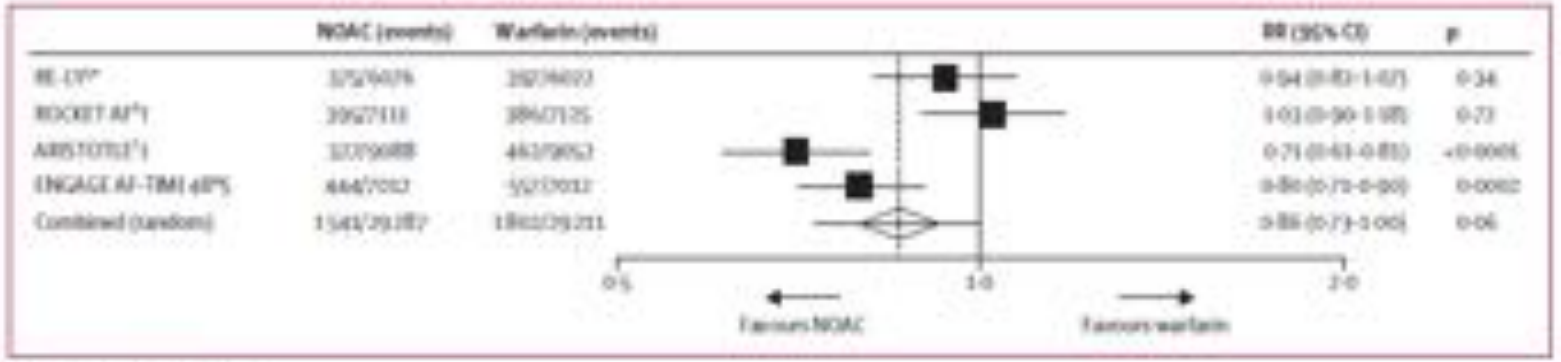
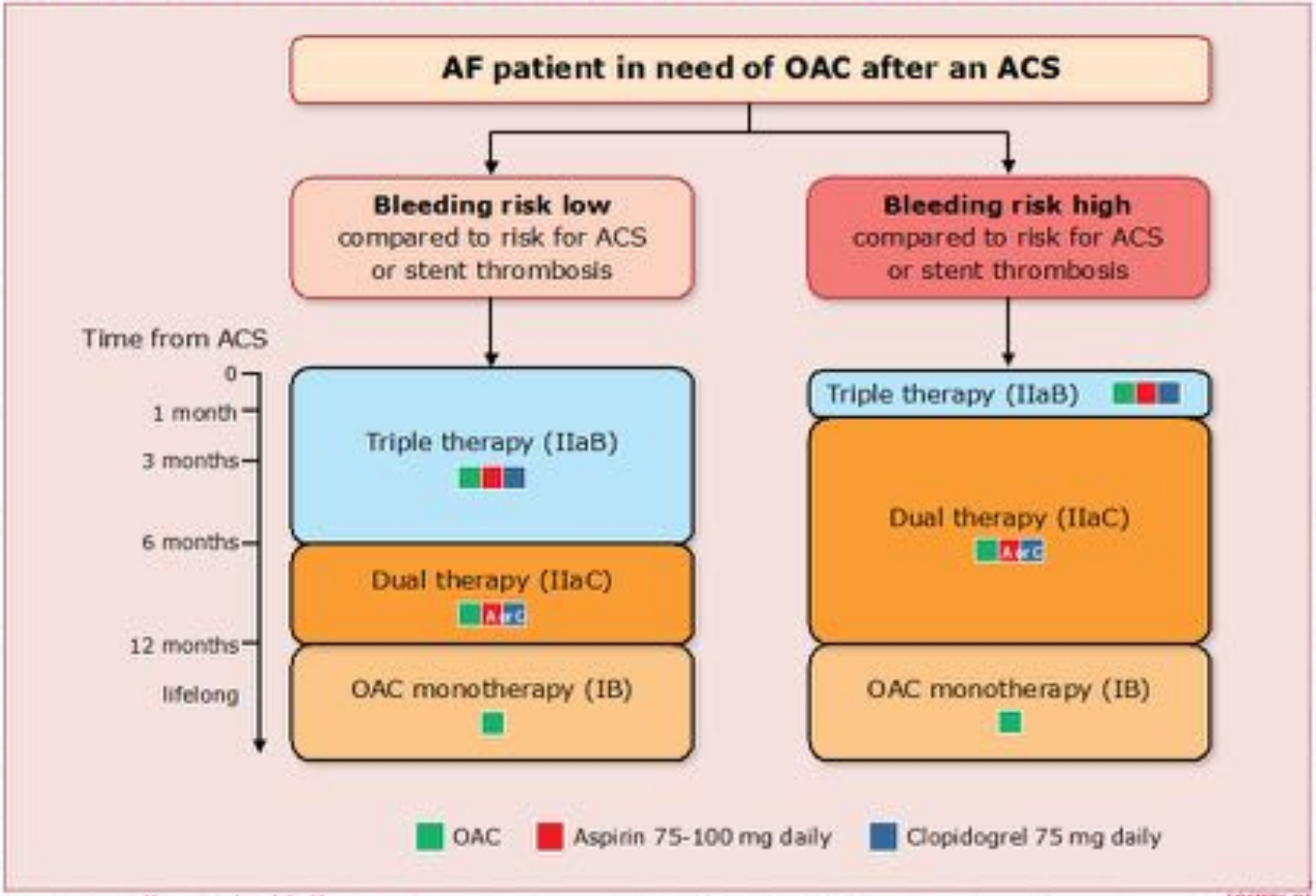


Figure 3: Major bleeding

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=82%, 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.

Ruff CT, et al. Lancet. 2014;383:955-962.

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



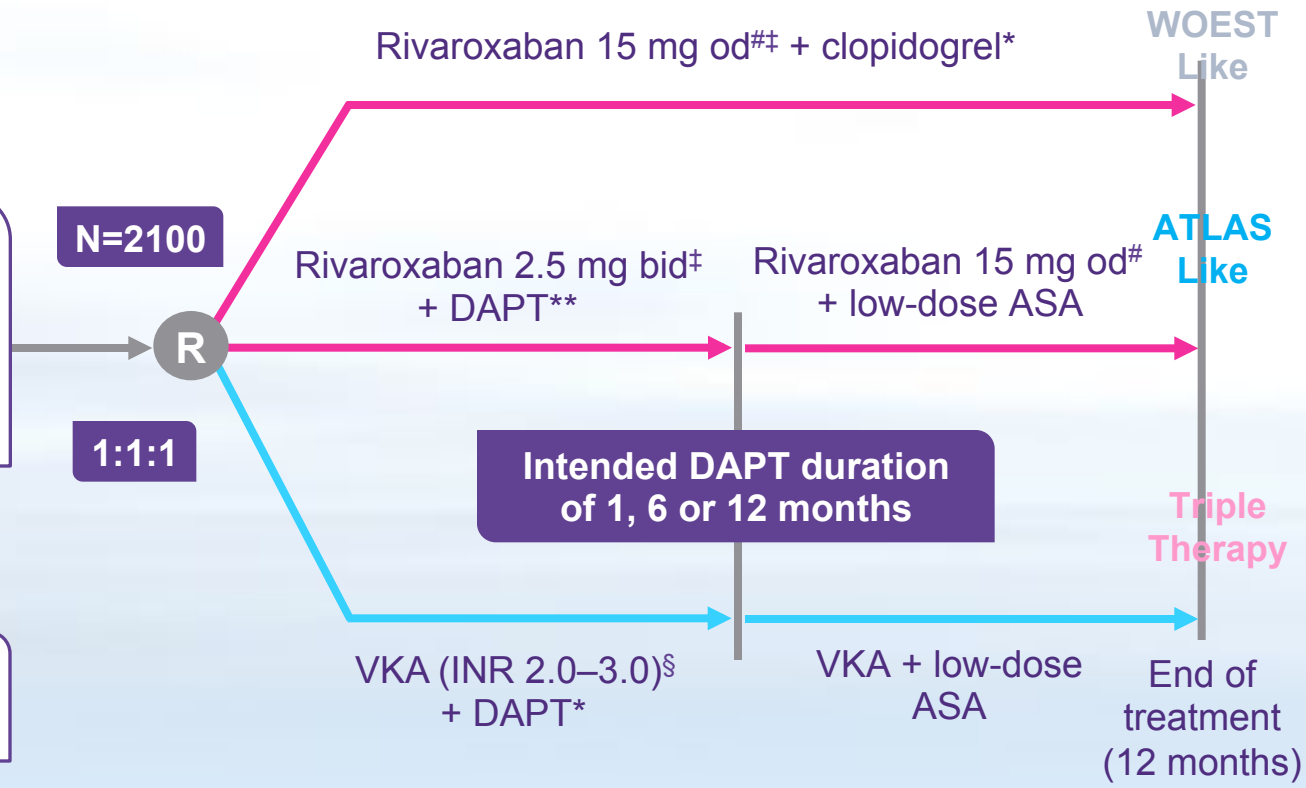
European Heart Journal - doi:10.1093/eurheartj/ehw210

PIONEER AF-PCI: overview
PCI study

Objective: safety of two rivaroxaban regimens vs VKA after PCI (with stent placement) in non-valvular AF

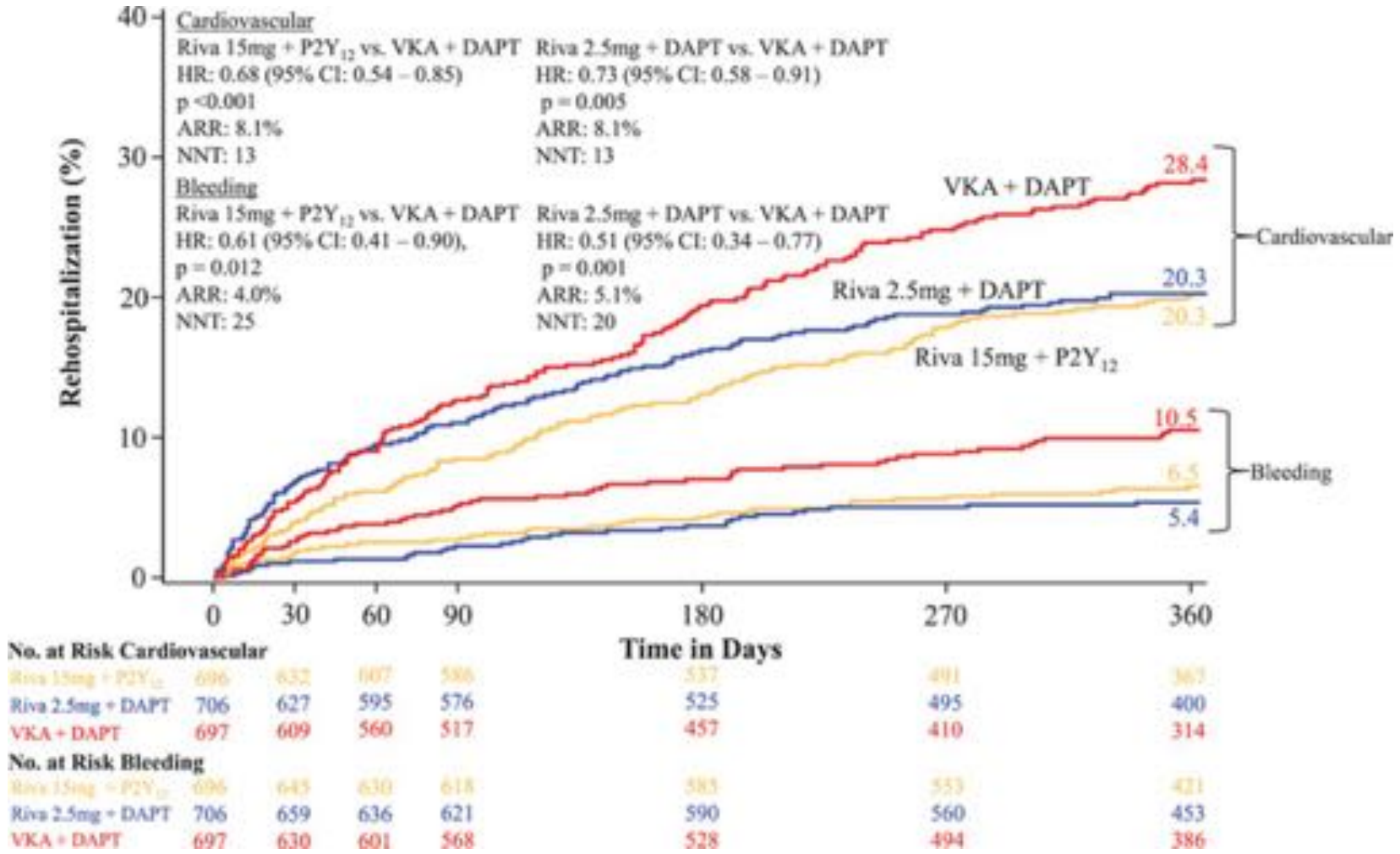
Population:
Paroxysmal, persistent or permanent AF, undergoing PCI (with stent placement)

Start: Q2-13
End: ~Q3-15



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

Time to first recurrent hospitalization caused by cardiovascular or bleeding event.



C. Michael Gibson et al. Circulation. 2017;135:323-333

American Heart Association.


Design 2010
Années
Etudes Randomisées 2011
Sous Groupes des Etudes Randomisées
Cohortes Big-Data
Long Terme

Stroke prevention in atrial fibrillation

Key points from the landmark NOAC trials in patients with non-valvular atrial fibrillation*

- NOACs were superior to warfarin (dabigatran 150 mg or apixaban) or similarly effective as warfarin (dabigatran 110 mg, rivaroxaban, or edoxaban in both doses) at reducing stroke or systemic embolism.
- Stroke reduction was largely driven by the reduction in haemorrhagic stroke (significant for all NOACs vs VKAs) with minimal effect on ischaemic stroke, in which a significant reduction was only reported for dabigatran 150 mg.
- NOACs were either safer than warfarin (dabigatran 110 mg, apixaban, or edoxaban in both doses) or as safe as warfarin (dabigatran 150 mg or rivaroxaban) with respect to major bleeding.
- Apixaban was more effective than aspirin in the prevention of stroke or systemic embolism, with comparable safety (regarding major bleeding, haemorrhagic stroke, ICH, and gastrointestinal bleeding), and was better tolerated.

Freedman B et al. Lancet, 2016;388:806-17.

Stroke prevention in atrial fibrillation

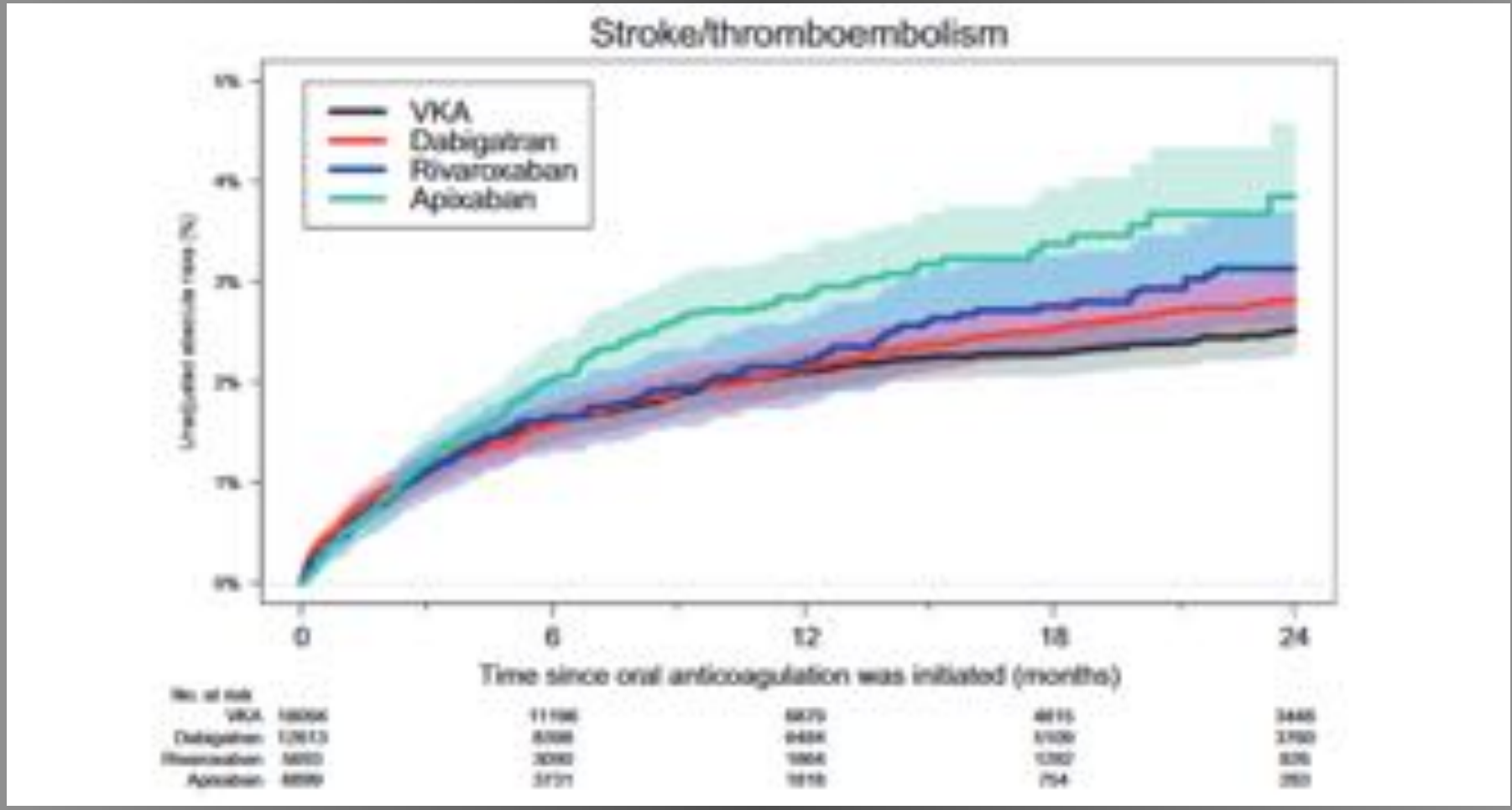
Key points from large real-world administrative dataset analyses of NOAC use[32]†

- Effectiveness and safety of dabigatran, rivaroxaban, and apixaban in real-world data were broadly consistent with findings from landmark trials; however, the ROCKET-AF study included higher-risk patients with more events than real-world studies.
- Gastrointestinal bleeding was the most common major bleeding event.
- ICH or fatal bleeding was rare.
- Risk of bleeding during OAC initiation is higher with warfarin than with dabigatran.

Freedman B et al. Lancet, 2016;388:806-17.

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

43 299 AF patients



Staerk L, et al. Eur Heart J. 2017;38(12):907-915.

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

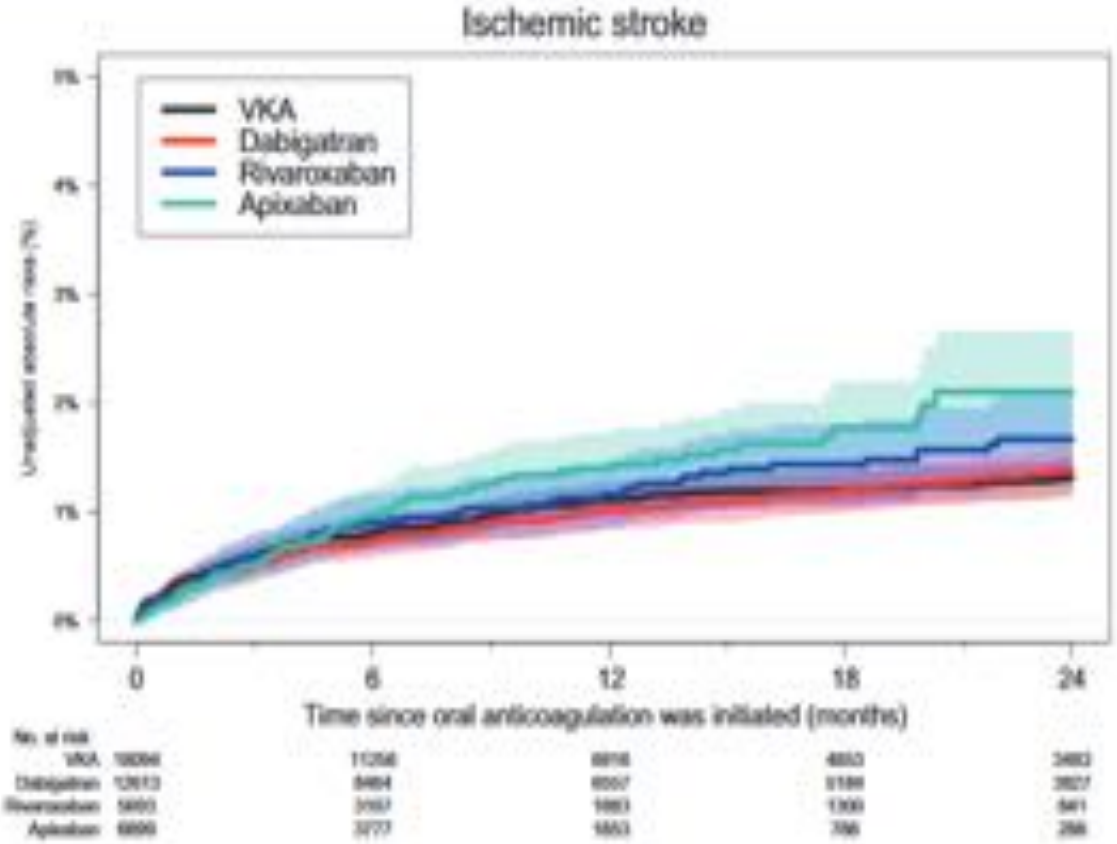


Figure 4 Unadjusted absolute risks of ischaemic stroke.

Staerk L, et al. Eur Heart J. 2017;38(12):907-915.

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

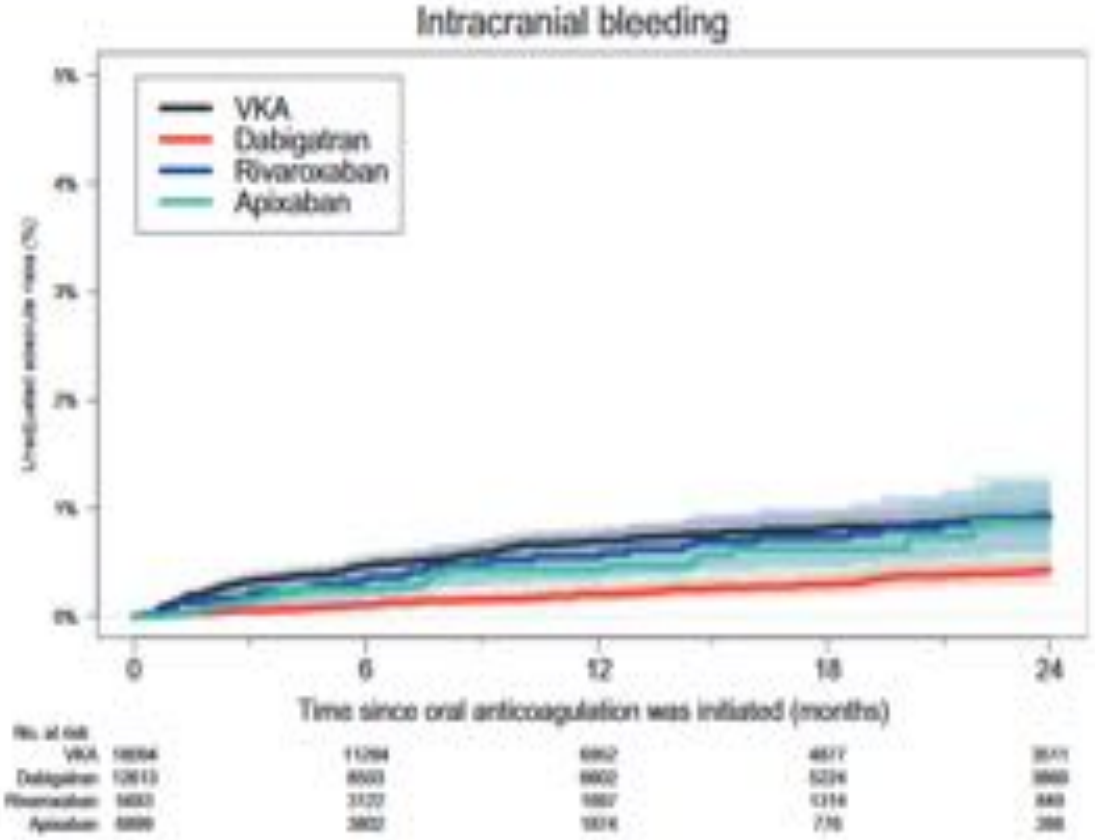


Figure 5 Unadjusted absolute risks of intracranial bleeding.

Staerk L, et al. Eur Heart J. 2017;38(12):907-915.

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

43 299 AF patients

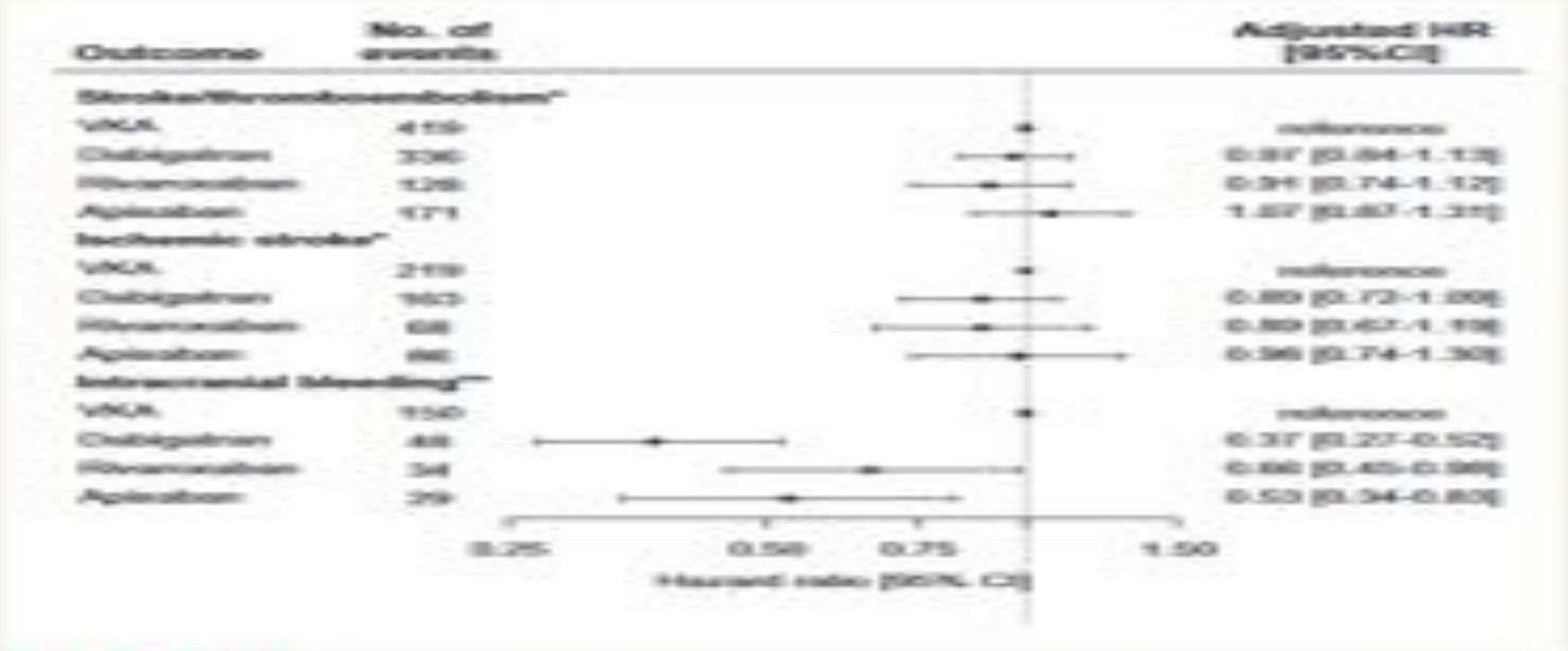


Figure 3 Number of events and adjusted hazard ratios from multiple Cox regression. *Adjusted for sex, age, heart failure, hypertension, diabetes, prior stroke, and vascular disease. **Additional adjusted for prior bleeding, liver disease, chronic kidney disease, alcohol abuse, ADP receptor antagonists, aspirin, dipyridamole, and non-steroidal anti-inflammatory drugs.

Staerk L, et al. Eur Heart J. 2017;38(12):907-915.

A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants

32 675 AF patients

OAC	IR	HR (95% CI)	P
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

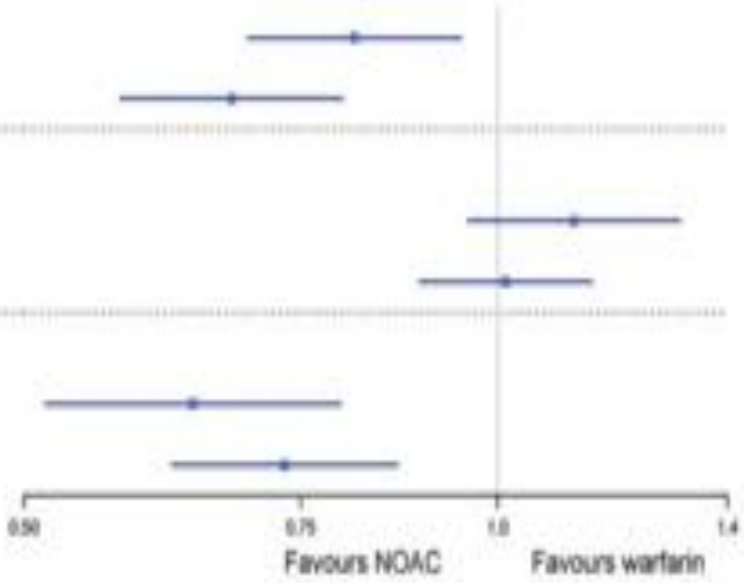


Figure 4 Risk of major or CRNM bleeding for the reduced and standard dose of dabigatran, rivaroxaban, and apixaban compared with warfarin. Crude IR for first bleeding episode are given as events per 100 person-years. CI, confidence interval; CRNM, clinically relevant non-major bleeding; HR, adjusted hazard ratio; IR, incidence rate; OAC, oral anticoagulant.

Halvorsen S, et al. Eur Heart J - Cardiovascular Pharmacotherapy. 2017;3: 28–36

A Comparison of the Rate of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin

Table 3. Sources of GIB

	NOAC users	Warfarin users
Upper GI source	1 (20%)	55 (34.8%)
Angioectasias	1	6
Peptic ulcer disease	0	17
Esophagitis	0	5
Gastritis	0	1
GAVE	0	1
Varices (gastric or esophageal)	0	1
Dieulafoy	0	1
Mallory Weiss tear	0	1
Portal hypertensive gastropathy	0	2
Other	0	20
Small bowel source	1 (20%)	7 (4.4%)
Angioectasias	1	4
Ulcers	0	2
Malignancy	0	1
Lower GI source	3 (60%)	42 (26.6%)
Hemorrhoids	2	5
Postpolypectomy bleed	1	1
Angioectasias	0	4
Malignancy	0	5
Diverticulosis	0	13
Ischemia	0	5
Radiation/anastomotic inflammation	0	2
Colon ulcers	0	6
Proctitis	0	1
Unknown source	2 (40%)	36 (22.8%)

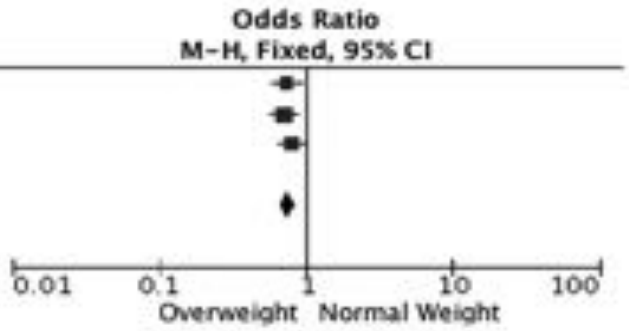
Cangemi DJ, et al. Am J Gastroenterol. 2017. 112:734-739.

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

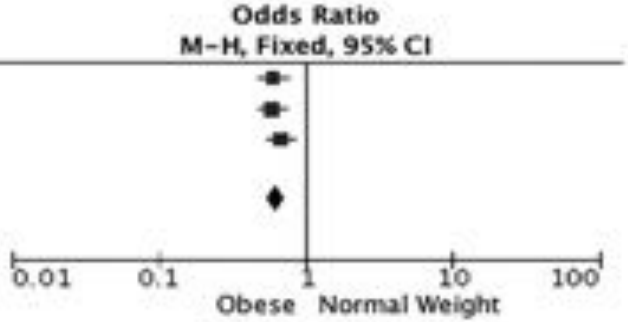
Study or Subgroup	Overweight Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	174	6702	142	4052	29.4%	0.73 [0.59, 0.92]
RE-LY	196	7111	182	4697	36.4%	0.70 [0.57, 0.86]
ROCKET AF	225	5523	167	3314	34.2%	0.80 [0.65, 0.98]
Total (95% CI)		**19336**		**12063**	**100.0%**	**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: $Z = 4.73$ ($P < 0.00001$)



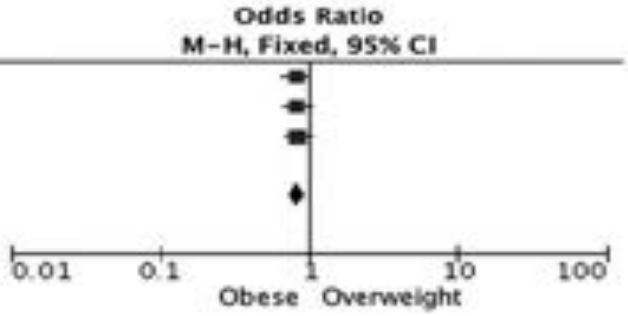
Study or Subgroup	Obese Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	152	7159	142	4052	30.7%	0.60 [0.47, 0.75]
RE-LY	145	6279	182	4697	35.2%	0.59 [0.47, 0.73]
ROCKET AF	179	5194	167	3314	34.1%	0.67 [0.54, 0.83]
Total (95% CI)		**18632**		**12063**	**100.0%**	**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: $Z = 2.98$ ($P = 0.003$)



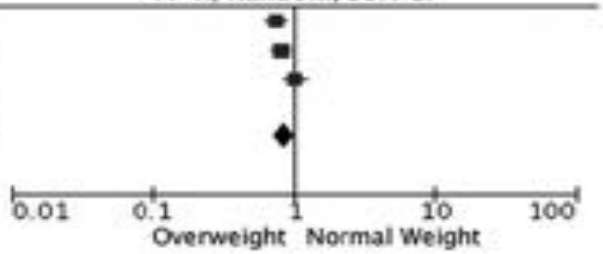
Proietti M, el al. Stroke. 2017; 48(4):857-866.

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

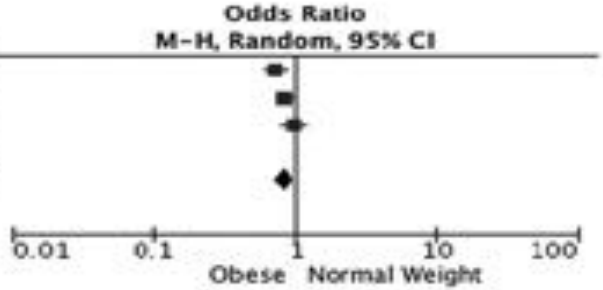
Study or Subgroup	Overweight Events	Overweight Total	Normal Weight Events	Normal Weight Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	271	6687	219	4035	32.1%	0.74 [0.61, 0.88]
RE-LY	424	7111	344	4697	36.3%	0.80 [0.69, 0.93]
ROCKET AF	312	5555	183	3327	31.5%	1.02 [0.85, 1.23]
Total (95% CI)		**19353**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



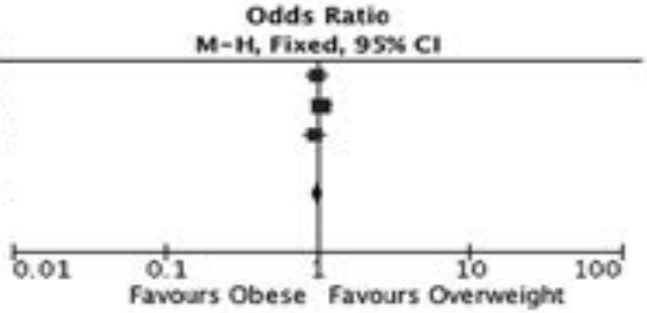
Study or Subgroup	Obese Events	Obese Total	Normal Weight Events	Normal Weight Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	285	7134	219	4035	32.2%	0.73 [0.61, 0.87]
RE-LY	394	6279	344	4697	37.3%	0.85 [0.73, 0.98]
ROCKET AF	279	5214	183	3327	30.5%	0.97 [0.80, 1.18]
Total (95% CI)		**18627**	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



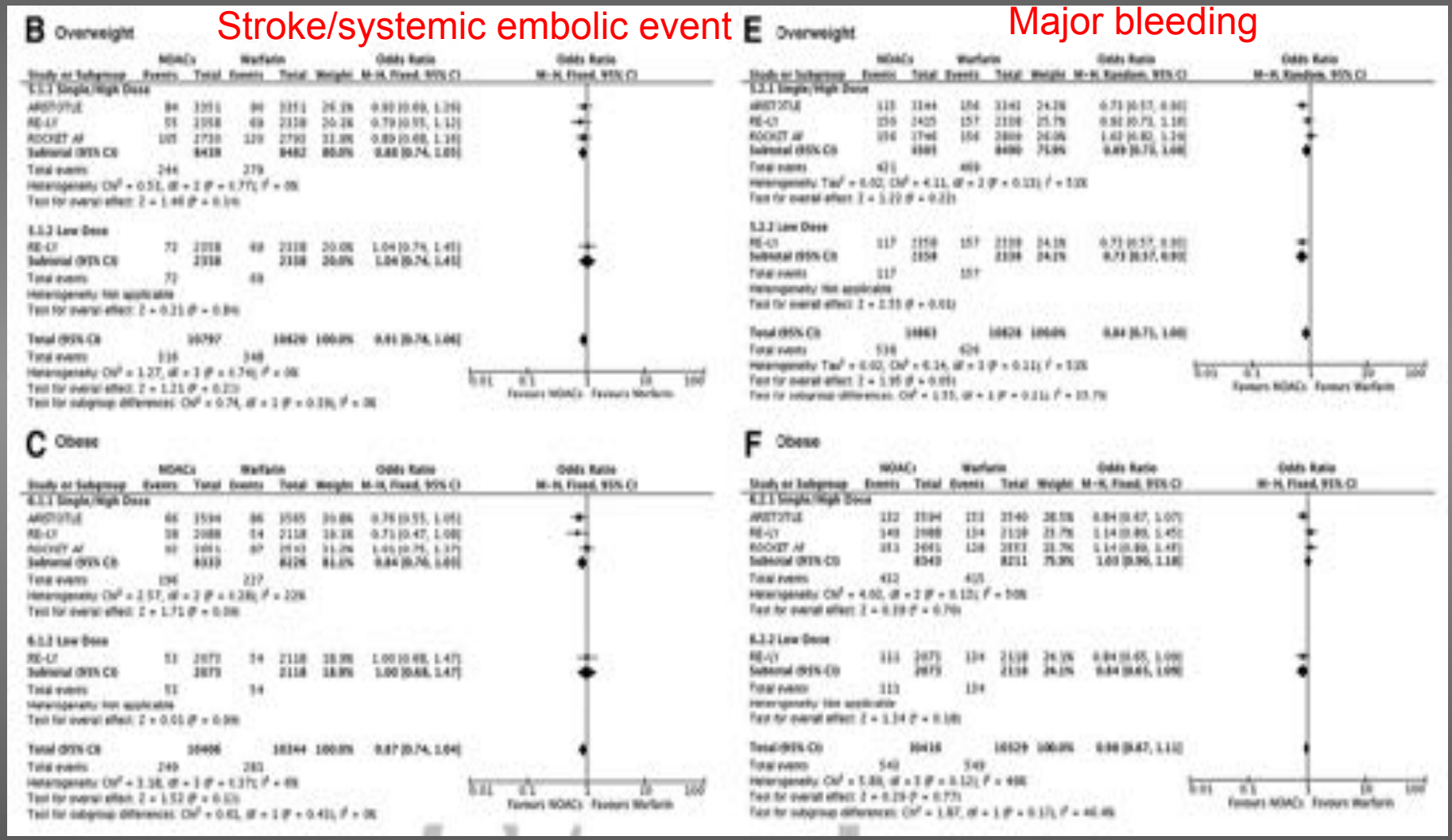
Study or Subgroup	Obese Events	Obese Total	Overweight Events	Overweight Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	285	7134	271	6687	29.0%	0.99 [0.83, 1.17]
RE-LY	394	6279	424	7111	40.2%	1.06 [0.92, 1.22]
ROCKET AF	279	5214	312	5555	30.8%	0.95 [0.80, 1.12]
Total (95% CI)		**18627**		**19353**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



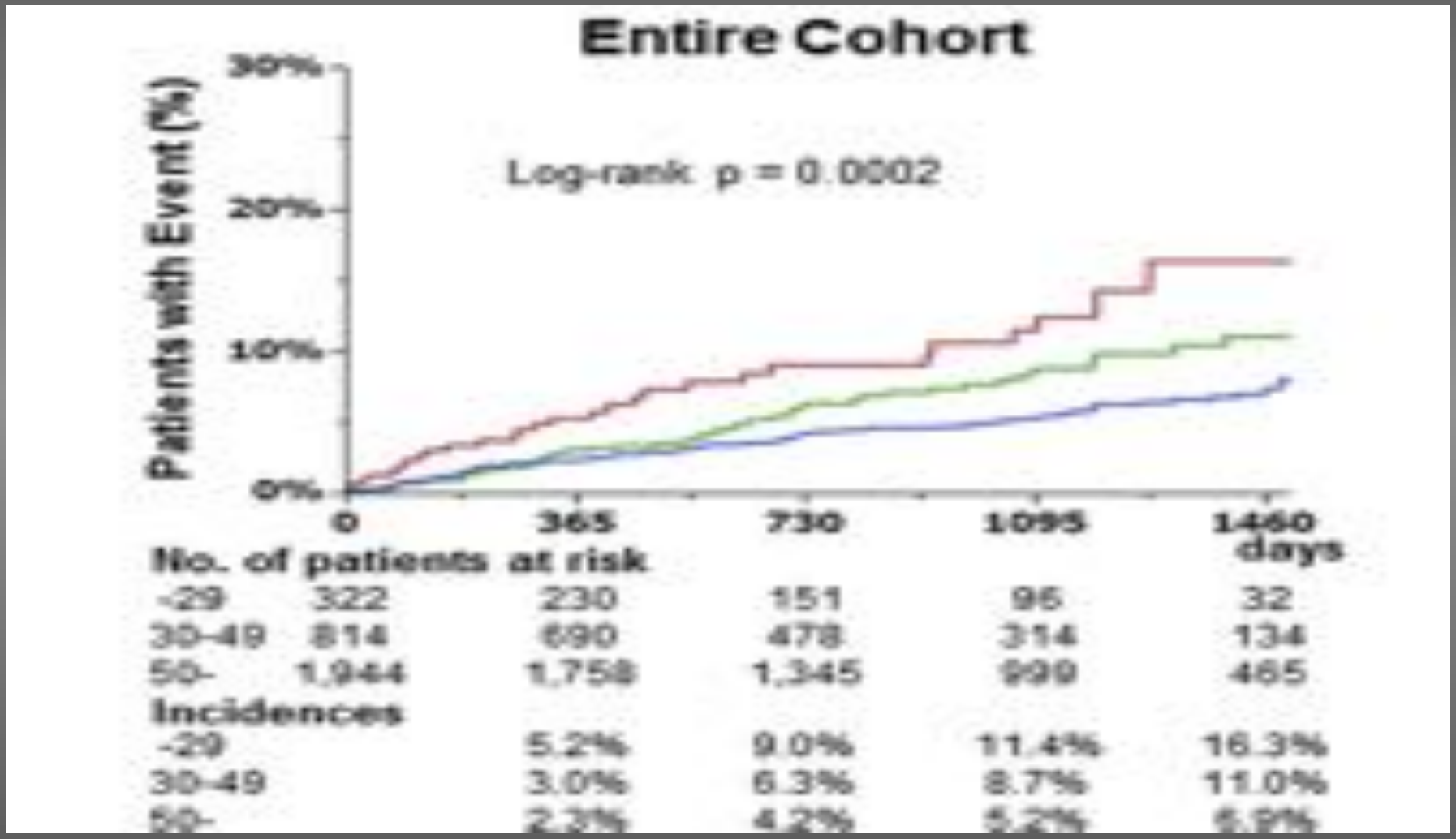
Proietti M, el al. Stroke. 2017; 48(4):857-866.

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



Proietti M, el al. Stroke. 2017; 48(4):857-866.

Relation of Stroke and Major Bleeding to Creatinine Clearance in Patients With Atrial Fibrillation (from the Fushimi AF Registry)



Abe M, et al. Am J Cardiol. 2017 ;119(8):1229-1237

Relation of Stroke and Major Bleeding to Creatinine Clearance in Patients With Atrial Fibrillation (from the Fushimi AF Registry)

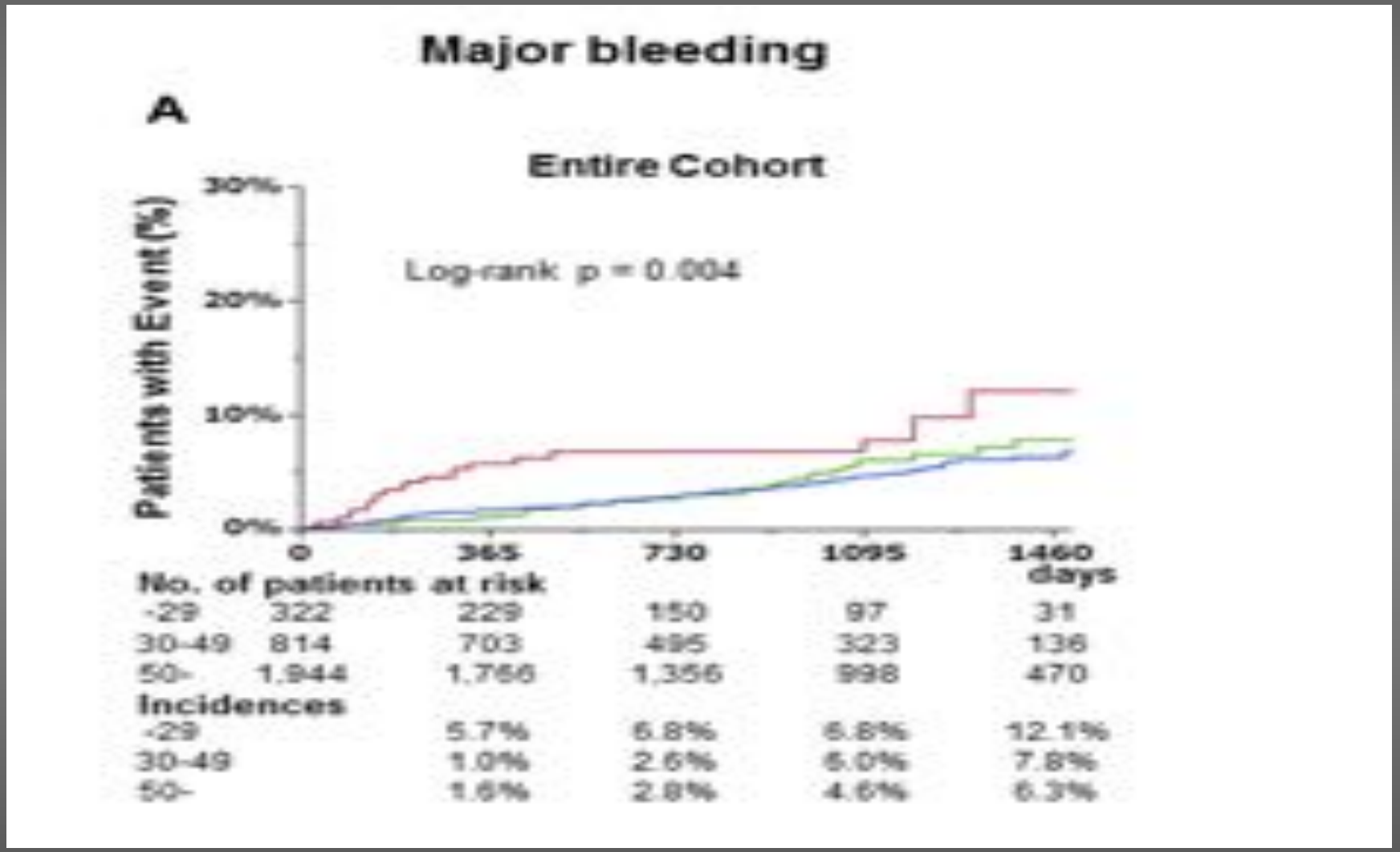
Univariate and multivariate analysis of the risk factors for stroke/SE

Variables	Univariate	Multivariate	
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	p Value
CrCl <30 (vs. CrCl ≥50)	2.05 (1.34 to 3.02)	1.68 (1.04 to 2.65)	0.04
30≤ CrCl <50 (vs. CrCl ≥50)	1.29 (0.93 to 1.76)	1.10 (0.76 to 1.58)	0.6
OAC prescription	1.17 (0.87 to 1.58)	1.06 (0.76 to 1.44)	0.7
Congestive heart failure	1.27 (0.92 to 1.72)	1.06 (0.76 to 1.47)	0.7
Hypertension	1.12 (0.83 to 1.53)	1.06 (0.78 to 1.45)	0.7
Age, ≥75 years old	2.12 (1.56 to 2.92)	1.97 (1.19 to 3.44)	0.008
Age, 65-74 years old	0.59 (0.41 to 0.82)	1.09 (0.64 to 1.96)	0.8
Diabetes mellitus	1.10 (0.79 to 1.51)	1.08 (0.77 to 1.50)	0.6
Prior stroke/TIA/SE	2.00 (1.46 to 2.71)	1.79 (1.30 to 2.45)	0.0005
Vascular disease	1.22 (0.75 to 1.88)	1.00 (0.61 to 1.55)	1.0
Female sex	1.03 (0.76 to 1.38)	0.88 (0.64 to 1.20)	0.4

CI = confidence interval; CrCl = creatinine clearance; OAC = oral anticoagulant; SE = systemic embolism; TIA = transient ischemic attack

Abe M, et al. Am J Cardiol. 2017 ;119(8):1229-1237

Relation of Stroke and Major Bleeding to Creatinine Clearance in Patients With Atrial Fibrillation (from the Fushimi AF Registry)



Abe M, et al. Am J Cardiol. 2017 ;119(8):1229-1237

Relation of Stroke and Major Bleeding to Creatinine Clearance in Patients With Atrial Fibrillation (from the Fushimi AF Registry)

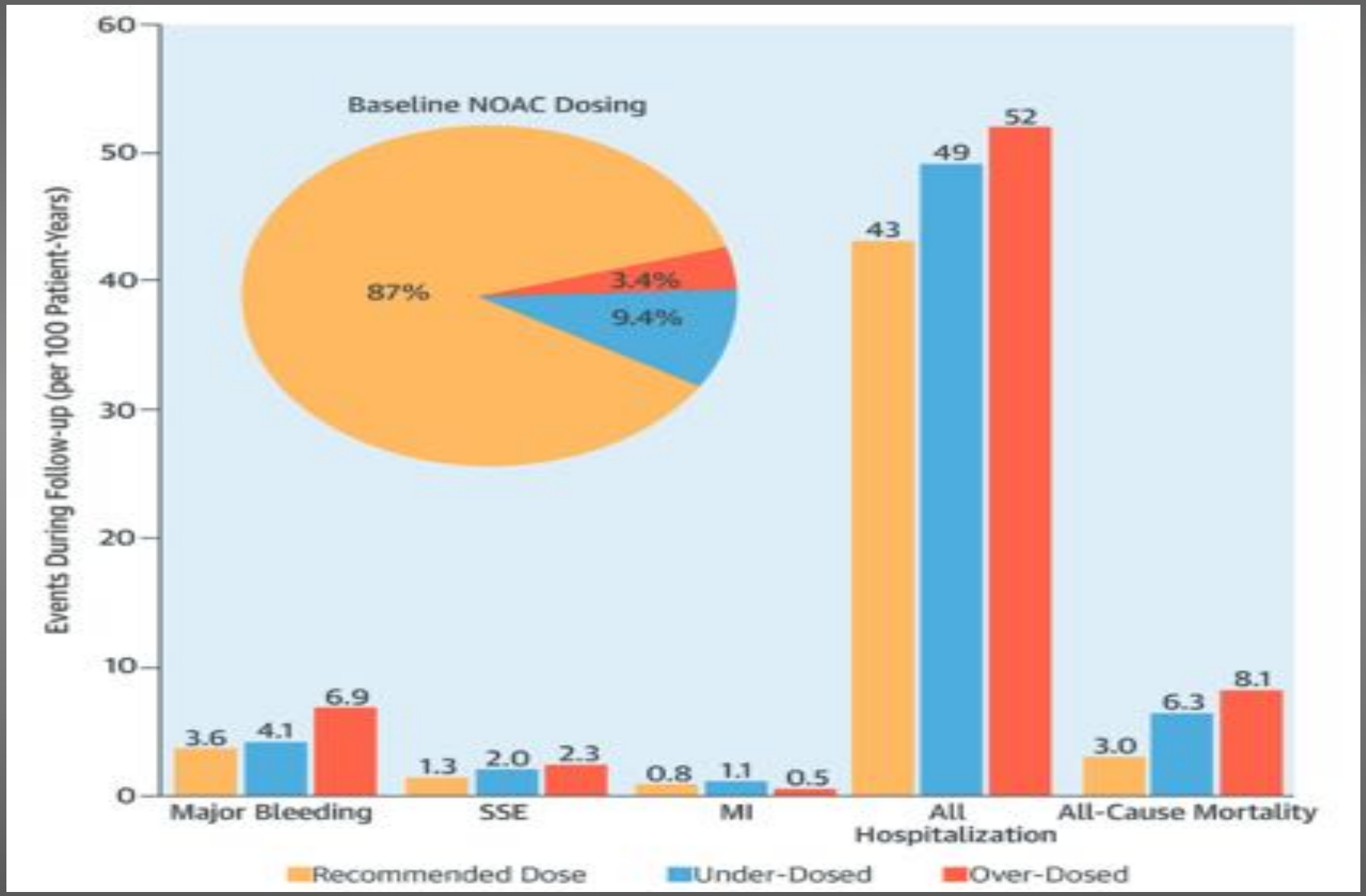
Table 5
Univariate and multivariate analysis of the risk factors for major bleeding

Variables	Univariate	Multivariate	
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	p Value
CrCl <30 (vs. CrCl >50)	2.14 (1.31 to 3.34)	2.08 (1.23 to 3.39)	0.008
30< CrCl <50 (vs. CrCl >50)	0.98 (0.65 to 1.44)	0.98 (0.63 to 1.48)	0.9
OAC prescription	1.33 (0.94 to 1.90)	1.41 (0.99 to 2.03)	0.06
Hypertension, SBP >160mmHg	1.32 (0.41 to 3.14)	1.40 (0.43 to 3.33)	0.5
Abnormal liver function	1.36 (0.22 to 4.27)	1.48 (0.24 to 4.68)	0.6
Prior stroke	1.31 (0.86 to 1.95)	0.87 (0.55 to 1.35)	0.5
History of major bleeding	3.44 (1.89 to 5.77)	3.69 (1.95 to 6.48)	0.0002
Age, >65 years old	1.97 (1.19 to 3.51)	1.82 (1.07 to 3.29)	0.03
Antiplatelet prescription	1.40 (0.98 to 1.98)	1.41 (0.98 to 2.01)	0.07
Alcohol abuse	1.30 (0.87 to 1.90)	1.48 (0.98 to 2.19)	0.06

CI = confidence interval; CrCl = creatinine clearance; OAC = oral anticoagulant; SBP = systolic blood pressure.

Abe M, et al. Am J Cardiol. 2017 ;119(8):1229-1237

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry



Steinberg BA, et al. J Am Coll Cardiol. 2016;68:2597-2604

ACC.17

66th Annual Scientific Session & Expo

EFFECTIVENESS AND SAFETY OF DIRECT ORAL ANTICOAGULANTS COMPARED WITH VITAMIN-K ANTAGONISTS: INITIAL RESULTS FROM A COHORT STUDY IN THE NATIONWIDE FRENCH CLAIMS AND HOSPITALIZATION DATABASE (SNIIRAM)

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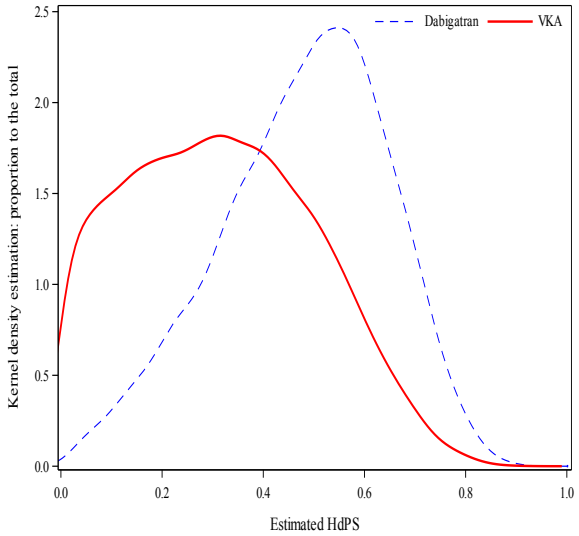
WASHINGTON, DC
FRI • SAT • SUN
MARCH 17 – 19, 2017

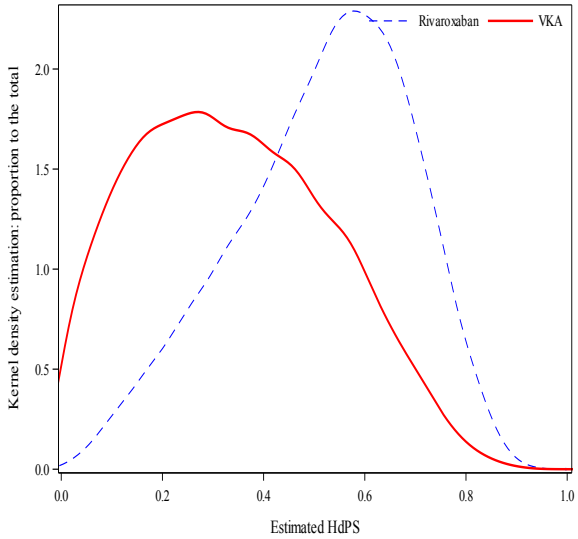
HdPS distribution

Dabigatran versus VKA

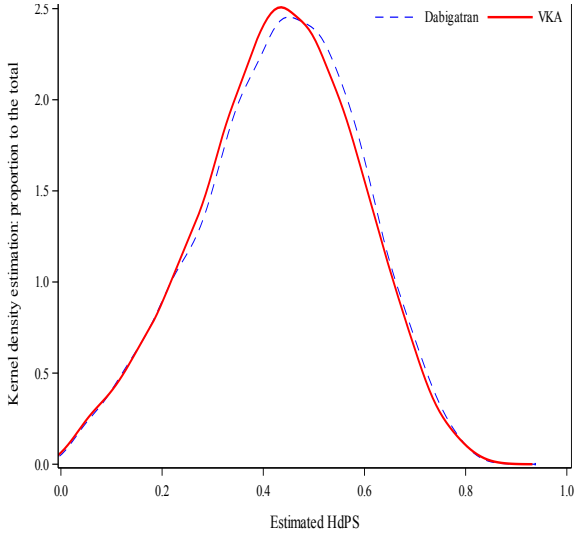
Rivaroxaban versus VKA

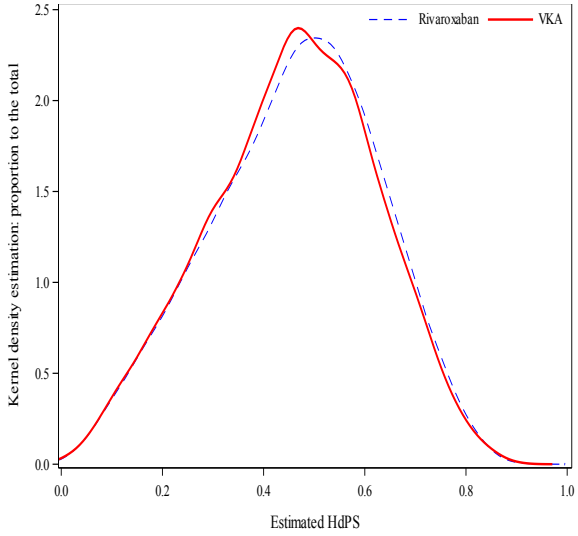
All patients



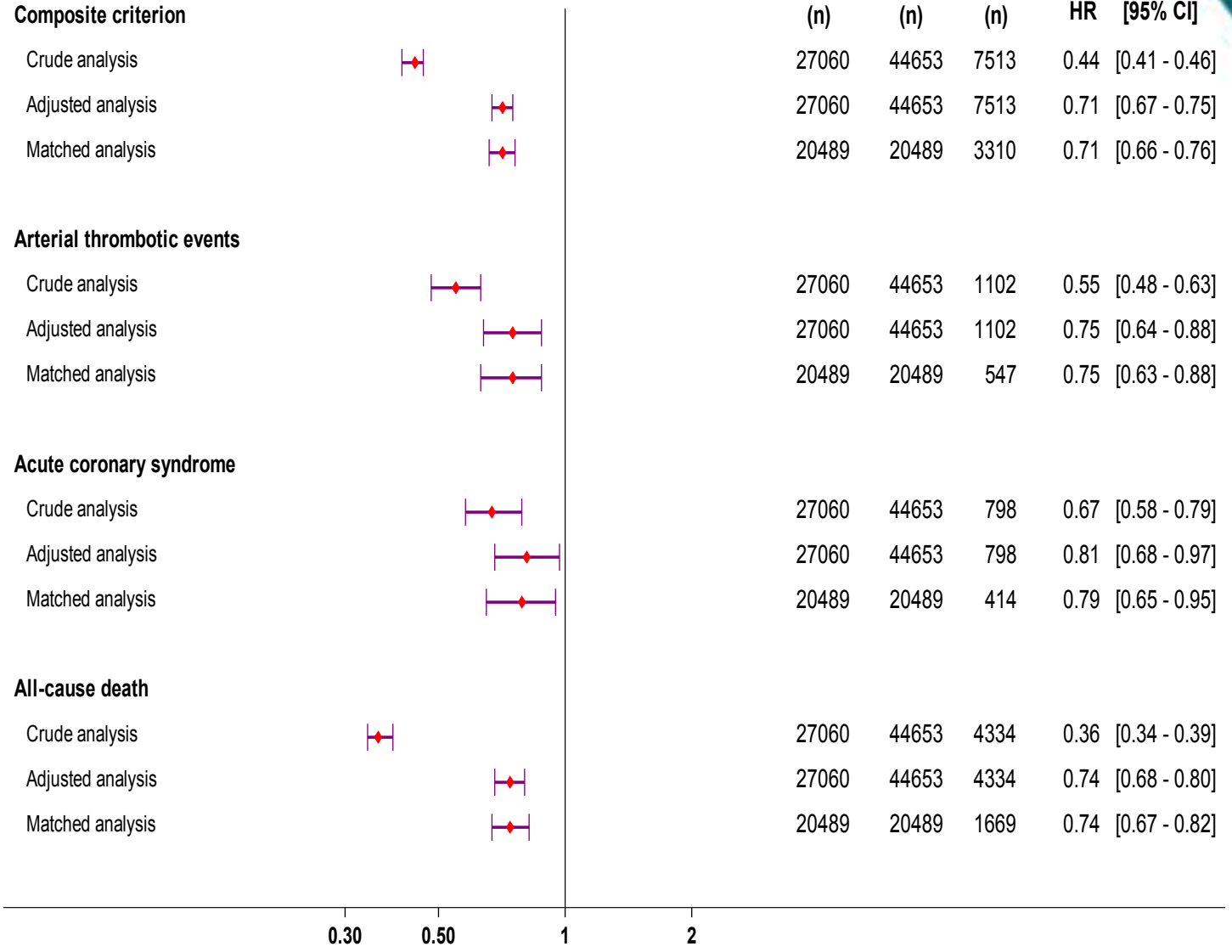


Matched patients





Effectiveness: D versus VKA



	Dabigatran (n)	VKA (n)	Events (n)	HR	[95% CI]
Composite criterion					
Crude analysis	27060	44653	7513	0.44	[0.41 - 0.46]
Adjusted analysis	27060	44653	7513	0.71	[0.67 - 0.75]
Matched analysis	20489	20489	3310	0.71	[0.66 - 0.76]
Arterial thrombotic events					
Crude analysis	27060	44653	1102	0.55	[0.48 - 0.63]
Adjusted analysis	27060	44653	1102	0.75	[0.64 - 0.88]
Matched analysis	20489	20489	547	0.75	[0.63 - 0.88]
Acute coronary syndrome					
Crude analysis	27060	44653	798	0.67	[0.58 - 0.79]
Adjusted analysis	27060	44653	798	0.81	[0.68 - 0.97]
Matched analysis	20489	20489	414	0.79	[0.65 - 0.95]
All-cause death					
Crude analysis	27060	44653	4334	0.36	[0.34 - 0.39]
Adjusted analysis	27060	44653	4334	0.74	[0.68 - 0.80]
Matched analysis	20489	20489	1669	0.74	[0.67 - 0.82]

Safety: R versus VKA