Advances in Cardiac Arrhythmias and Great Innovations in Cardiology - Torino, 27/28 ottobre 2017

Rivaroxaban:

safety and efficacy in comorbidity patients, from the past to the future

Claudio Moretti, MD, PhD
Division of Cardiology
Department of Medical Sciences
University of Turin

THE PAST

Patient Characteristics in Phase III Trials

		ROCKET AF[1] (n=14,264)	ARISTOTLE[2] (n=18,201)	ENGAGE AF[3] (n=21,105)	RE-LY[4,5] (n=18,113)
Mean $CHADS_2$-Score		**3.5**	2.1	2.8	2.1
C	CHF*	**64%**	35%	57%	32%
H	Hypertension	**91%**	87%	94%	79%
A	Age ≥75 years	**43%**	31%	40%	40%
D	Diabetes mellitus	**40%**	25%	36%	23%
S2	Prior stroke or TIA#	**55%**	19%	28%	20%
Moderate renal impairment		**21%**	**15%**	**19%**	**19%**
Specific dose studied prospectively		✓	✗	✗	✗

* LVEF <40%; #Data include patients with systemic embolism

AF Patients studied in ROCKET AF had higher risk of stroke than patients in other phase III trials with novel OACs.

Elderly patients

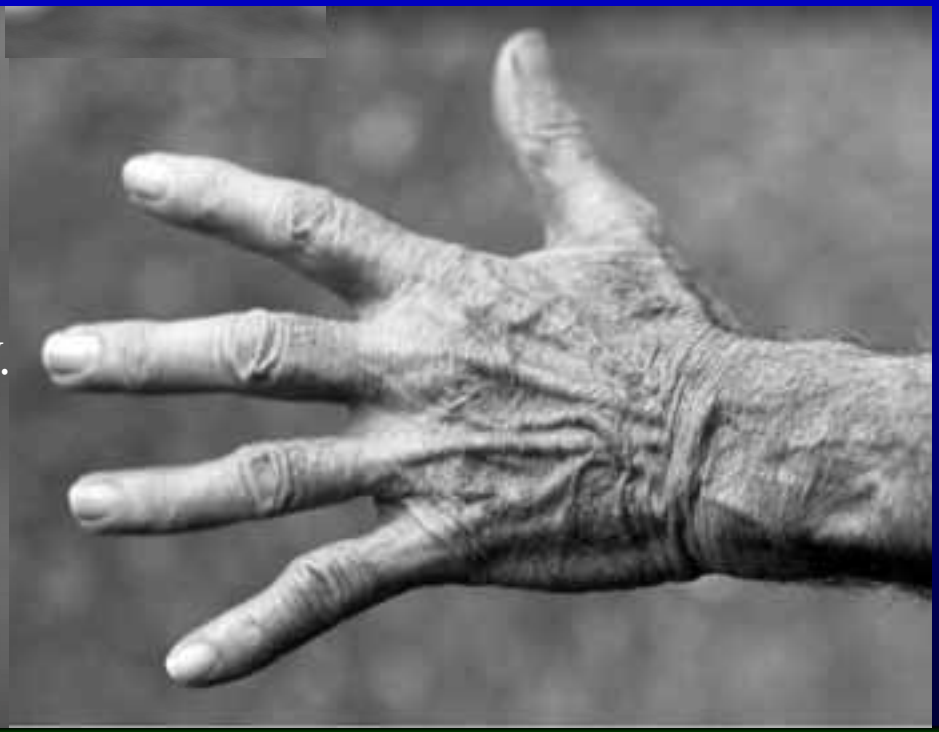
- The prevalence of NVAF increases with age and is a major cause of disability

- <u>STABLE ANTI-COAGULATION IS DIFFICULT:</u>

POLIFARMACY

SENSITIVITY TO W.

COMORBIDITIES

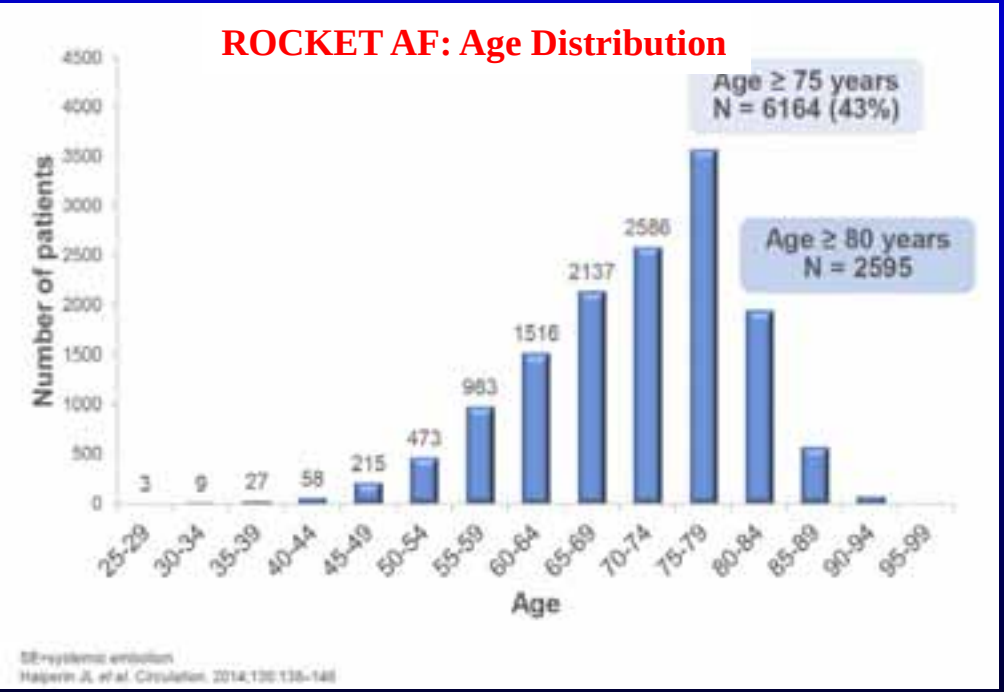


Efficacy and Safety of Rivaroxaban Compared With Warfarin Among Elderly Patients With Nonvalvular Atrial Fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

Jonathan L. Halperin, MD; Graeme J. Hankey, MD; Daniel M. Wojdyla, MS; Jonathan P. Piccini, MD, MHS; Yuliya Lokhnygina, PhD; Manesh R. Patel, MD; Günter Breithardt, MD; Daniel E. Singer, MD; Richard C. Becker, MD; Werner Hacke, MD; John F. Paolini, MD; Christopher C. Nessel, MD; Kenneth W. Mahaffey, MD; Robert M. Califf, MD; Keith A.A. Fox, MB, ChB; on behalf of the ROCKET AF Steering Committee and Investigators*

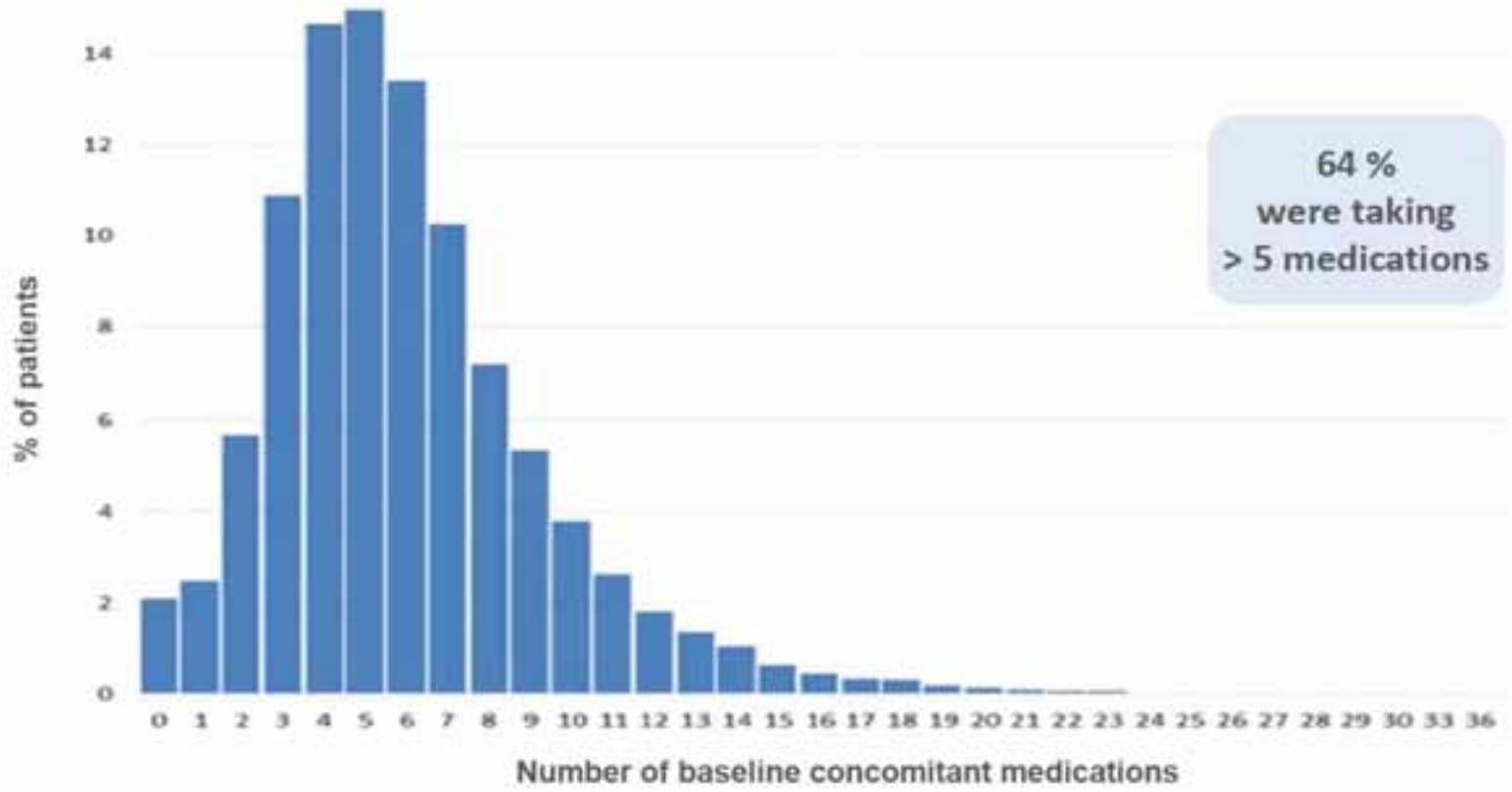
(*Circulation*. 2014;130:138-146.)

ROCKET AF trial provides the largest prosp. experience involving high-risk elderly pts with AF using OAC



ROCKET AF: Polifarmacy

Objective: to examine the prevalence of polypharmacy and the impact of concomitant medications on ischemic and hemorrhagic events.



Piccini JP *et al. Circulation*. 2016;133:352-360

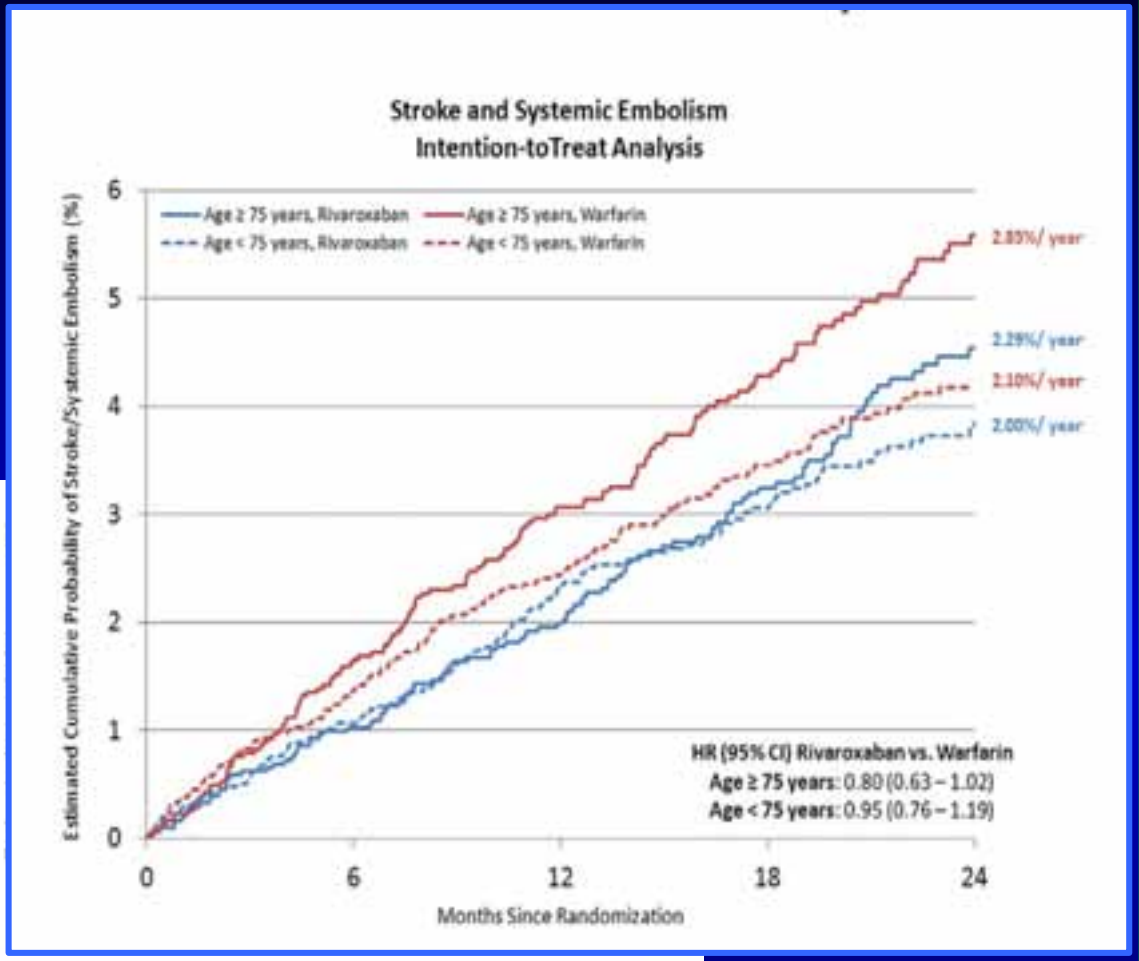
INTERACTION between NOACs and CV drugs

	Mechanism	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Amiodarone	Limited competition with P-gp	+ 12-60%	"Minor" effects Caution if GFR<50 ml/min	No data	+40%
Digoxin	Competition with P-gp	No effects	No effects	No data	No data
Diltiazem	Competition with P-gp Slight CYP3A4 inhibition	No effects	"Minor" effects Caution if GFR 15-50 ml/min	+ 40%	No data
Dronedarone	Competition with P-gp CYP3A4 inhibition	+70-100% **USE: 75 mg twice daily if GFR 30-50 ml/min**	No data: caution	No data: caution	+85% Reduce dose by 50%
Quinidine	Competition with P-gp	+53%	No data: caution	No data	+77%
Verapamil	Competition with P-gp Slight CYP3A4 inhibition	+ 12-180% Reduce dose and take simultaneously	"Minor" effects Caution if GFR 15-50 ml/min	No data	+ 53%
Atorvastatin	Competition with P-gp CYP3A4 inhibition	+18%. No effects	No effects	No data	No effects

ELDERLY in ROCKET -AF

Results

- 6,229 patients (44%) were aged ≥75 years at enrolment
- Higher rates of stroke/SE and bleeding in elderly patients than in younger patients
- Elderly patients had similar rates of efficacy and safety outcomes, whether they were receiving rivaroxaban or warfarin



	Age ≥75 years (%/year)		Age <75 years (%/year)		*p*-value (int.)
	Riva.	Warf.	Riva.	Warf.	
Major bleeding	4.86	4.40	2.69	2.79	0.34
ICH	0.66	0.83	0.37	0.68	0.27

Halperin JL et al. Circulation 2014;130(2):138-148

ROCKET AF: Elderly sub-analysis RESULTS

- RIVAROXABAN AS EFFECTIVE AS WARFARIN
- MORE CLINICALLY RELEVANT NONMAJOR BLEEDING
- LESS RISK OF INTRACRANIAL BLEEDING

NET CLINICAL BENEFIT

Avoidance of ischemic stroke, severe bleeding (including ICH), and all cause mortality.

THE BENEFIT OF RIVAROXABAN IS MORE PRONOUNCED IN ELEDERLY PTS AS A RESULT OF PREVENTION OF NON HEMORRHAGIC STROKE

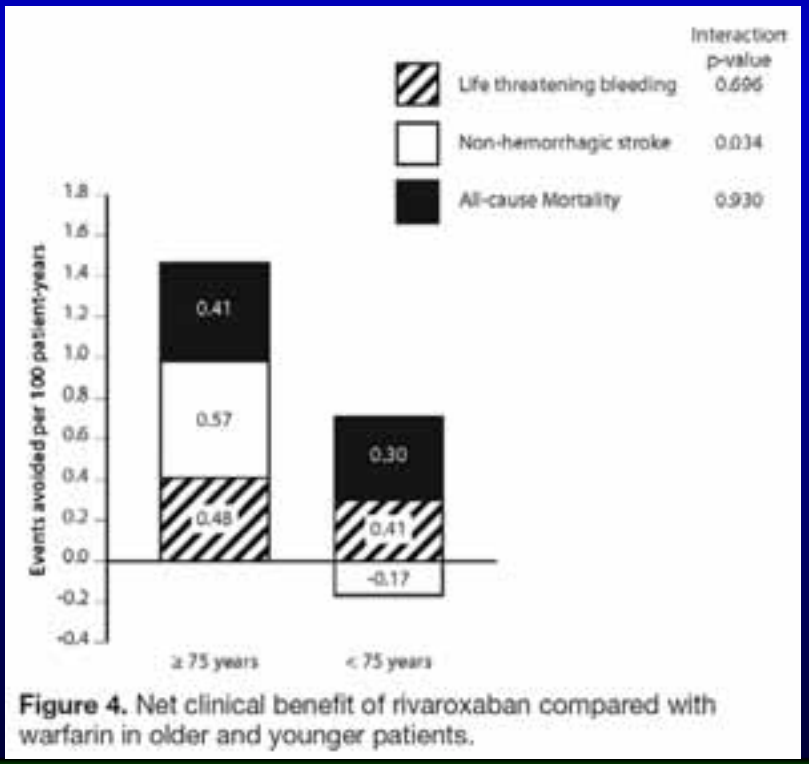


Figure 4. Net clinical benefit of rivaroxaban compared with warfarin in older and younger patients.

Efficacy and Safety of Rivaroxaban in Patients With Heart Failure and Nonvalvular Atrial Fibrillation

Insights From ROCKET AF

Sean van Diepen, MD, MSc; Anne S. Hellkamp, MS; Manesh R. Patel, MD; Richard C. Becker, MD; Günter Breithardt, MD; Werner Hacke, MD; Jonathan L. Halperin, MD; Graeme J. Hankey, MD; Christopher C. Nessel, MD; Daniel E. Singer, MD; Scott D. Berkowitz, MD; Robert M. Califf, MD; Keith A.A. Fox, MD; Kenneth W. Mahaffey, MD

(*Circ Heart Fail.* 2013;6:740-747.)

- AF occurs in 12% to 41% of pts with HF
- AF prevalence correlates with HF severity
- HF is a recognized risk for reduced TTR
- Pts receiving warfarin may be predisposed to reduced efficacy and increased bleeding.

ROCKET AF: Heart failure

HF = 9.033 (64%)

Mean age = 72 years

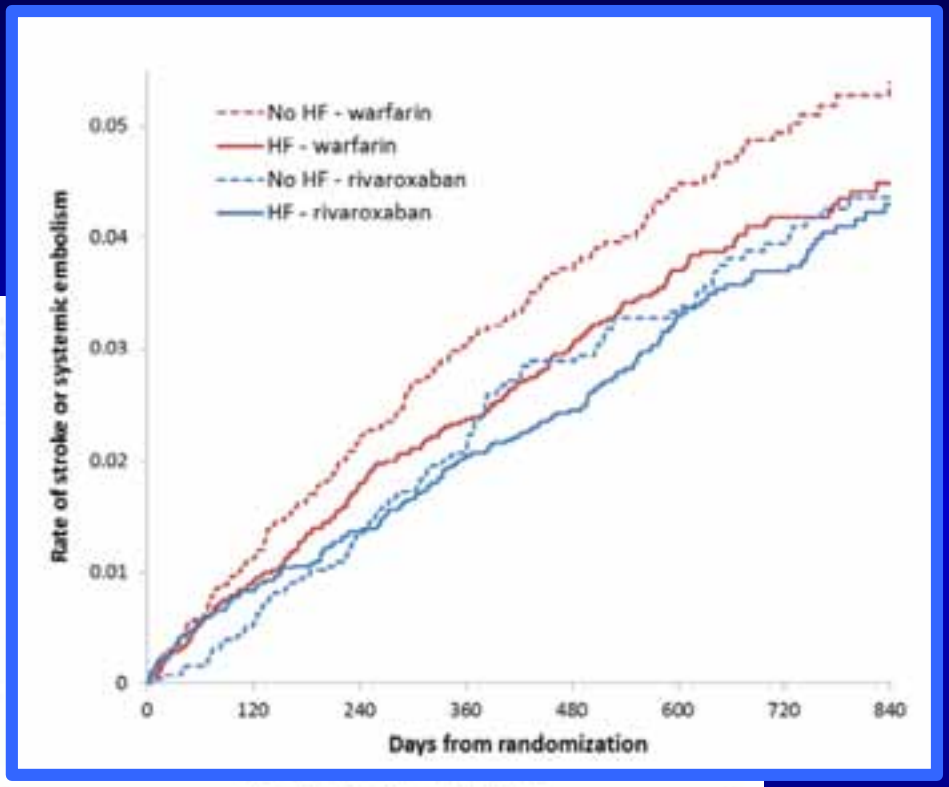
Mean $CHADS_2$-score = 3,7

$CHADS_2$-score ≥ 3 = 93%

CrCl 30-50 ml/min = 35%

Van Diepen S. *et al. Circ Heart Fail* 2013;6:740-747

ROCKET AF: Rivaroxaban in AF Patients With Heart Failure



Results

- 9,033 (63.7%) patients had HF or reduced LVEF
- Similar rates of stroke/SE in AF patients with or without HF
- Similar efficacy and safety of rivaroxaban compared with warfarin in AF patients with and without HF; results consistent with overall trial results

Conclusion

- Results support use of rivaroxaban as an effective alternative to warfarin for stroke prevention in patients with AF and HF

	With HF (%/year)		Without HF (%/year)		*p*-value (int.)
	Riva.	Warf.	Riva.	Warf.	
Major/NMCR bleeding	14.22	14.02	16.12	15.35	0.99
Haemorrhagic stroke	0.16	0.43	0.43	0.47	0.067
Intracranial haemorrhage	0.40	0.65	0.64	0.89	0.71

Van Diepen S et al. Circ Heart Fail. 2013;6(4):740-747

ROCKET AF: Moderate renal impairment

CrCl 30-49 ml/min = 2.950 (20,7%)

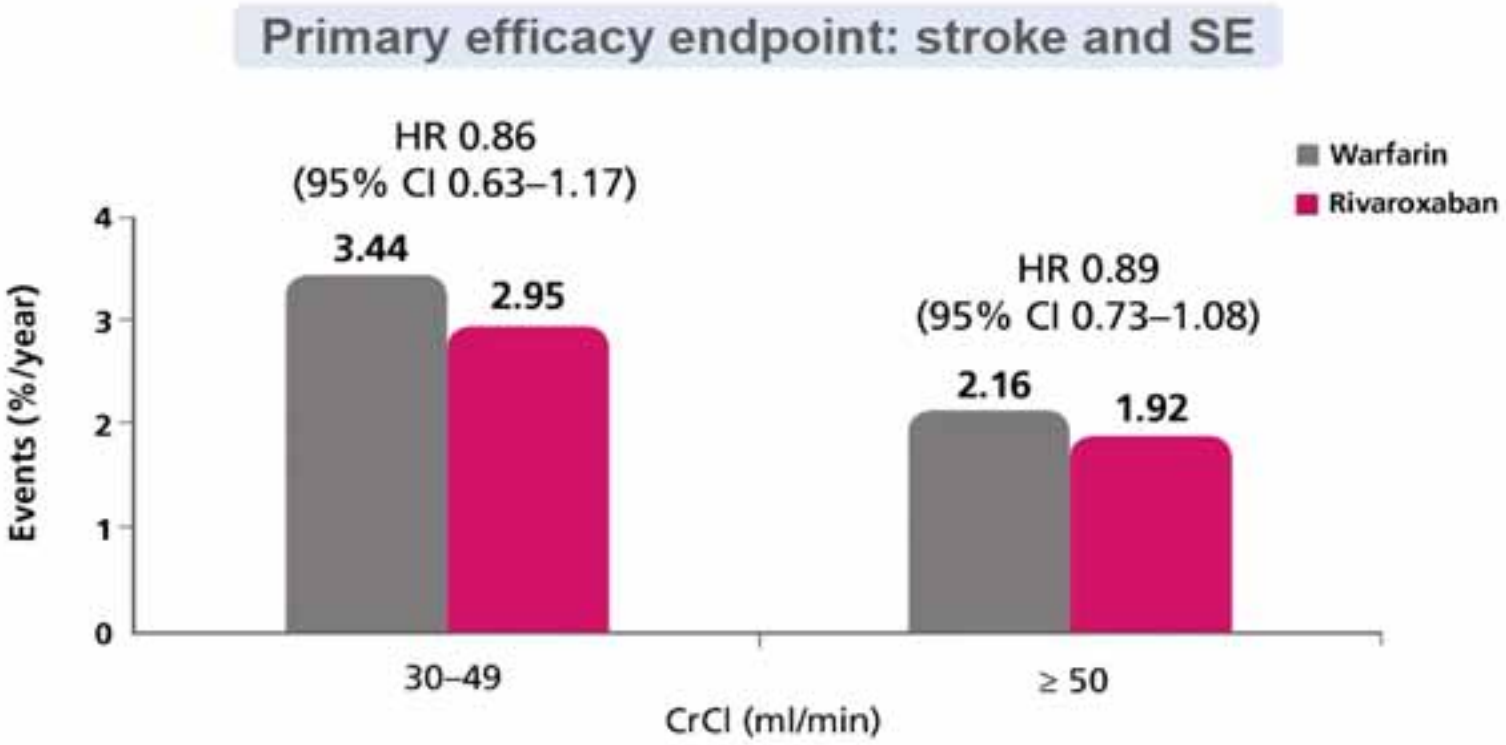
Mean age = 79 years

Mean $CHADS_2$-score = 3,7

$CHADS_2$-score ≥ 3 = 91%

Fox KA et al. Eur Heart J. 2011;32(19):2387–2394.

ROCKET AF: Moderate renal impairment - efficacy

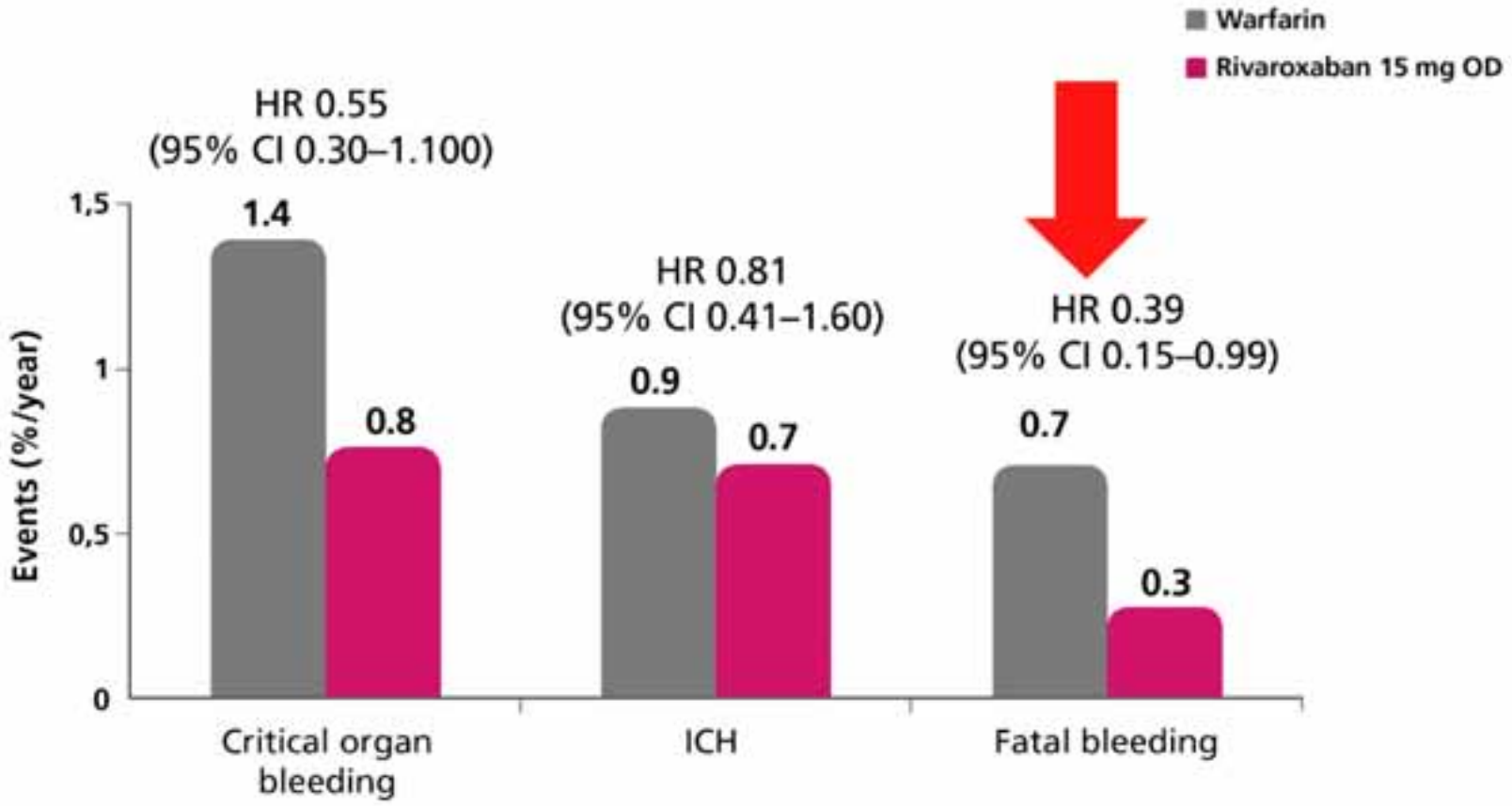


Consistent efficacy of rivaroxaban vs. warfarin in NVAF patients with moderate renal impairment

Intent-to-treat population

Fox KA et al. Eur Heart J. 2011;32(19):2387–2394.

ROCKET AF: Moderate renal impairment - safety



Safety on-treatment population

Fox KA et al. Eur Heart J. 2011;32(19):2387–2394.

Phase III Trials with NOACs: moderate renal impairment

	ROCKET AF[1] (n=14,264)	ARISTOTLE[2-4] (n=18,201)	ENGAGE AF[5,6] (n=21,105)	RE-LY[7,8] (n=18,113)
Specific renal dose studied to support safety	✓	✗	✗	✗
Proportion of patients with moderate renal impairment	21%*	15%†	19%‡	20%§
Number of patients studied with low dose	15 mg OD: 1474	2.5 mg BD: 428	30 mg BD#: 1784	110 mg BD: 6015
Number of patients studied with low dose with moderate renal impairment	1474	149¶	1379#	1196
Number of patients studied with low dose with moderate renal impairment – as a proportion of all patients studied with the NOAC	20.7%	1.6%	19.6%#	9.9%

Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: The Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial)

Sameer Bansilal, MD,[a] Zachary Bloomgarden, MD,[a] Jonathan L. Halperin, MD,[a] Anne S. Hellkamp, MS,[b] Yuliya Lokhnygina, PhD,[b] Manesh R. Patel, MD,[b] Richard C. Becker, MD,[c] Günter Breithardt, MD,[d] Werner Hacke, MD,[e] Graeme J. Hankey, MD,[f] Christopher C. Nessel, MD,[g] Daniel E. Singer, MD,[h] Scott D. Berkowitz, MD,[i]

- DM associated with a 35% increase in the incidence of AF (ARIC Study)
- Greater risk in pts with elevated levels of glycated hemoglobin
- DM pts with AF had an 8-fold greater risk of stroke (UKPDS)

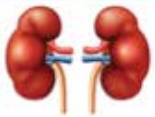
ROCKET AF
Diabetes Mellitus (MD) – patients characteristics

MD = 5.695 (40%)

Mean age = 71 years

Mean $CHADS_2$-score = 3,7

$CHADS_2$-score 5-6 = 23%



CrCl 30-50 ml/min = 32%

Bansilal S *et al. Am Heat J* 2015;170:675-682

ROCKET AF: Rivaroxaban in AF Patients With Diabetes Mellitus (DM)

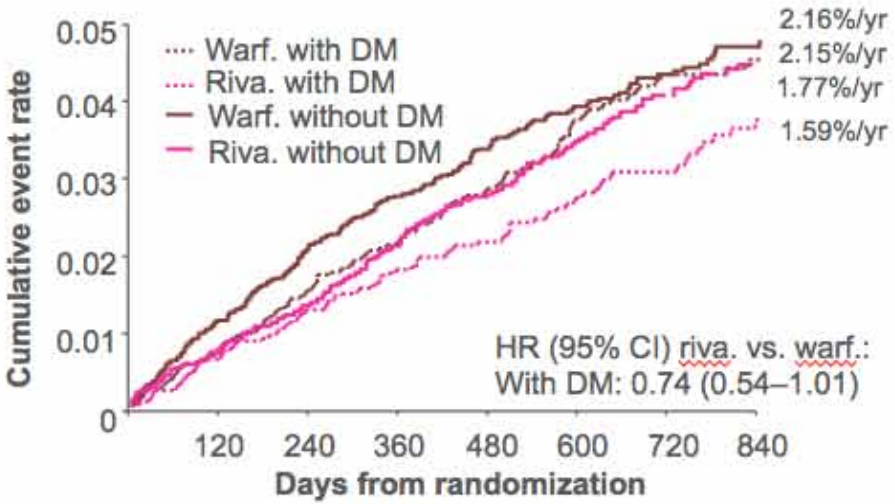
Results

- 5,635 patients (39.9%) had DM
- Similar rates of efficacy and safety outcomes for patients with and without DM

Conclusion

- Results support the use of rivaroxaban as an effective alternative to warfarin for stroke prevention in patients with AF, with or without DM

Primary endpoint: Stroke/SE



	With DM (%/year)		Without DM (%/year)		*p*-value (int.)
	Riva.	Warf.	Riva.	Warf.	
Major/NMCR bleeding	14.9	15.4	15.0	14.0	0.16
Major bleeding	3.8	3.9	3.5	3.2	0.42

Bansilal S *et al. Am Heat J* 2015;170:675-682

ROCKET AF
Prior Stroke or TIA– patients characteristics

Prior Stroke or TIA = 6.796 (55%)

Mean age = 75 years

Mean $CHADS_2$-score = 3

Hankey GJ et al. Lancet Neurol. 2012;11(4):315-322

ROCKET AF: Rivaroxaban in AF Patients With Prior Stroke or TIA

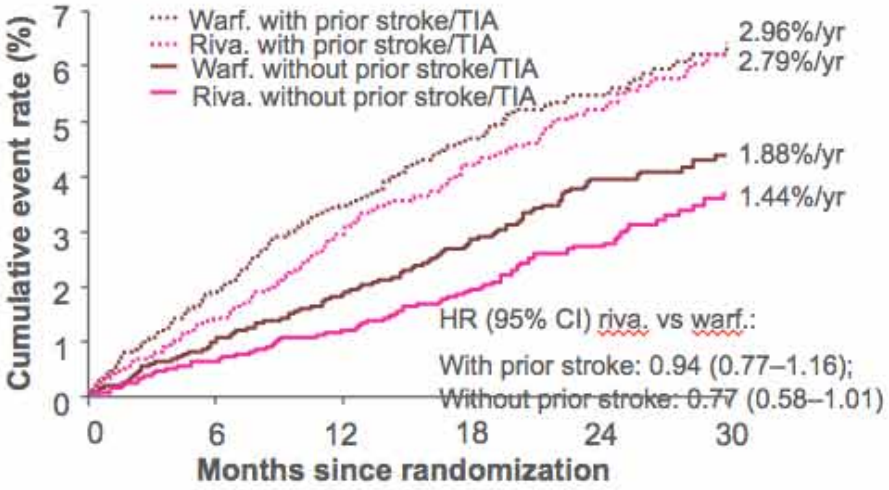
Results

- 7,468 patients (52%) had prior stroke/TIA
- Prior stroke/TIA was associated with higher stroke rates and lower major bleeding rates
- Efficacy and safety results were consistent with those in patients without prior stroke/TIA and with overall ROCKET AF population

Conclusion

- Results support the use of rivaroxaban as an effective alternative to warfarin for both primary and secondary stroke prevention in AF

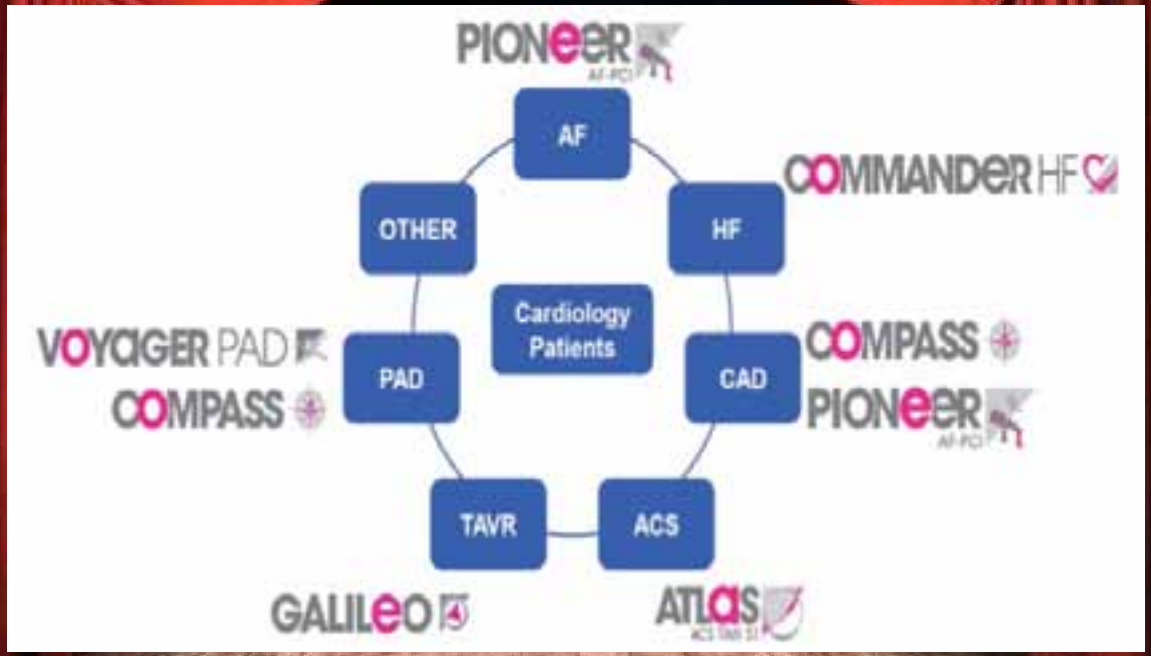
Primary endpoint: Stroke/SE



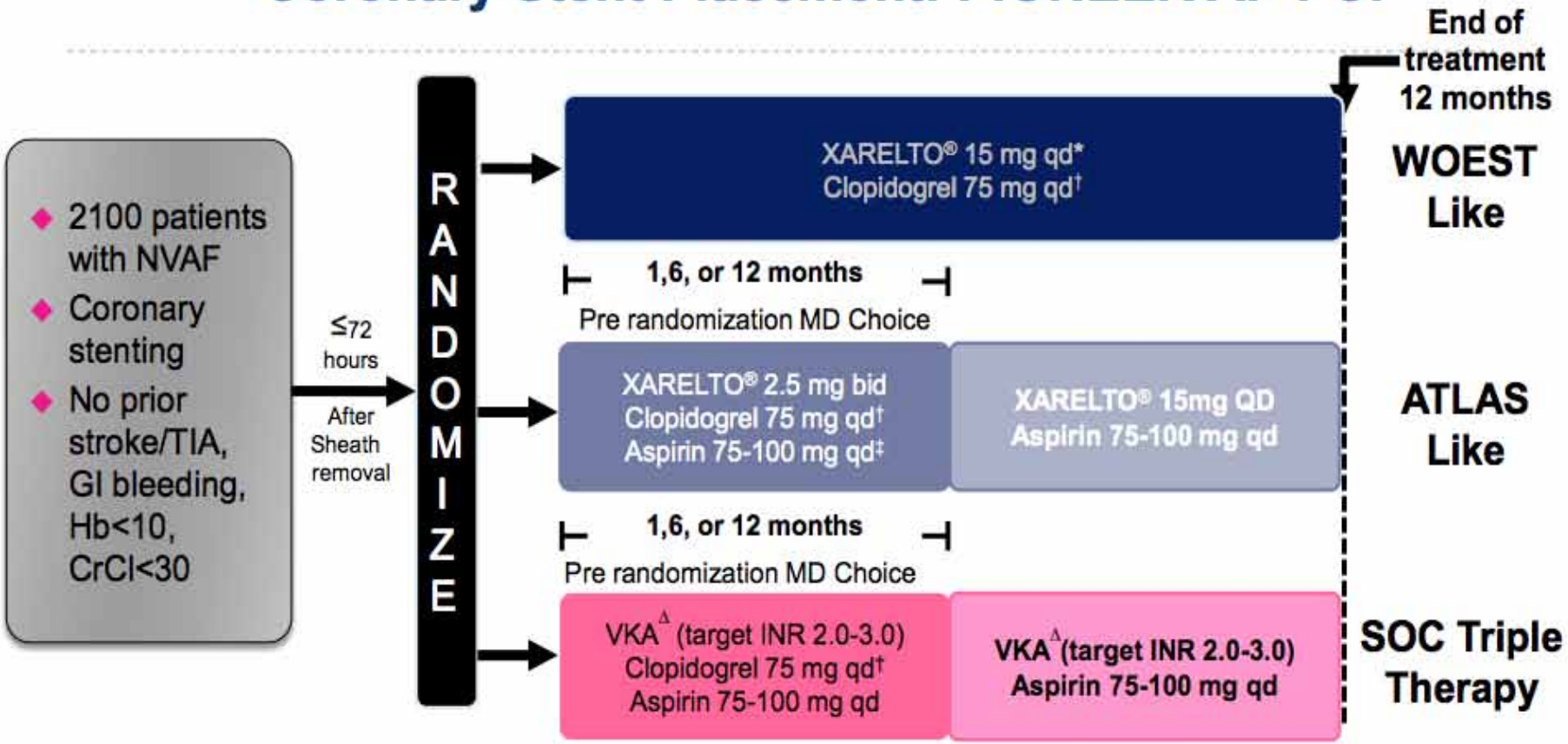
	With prior stroke/TIA (%/year)		Without prior stroke/TIA (%/year)		*p*-value (int.)
	Riva.	Warf.	Riva.	Warf.	
Major/NMCR bleeding	13.31	13.97	16.69	15.19	0.08
Major bleeding	3.13	3.22	4.10	3.69	0.36

Hankey GJ et al. Lancet Neurol. 2012;11(4):315-322

THE FUTURE


PIONEER AF-PCI
AF
COMMANDER HF
OTHER
HF
Cardiology Patients
VOYAGER PAD
COMPASS
PAD
CAD
COMPASS
PIONEER AF-PCI
TAVR
ACS
GALILEO
ATLAS

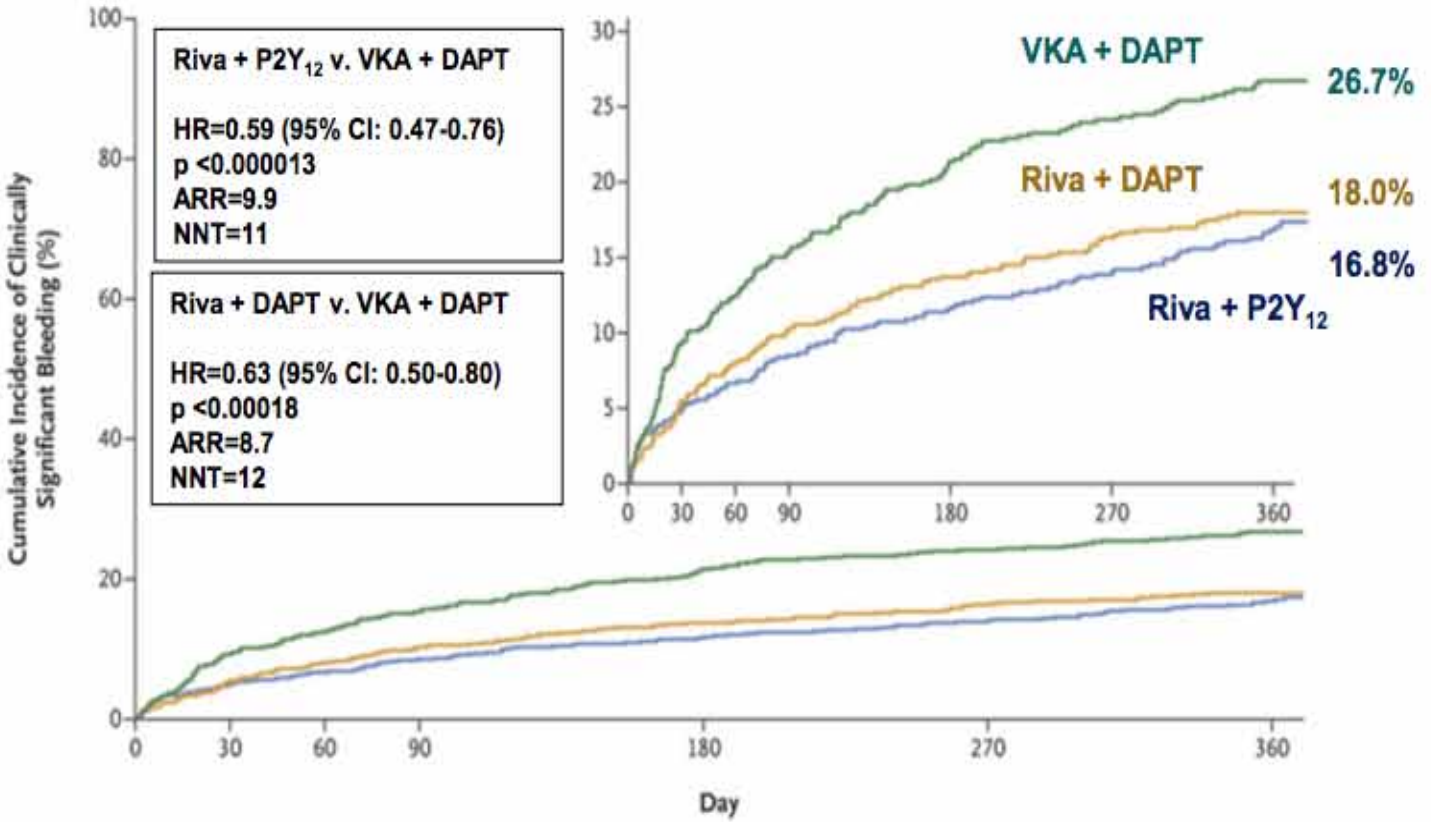
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

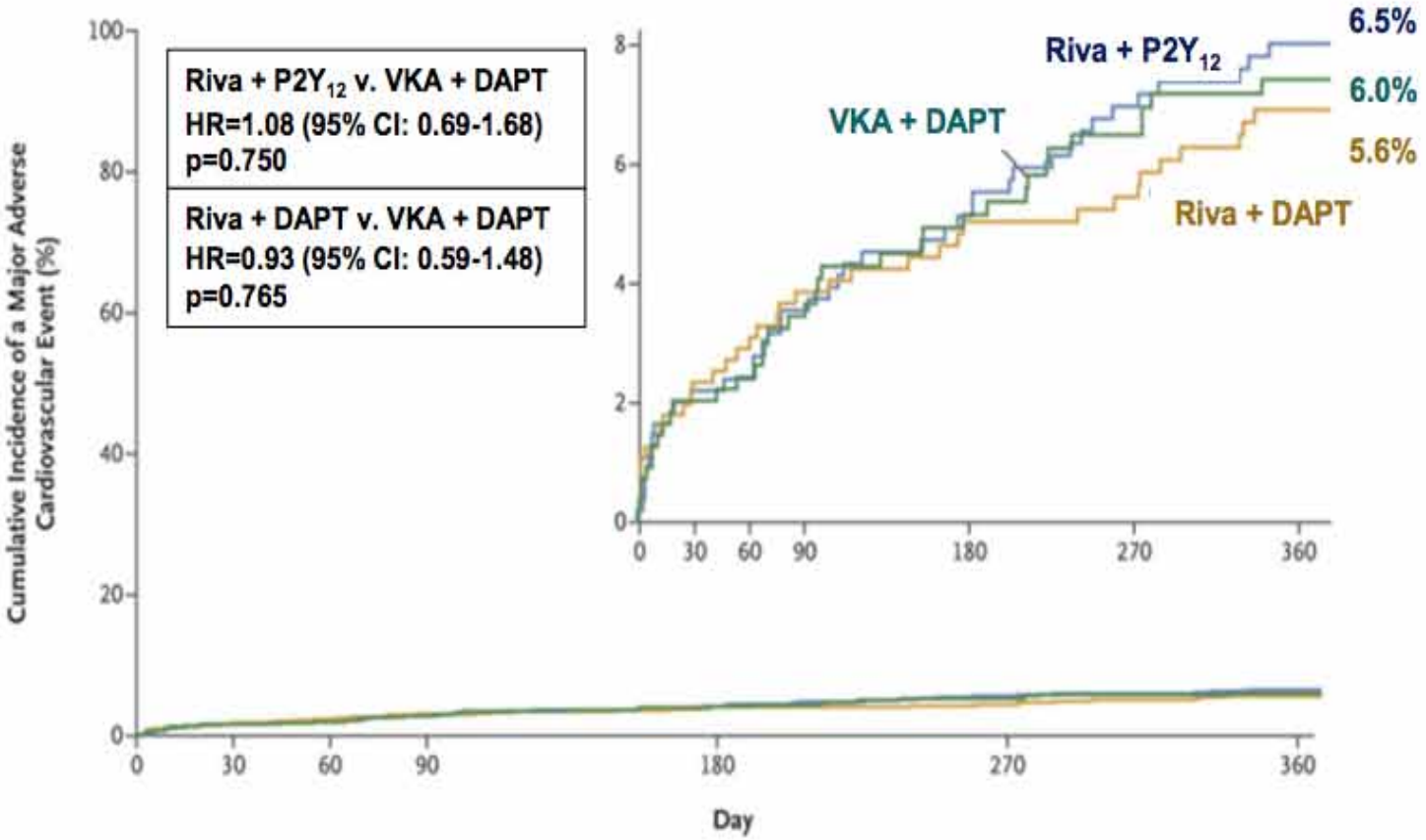
*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75–100 mg/d). Δ Open label VKA

Rivaroxaban plus DAPT or $P2Y_{12}$ reduces clinically relevant bleeding compared with standard therapy



No. at Risk							
Group 1	696	628	606	585	543	510	383
Group 2	706	636	600	579	543	509	409
Group 3	697	593	555	521	461	426	329

Similar incidence of MACE with rivaroxaban compared with standard therapy



No. at Risk							
Group 1	694	648	633	621	590	562	430
Group 2	704	662	640	628	596	570	457
Group 3	695	635	607	579	543	514	408

PIONEER AF-PCI

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Iasus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

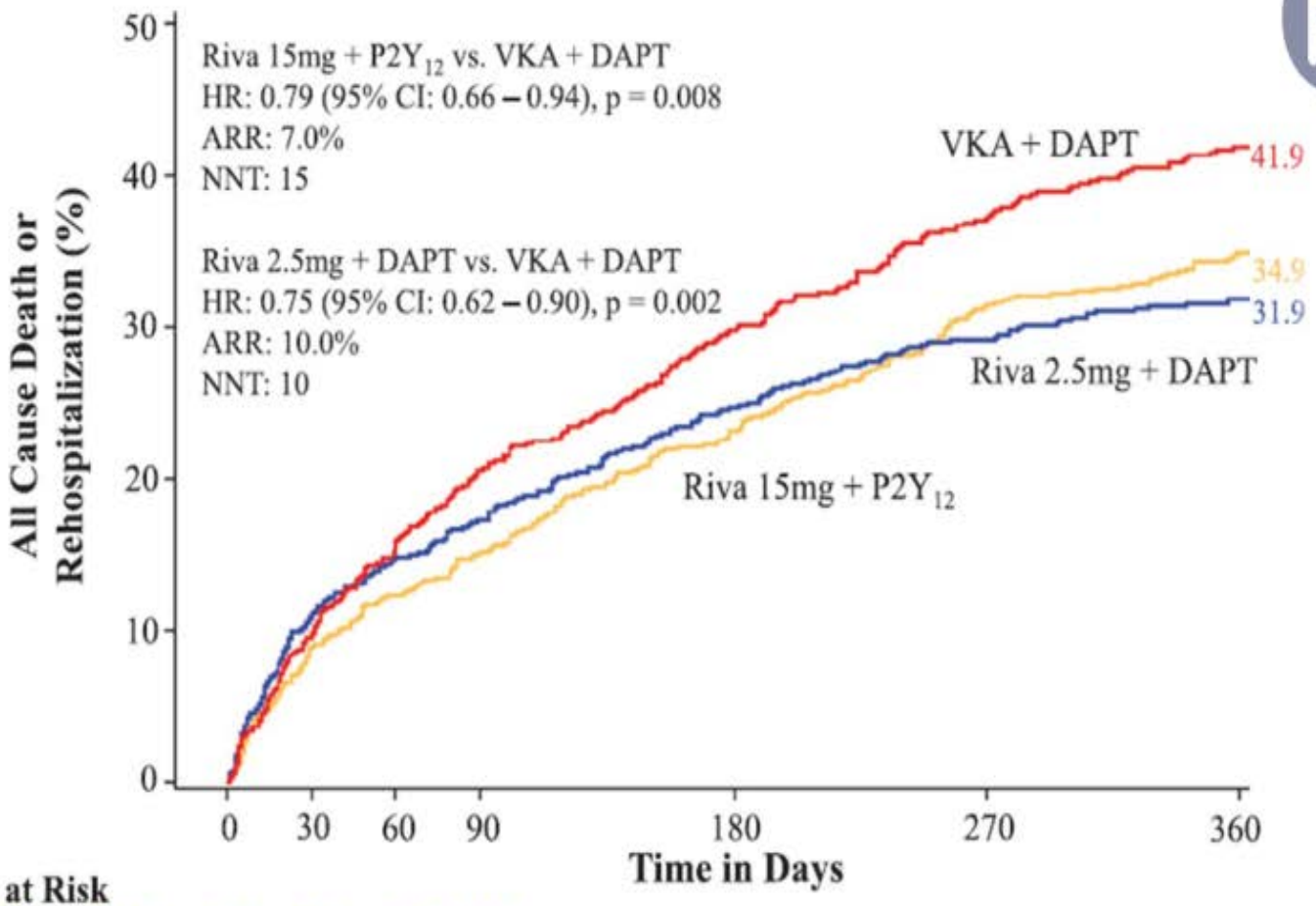
- **DAPT duration** was:
  - 1 month in 16%,
  - 6 months in 35%,
  - **and 12 months in 49%.**

- **Clopidogrel** was the $P2Y_{12}$ inhibitor used **in 95%** of patients, with ticagrelor (Brilique; AstraZeneca) and prasugrel (Efient; Daiichi Sankyo) used in the rest.
- The **time in therapeutic range** for warfarin-treated patients was 65%.

PIONEER AF-PCI

Recurrent hospitalisation or death

POST HOC



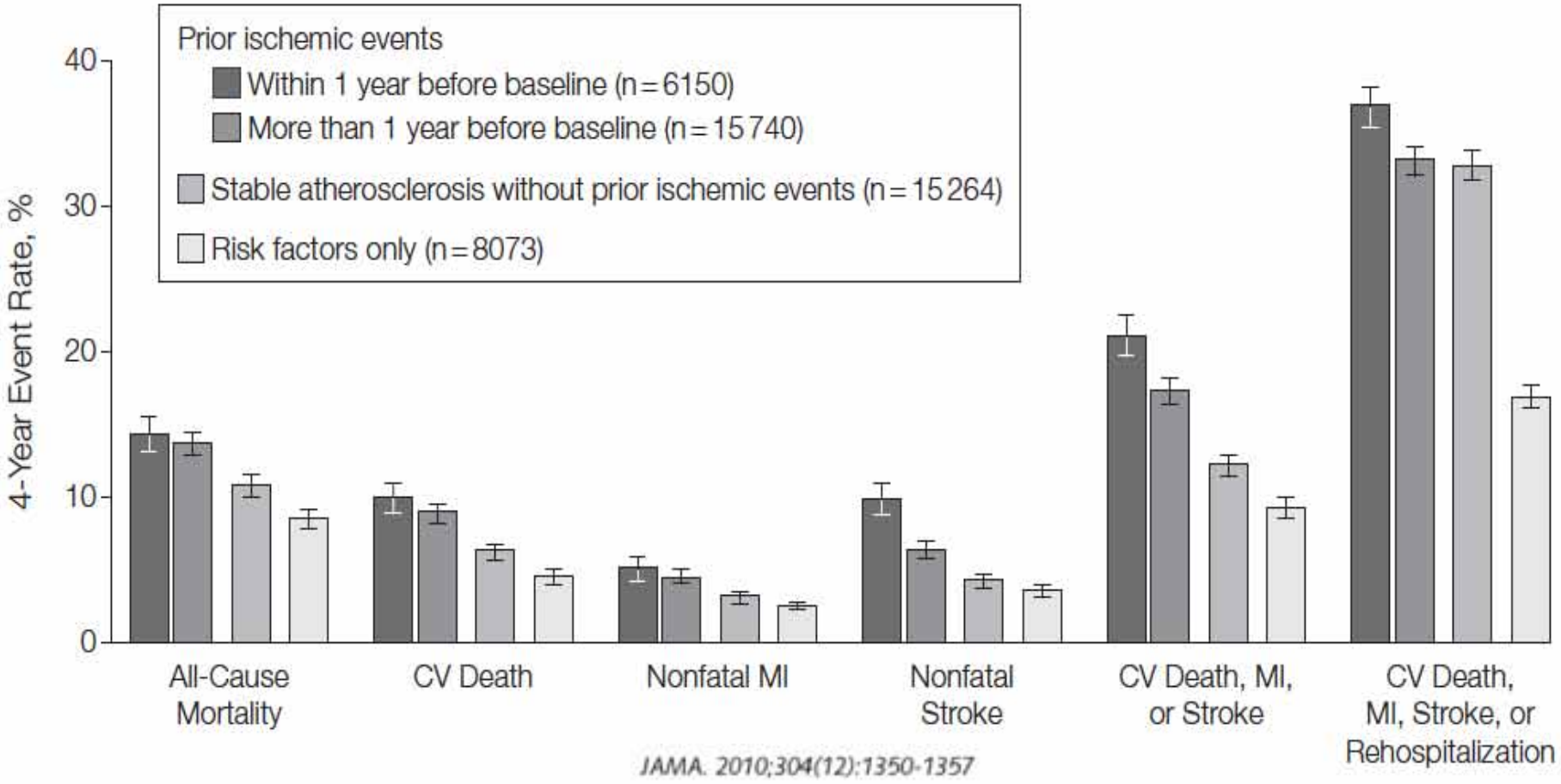
No. at Risk

Riva 15mg + $P2Y_{12}$	696	609	582	559	496	437	322
Riva 2.5mg + DAPT	706	607	570	548	493	454	367
VKA + DAPT	697	592	540	490	422	369	272

IS THERE A NEED FOR MORE DATA AFTER PIONEER ?

- DAPT DURATION IN THE WARFARIN ARM WAS STILL 12 MONTHS IN 49% OF PATIENTS
- LACK OF A WOEST-LIKE WARFARIN ARM
- NO FORMAL TESTING OF THE NON-INFERIORITY OF THE RIVAROXABAN-BASED REGIMENS

Comparative Determinants of 4-Year CV Event Rates In Stable Outpatients at Risk or With Atherothrombosis REACH REGISTRY

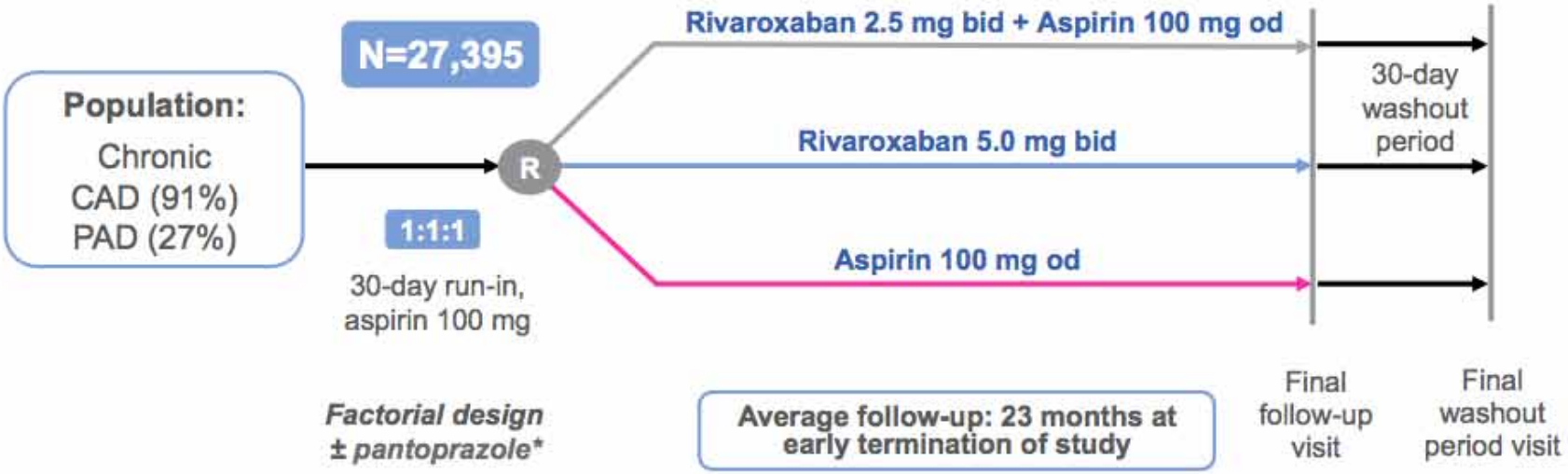


JAMA. 2010;304(12):1350-1357

Approval Number: L.IT.MA.09.2017.2889

A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

COMPASS

COMPASS Baseline Characteristics

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
Age — yr	68.3±7.9	68.2±7.9	68.2±8.0
Female sex — no. (%)	2059 (22.5)	1972 (21.6)	1989 (21.8)
Body-mass index†	28.3±4.8	28.3±4.6	28.4±4.7
Blood pressure — mm Hg			
Systolic	136±17	136±18	136±18
Diastolic	77±10	78±10	78±10
Cholesterol — mmol/liter	4.2±1.1	4.2±1.1	4.2±1.1
Tobacco use — no. (%)	1944 (21.2)	1951 (21.4)	1972 (21.6)
Hypertension — no. (%)	6907 (75.5)	6848 (75.1)	6877 (75.4)
Diabetes — no. (%)	3448 (37.7)	3419 (37.5)	3474 (38.1)
Previous stroke — no. (%)	351 (3.8)	346 (3.8)	335 (3.7)
Previous myocardial infarction — no. (%)	5654 (61.8)	5653 (62.0)	5721 (62.7)
Heart failure — no. (%)	1963 (21.4)	1960 (21.5)	1979 (21.7)
Coronary artery disease — no. (%)‡	8313 (90.8)	8250 (90.5)	8261 (90.5)
Peripheral arterial disease — no. (%)§	2492 (27.2)	2474 (27.1)	2504 (27.4)
Estimated GFR — no. (%)¶			
<30 ml/min	77 (0.8)	80 (0.9)	86 (0.9)
30 to <60 ml/min	1977 (21.6)	2028 (22.2)	2028 (22.2)
≥60 ml/min	7094 (77.5)	7005 (76.8)	7012 (76.8)

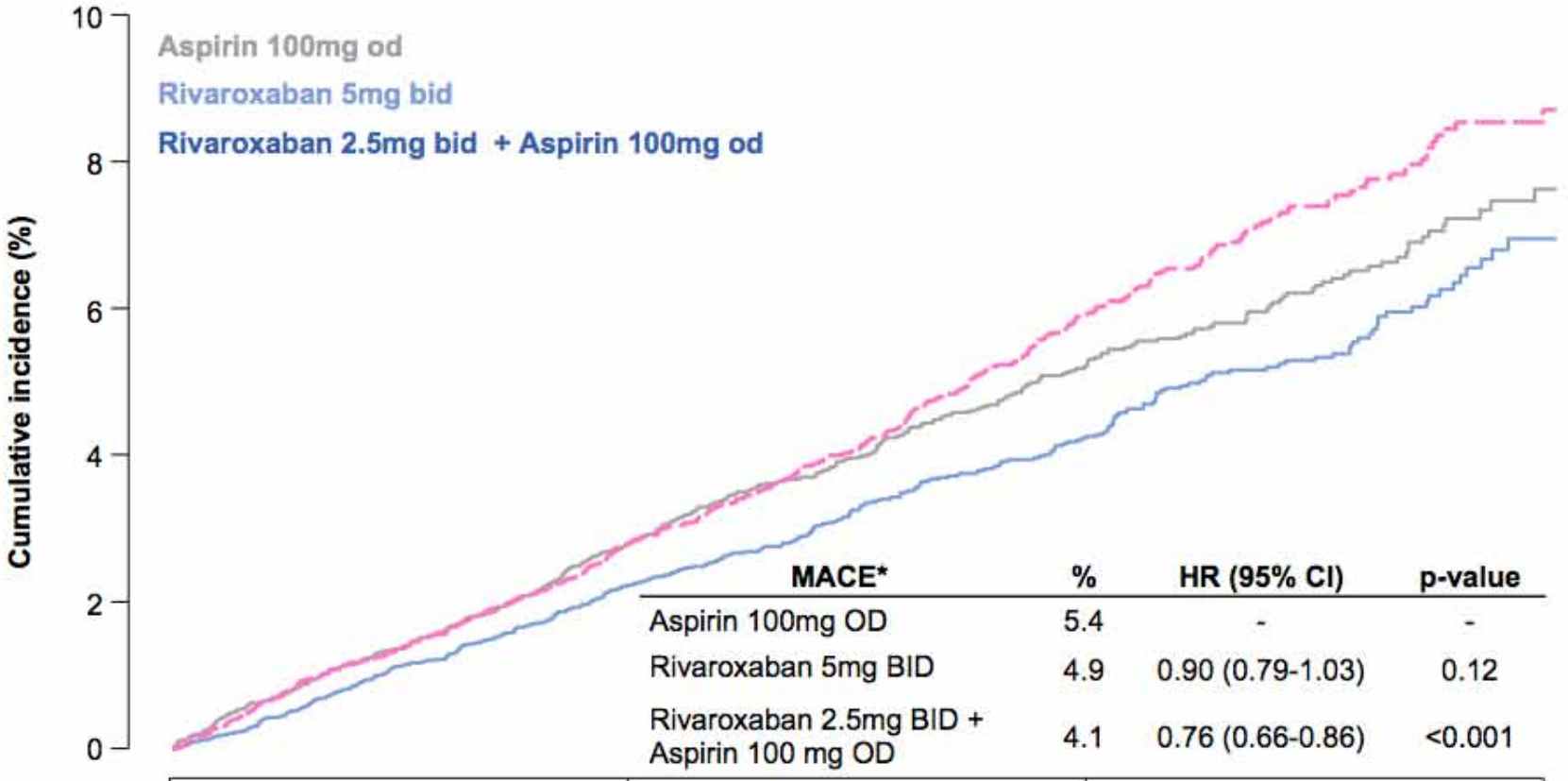
COMPASS Efficacy Outcomes

Table 2. Efficacy Outcomes.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66–0.86)	<0.001	0.90 (0.79–1.03)	0.12
Secondary outcomes‡							
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	397 (4.4)	450 (4.9)	0.72 (0.63–0.83)	<0.001	0.88 (0.77–1.01)	0.06
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	453 (5.0)	516 (5.7)	0.74 (0.65–0.85)	<0.001	0.88 (0.77–0.99)	0.04
Death from any cause	313 (3.4)	366 (4.0)	378 (4.1)	0.82 (0.71–0.96)	0.01	0.97 (0.84–1.12)	0.67
Other outcomes§							
CV death	160 (1.7)	195 (2.1)	203 (2.2)	0.78 (0.64–0.96)	0.02	0.96 (0.79–1.17)	0.69
Non-CV death	153 (1.7)	171 (1.9)	175 (1.9)	0.87 (0.70–1.08)	0.20	0.98 (0.79–1.21)	0.84
Death from CHD	86 (0.9)	128 (1.4)	117 (1.3)	0.73 (0.55–0.96)	0.03	1.09 (0.85–1.41)	0.48
Stroke¶	83 (0.9)	117 (1.3)	142 (1.6)	0.58 (0.44–0.76)	<0.001	0.82 (0.65–1.05)	0.12
Ischemic or uncertain type	68 (0.7)	91 (1.0)	132 (1.4)	0.51 (0.38–0.68)	<0.001	0.69 (0.53–0.90)	0.006
Hemorrhagic	15 (0.2)	27 (0.3)	10 (0.1)	1.49 (0.67–3.31)	0.33	2.70 (1.31–5.58)	0.005
Myocardial infarction	178 (1.9)	182 (2.0)	205 (2.2)	0.86 (0.70–1.05)	0.14	0.89 (0.73–1.08)	0.24
Heart failure	197 (2.2)	191 (2.1)	192 (2.1)	1.02 (0.84–1.24)	0.84	0.99 (0.81–1.21)	0.95
Venous thromboembolism	25 (0.3)	36 (0.4)	41 (0.4)	0.61 (0.37–1.00)	0.05	0.88 (0.56–1.38)	0.58
Hospitalization							
For CV causes	1303 (14.2)	1317 (14.4)	1394 (15.3)	0.92 (0.86–1.00)	0.04	0.94 (0.87–1.01)	0.11
For non-CV causes	1701 (18.6)	1649 (18.1)	1624 (17.8)	1.05 (0.98–1.13)	0.14	1.02 (0.95–1.09)	0.54

Approval Number: L.IT.MA.09.2017.2889

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI



MACE*	%	HR (95% CI)	p-value
Aspirin 100mg OD	5.4	-	-
Rivaroxaban 5mg BID	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5mg BID + Aspirin 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

Number at risk				
Aspirin 100mg od	9126	7808	3860	669
Riva 5mg bid	9117	7824	3862	670
Riva 2.5mg bid + Aspirin 100mg od	9152	7904	3912	658

*Rates as at mean follow up of 23 months

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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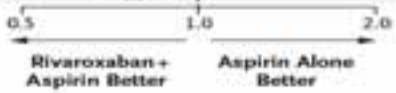
COMPASS Subgroup Analysis

Subgroup	Rivaroxaban + Aspirin	Aspirin Alone	Hazard Ratio for Cardiovascular Death, Stroke, or Myocardial Infarction (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All participants	379/9152 (4.1)	496/9126 (5.4)	0.76 (0.66–0.86)	
Age				0.20
<65 yr	79/2150 (3.7)	126/2184 (5.8)	0.63 (0.48–0.84)	
65–74 yr	179/5078 (3.5)	238/5045 (4.7)	0.74 (0.61–0.90)	
≥75 yr	121/1924 (6.3)	132/1897 (7)	0.89 (0.69–1.14)	
Sex				0.75
Male	300/7093 (4.2)	393/7137 (5.5)	0.76 (0.66–0.89)	
Female	79/2059 (3.8)	103/1989 (5.2)	0.72 (0.54–0.97)	
Geographic region				0.56
North America	63/1304 (4.8)	80/1309 (6.1)	0.78 (0.56–1.08)	
South America	93/2054 (4.5)	111/2054 (5.4)	0.84 (0.63–1.10)	
Western Europe	117/2855 (4.1)	141/2855 (4.9)	0.82 (0.64–1.05)	
Eastern Europe	59/1607 (3.7)	90/1604 (5.6)	0.65 (0.46–0.90)	
Asia–Pacific	47/1332 (3.5)	74/1304 (5.7)	0.62 (0.43–0.89)	
Race				0.37
White	235/5673 (4.1)	306/5682 (5.4)	0.76 (0.64–0.90)	
Black	2/76 (2.6)	8/92 (8.7)	0.30 (0.06–1.46)	
Asian	54/1451 (3.7)	81/1397 (5.8)	0.64 (0.45–0.90)	
Other	88/1952 (4.5)	101/1955 (5.2)	0.87 (0.65–1.16)	
Body weight				0.64
≤60 kg	41/901 (4.6)	45/836 (5.4)	0.83 (0.55–1.27)	
>60 kg	335/8241 (4.1)	448/8285 (5.4)	0.75 (0.65–0.86)	
Estimated GFR				0.95
<60 ml/min	132/2054 (6.4)	177/2114 (8.4)	0.75 (0.60–0.94)	
≥60 ml/min	247/7094 (3.5)	319/7012 (4.5)	0.76 (0.64–0.90)	
Baseline tobacco use				0.29
Yes	80/1944 (4.1)	122/1972 (6.2)	0.66 (0.50–0.88)	
No	299/7208 (4.1)	374/7154 (5.2)	0.79 (0.68–0.92)	
Baseline diabetes				0.77
Yes	179/3448 (5.2)	239/3474 (6.9)	0.74 (0.61–0.90)	
No	200/5704 (3.5)	257/5652 (4.5)	0.77 (0.64–0.93)	
History of hypertension				0.68
Yes	317/6907 (4.6)	409/6877 (5.9)	0.76 (0.66–0.89)	
No	62/2245 (2.8)	87/2249 (3.9)	0.71 (0.51–0.98)	
Baseline dyslipidemia				0.47
Yes	325/8239 (3.9)	428/8158 (5.2)	0.74 (0.64–0.86)	
No	54/913 (5.9)	68/968 (7)	0.85 (0.60–1.22)	
Coronary artery disease				0.47
Yes	347/8313 (4.2)	460/8261 (5.6)	0.74 (0.65–0.86)	
No	32/839 (3.8)	36/865 (4.2)	0.89 (0.55–1.43)	
Peripheral arterial disease				0.61
Yes	126/2492 (5.1)	174/2504 (6.9)	0.72 (0.57–0.90)	
No	253/6660 (3.8)	322/6622 (4.9)	0.77 (0.66–0.91)	



Approval Number: L.IT.MA.09.2017.2889

Bleeding Rates Increased but Low with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin Alone, with No Differences Seen in Fatal and Intracranial Bleeding

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Rivaroxaban 5 mg bid N=9117	Aspirin 100 mg N=9126
Modified major ISTH bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)
Non-fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg		Rivaroxaban 5 mg bid vs aspirin 100 mg	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Modified ISTH major bleeding	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Non-fatal ICH*	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Non-fatal other critical organ*	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06

The use of the standard ISTH major bleeding definition would have led to approximately one third fewer major bleeding events than with the use of the modified ISTH definition

Each event is counted in the most severe hierarchical category (fatal; critical organ bleeding; bleeding into surgical site requiring re-operation; bleeding leading to hospitalization) only. For each outcome, the first event experienced per patient is considered. Subsequent events of the same type are not shown. Therefore subcategories do not necessarily sum up to overall category. *Symptomatic

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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Net Clinical Benefit: 20% RRR with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin

- **Definition:** composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ
  - **In other words, net clinical benefit represented the composite of fatal and non-fatal events of irreversible harm**

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
Net clinical benefit	431 (4.7%)	534 (5.9%)	0.80 (0.70–0.91)	<0.001

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Approval Number: L.IT.MA.09.2017.2889

COMPASS

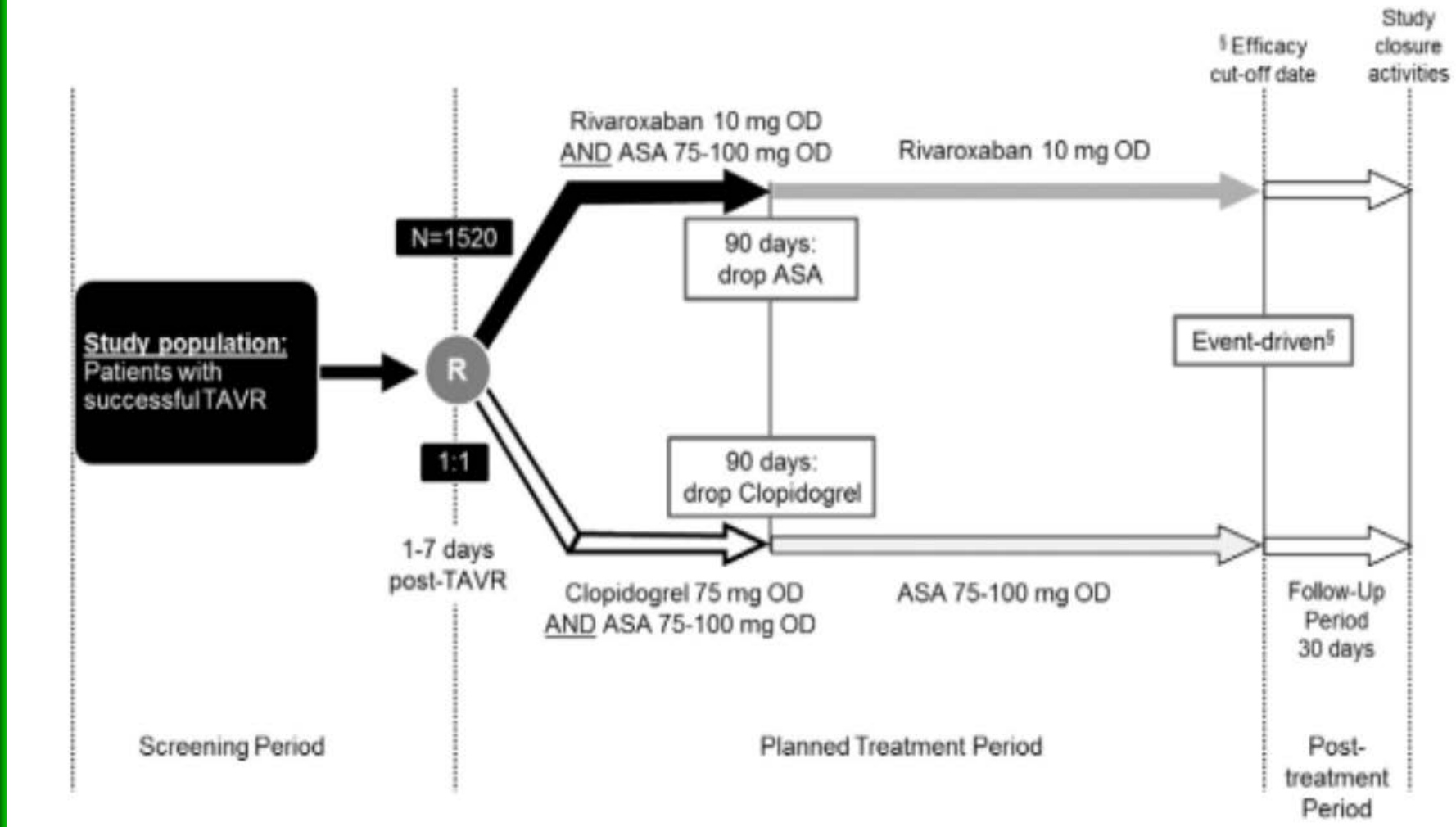
Trial design: Rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: Rationale and design of the GALILEO study

Stephan Windecker, MD,[a,b] Jan Tijssen, PhD,[b,c] Gennaro Giustino, MD,[d] Ana H. C. Guimarães, PhD,[e] Roxana Mehran, MD,[d] Marco Valgimigli, MD, PhD,[a,b] Pascal Vranckx, MD, PhD,[f,b] Robert C. Welsh, MD,[g] Usman Baber, MD,[d] Gerrit-Anne van Es, PhD,[b,e] Peter Wildgoose, PhD,[h] Albert A. Volkl, PharmD BCPS,[h] Ana Zazula, MD,[i] Karen Thomitzek, MD,[j] Melanie Hemmrich, MD,[j] and George D. Dangas, MD, PhD[d] *Bern, Switzerland; Rotterdam, Amsterdam, the Netherlands; NY, USA; Hasselt, Belgium; NJ, USA; Edmonton, Canada; São Paulo, Brazil; and Berlin, Germany*

Background Optimal antithrombotic treatment after transcatheter aortic valve replacement (TAVR) is unknown and determined empirically. The direct factor Xa inhibitor rivaroxaban may potentially reduce TAVR-related thrombotic complications and premature valve failure.

Design GALILEO is an international, randomized, open-label, event-driven, phase III trial in more than 1,520 patients without an indication for oral anticoagulation who underwent a successful TAVR (ClinicalTrials.gov NCT02556203). Patients are randomized (1:1 ratio), 1 to 7 days after a successful TAVR, to either a rivaroxaban-based strategy or an antiplatelet-based strategy. In the experimental arm, subjects receive rivaroxaban (10 mg once daily [OD]) plus acetylsalicylic acid (ASA, 75-100 mg OD) for 90 days followed by rivaroxaban alone. In the control arm, subjects receive clopidogrel (75 mg OD) plus ASA (as above) for 90 days followed by ASA alone. In case new-onset atrial fibrillation occurs after randomization, full oral anticoagulation will be implemented with maintenance of the original treatment assignment. The primary efficacy end point is the composite of all-cause death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep venous thrombosis, and systemic embolism. The primary safety end point is the composite of life-threatening, disabling, and major bleeding, according to the Valve Academic Research Consortium definitions.

Conclusions GALILEO will test the hypothesis that a rivaroxaban-based antithrombotic strategy reduces the risk of thromboembolic complications post-TAVR with an acceptable risk of bleeding compared with the currently recommended antiplatelet therapy–based strategy in subjects without need of chronic oral anticoagulation. (Am Heart J 2017;184:81-7.)


GALILEO
Study population:
Patients with
successful TAVR
N=1520
R
1:1
1-7 days
post-TAVR
Rivaroxaban 10 mg OD
AND ASA 75-100 mg OD
90 days:
drop ASA
Rivaroxaban 10 mg OD
Clopidogrel 75 mg OD
AND ASA 75-100 mg OD
90 days:
drop Clopidogrel
ASA 75-100 mg OD
[5] Efficacy
cut-off date
Event-driven[5]
Study
closure
activities
Follow-Up
Period
30 days
Screening Period
Planned Treatment Period
Post-
treatment
Period

European Heart Journal Advance Access published September 1, 2015

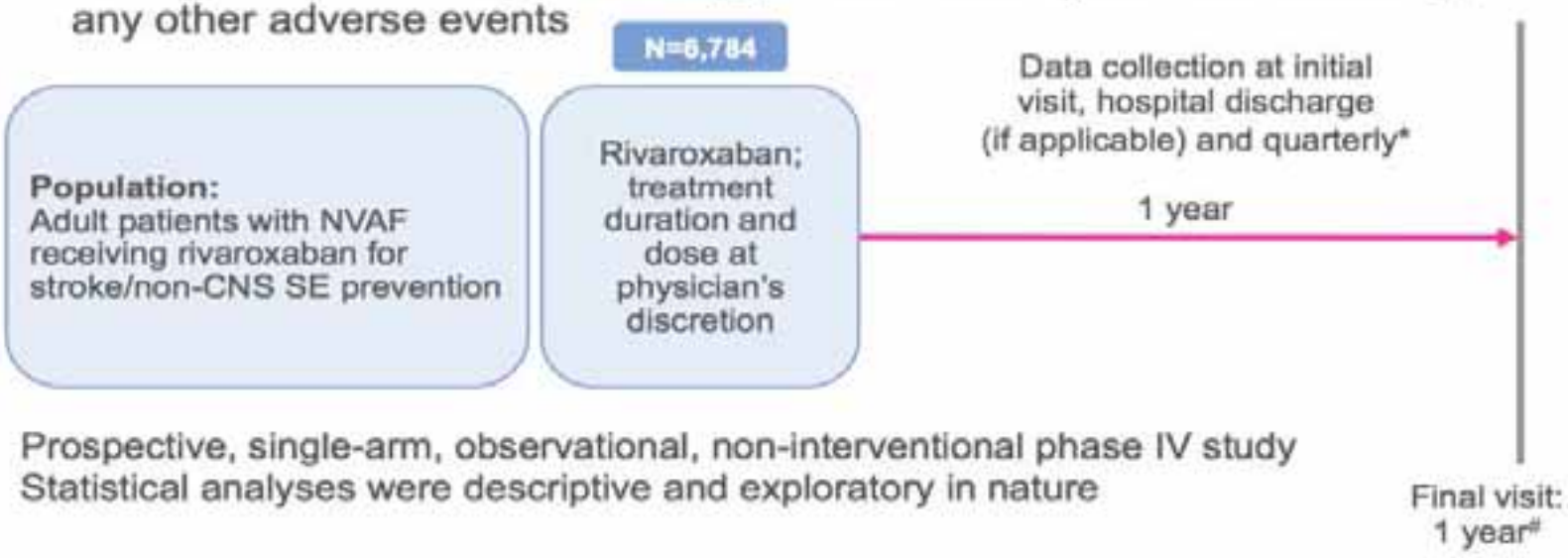
European Heart Journal
doi:10.1093/eurheartj/ehv466

FASTTRACK
ESC Clinical Registry

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

A. John Camm[1*], Pierre Amarenco[2], Sylvia Haas[3], Susanne Hess[4], Paulus Kirchhof[5,6], Silvia Kuhls[7], Martin van Eickels[4], and Alexander G.G. Turpie[8], on behalf of the XANTUS Investigators

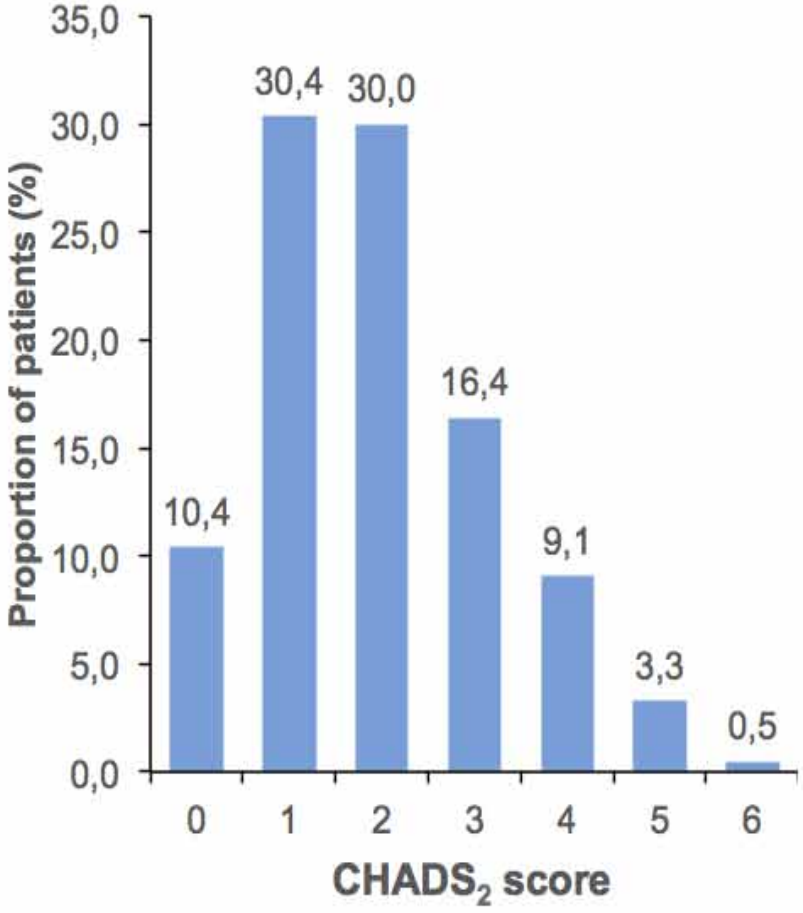
- Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events



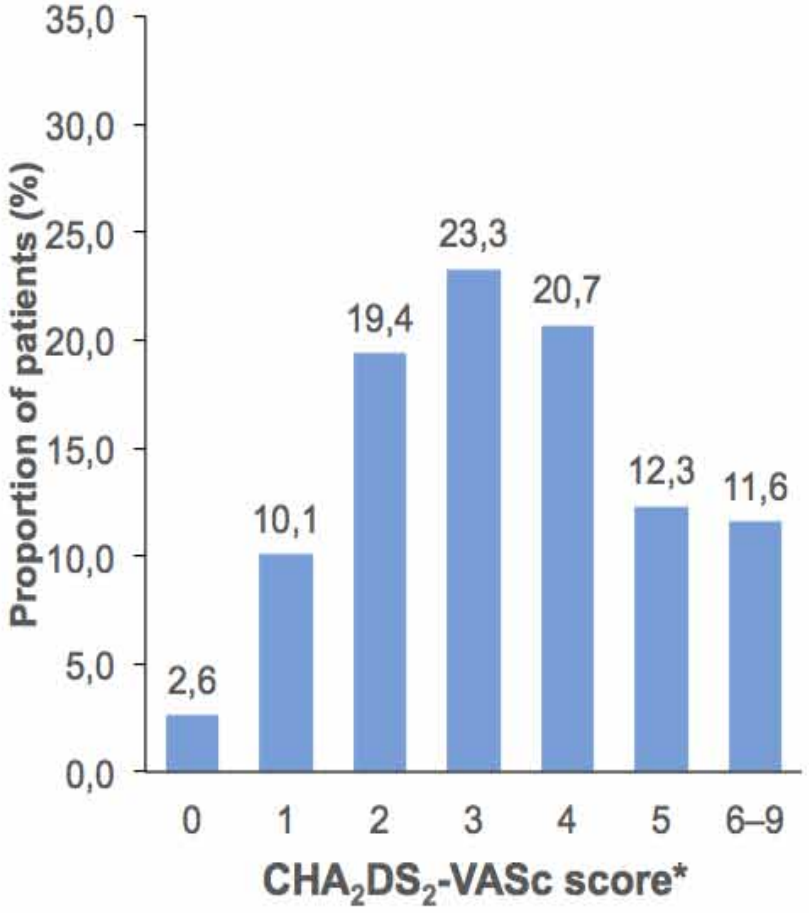
Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

XANTUS: Baseline Demographics – Distribution of Stroke Risk Factors

Mean score±SD = 2.0±1.3



Mean score±SD = 3.4±1.7



XANTUS: Treatment-Emergent Thromboembolic Events and All-Cause Death

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
All-cause death	118 (1.7)	1.9 (1.6–2.3)
Thromboembolic events (stroke, SE, TIA, and MI)	108 (1.6)	1.8 (1.5–2.1)
Stroke/SE	51 (0.8)	0.8 (0.6–1.1)
Stroke	43 (0.6)	0.7 (0.5–0.9)
Primary haemorrhagic	11 (0.2)	
Primary ischaemic	32 (0.5)	
SE	8 (0.1)	0.1 (0.1–0.3)
TIA	32 (0.5)	0.5 (0.4–0.7)
MI	27 (0.4)	0.4 (0.3–0.6)

*Events per 100 patient-years

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

XANTUS: Treatment-Emergent Bleeding Events

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
Major bleeding	128 (1.9)	2.1 (1.8–2.5)
Fatal	12 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	43 (0.6)	0.7 (0.5–0.9)
Intracranial haemorrhage	26 (0.4)	0.4 (0.3–0.6)
Mucosal bleeding#	60 (0.9)	1.0 (0.7–1.3)
Gastrointestinal	52 (0.8)	0.9 (0.6–1.1)
Haemoglobin decrease ≥2 g/dl‡	52 (0.8)	0.9 (0.6–1.1)
Transfusion of ≥2 units of packed RBCs or whole blood‡	53 (0.8)	0.9 (0.6–1.1)
Non-major bleeding events	878 (12.9)	15.4 (14.4–16.5)

Patients could experience multiple bleeding events in different categories. *Events per 100 patient-years; #numbers are for major mucosal and gastrointestinal bleeding events; ‡representing major bleeding

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

XANTUS: Module Summary

- XANTUS is the first large, international prospective study to describe rivaroxaban use in a broad patient population with NVAF
  - Patients were at lower overall risk than in the phase III ROCKET AF trial
- Over 96% patients receiving rivaroxaban did not experience any of the outcomes of stroke/SE, treatment-emergent major bleeding or all-cause death
- In XANTUS, rivaroxaban demonstrated low rates of stroke/SE and major bleeding, including intracranial and GI bleeding
  - Incidences of these outcomes generally increased with higher stroke risk scores
  - Major bleeding was mostly treated conservatively; reversal agents were rarely used
- Treatment persistence and patient satisfaction were high
  - 80% of patients remained on rivaroxaban
  - 75% reported they were satisfied with their treatment at 1 year


Welcome to the present moment.
Here. Now. The only moment there
ever is.
— Echhart Tolle —

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

ESC European Society of Cardiology

Recommendations	Class	Level
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel and OAC should be considered for 1 month, irrespective of the type of stent used.	IIa	B
Triple therapy with aspirin, clopidogrel and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, which outweigh the bleeding risk.	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

ESC European Society of Cardiology

When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AFib trials should be considered.	IIa	C
When rivaroxaban is used in combination with aspirin and/ or clopidogrel, rivaroxaban 15 mg *q.d.* may be used instead of rivaroxaban 20 mg *q.d.*	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

COMPASS Study: *Rivaroxaban Shows Overwhelming Efficacy and Meets Primary Endpoint Early*

Phase III COMPASS study with Bayer's Rivaroxaban in Patients with Coronary or Peripheral Artery Disease Shows Overwhelming Efficacy and Meets Primary Endpoint Early

Leverkusen, February 08, 2017, 04:35 p.m. CET

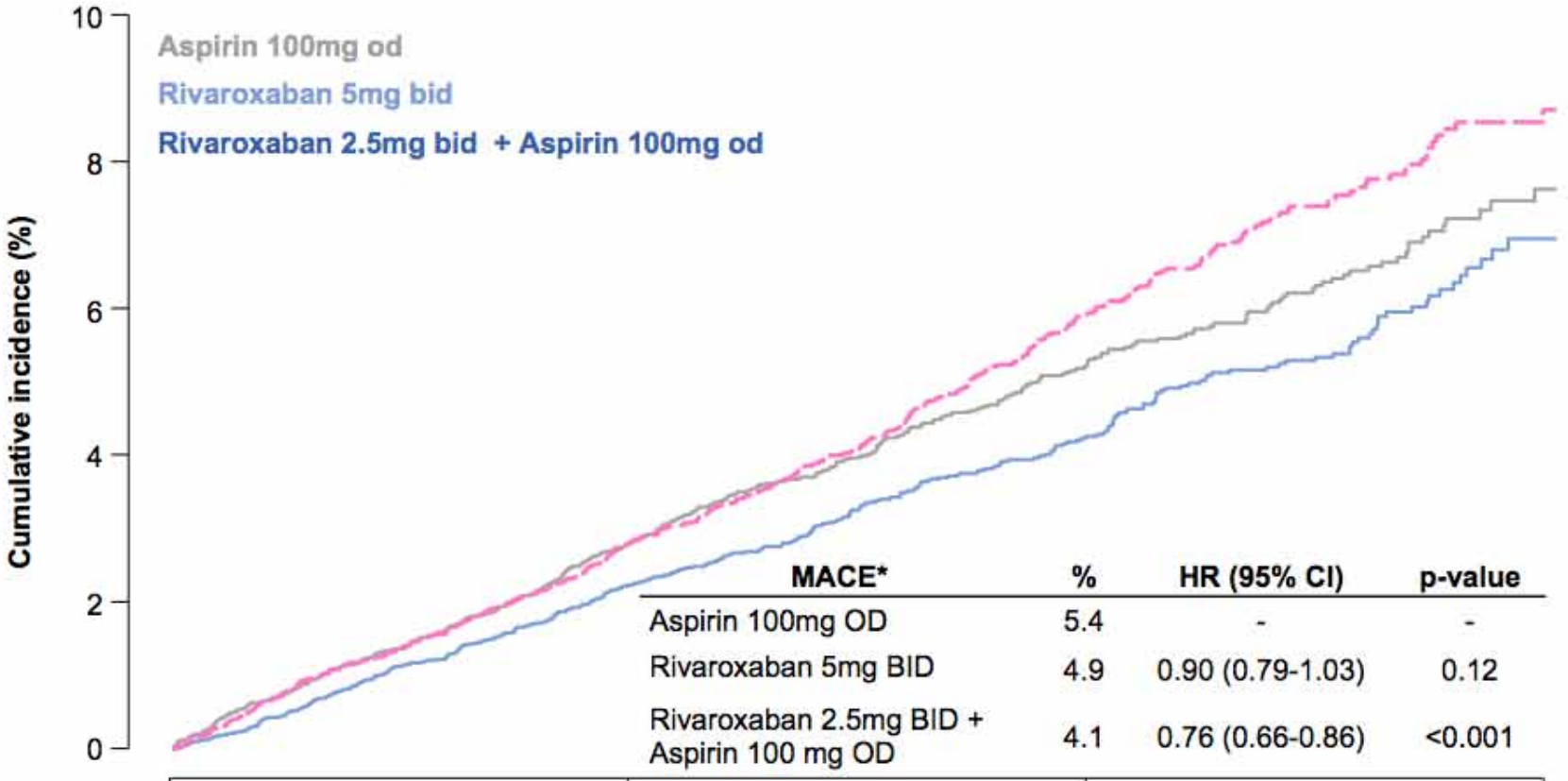
Bayer AG and its cooperation partner Janssen Research & Development, LLC today announced that the Phase III trial COMPASS evaluating the efficacy and safety of rivaroxaban (Xarelto®) for the prevention of major adverse cardiac events (MACE) including cardiovascular death, myocardial infarction and stroke in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) has met its primary endpoint ahead of time. Following a planned interim analysis conducted by the independent Data Monitoring Committee (DMC), the DMC recommended to stop the trial early as the primary MACE endpoint has reached its prespecified criteria for superiority. Owing to the magnitude of effect and the confirmation of the existing safety profile of rivaroxaban, Bayer, Janssen and the Population Health Research Institute (PHRI) will offer rivaroxaban to study participants in an open-label extension trial. The COMPASS study is the largest clinical study of rivaroxaban to date.

The Phase III COMPASS study was conducted in collaboration with the PHRI and has enrolled 27,402 patients from more than 600 sites across more than 30 countries worldwide. In the study, patients were randomized to receive either rivaroxaban 2.5 mg twice daily in addition to aspirin 100 mg once daily, rivaroxaban 5 mg twice daily alone, or aspirin 100 mg once daily alone.

A complete data analysis from this study is expected to be presented at an upcoming medical meeting in 2017.

Approval Number: L.IT.MA.09.2017.2889

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI



MACE*	%	HR (95% CI)	p-value
Aspirin 100mg OD	5.4	-	-
Rivaroxaban 5mg BID	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5mg BID + Aspirin 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

Number at risk				
Aspirin 100mg od	9126	7808	3860	669
Riva 5mg bid	9117	7824	3862	670
Riva 2.5mg bid + Aspirin 100mg od	9152	7904	3912	658

*Rates as at mean follow up of 23 months

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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Approval Number: L.IT.MA.09.2017.2889

Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin: Significantly Reduced CV Events by 24% Versus Aspirin

Outcomes, n (%)	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
CV death, stroke, or MI	379 (4.1)	496 (5.4)	0.76 (0.66–0.86)	<0.001
CV death	160 (1.7)	203 (2.2)	0.78 (0.64–0.96)	0.02
Stroke	83 (0.9)	142 (1.6)	0.58 (0.44–0.76)	<0.001
MI	178 (1.9)	205 (2.2)	0.86 (0.70–1.05)	0.14

Outcomes, n (%)	Rivaroxaban 5 mg bid N=9117	Rivaroxaban 5 mg bid vs aspirin 100 mg	
		HR (95% CI)	*p*-value
CV death, stroke, or MI	448 (4.9)	0.90 (0.79–1.03)	0.12
CV death	195 (2.1)	0.96 (0.79–1.17)	0.69
Stroke	117 (1.3)	0.82 (0.65–1.05)	0.12
MI	182 (2.0)	0.89 (0.73–1.08)	0.24

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

Approval Number: L.IT.MA.09.2017.2889

Bleeding Rates Increased but Low with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin Alone, with No Differences Seen in Fatal and Intracranial Bleeding

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Rivaroxaban 5 mg bid N=9117	Aspirin 100 mg N=9126
Modified major ISTH bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)
Non-fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)

Rates at mean follow-up of 23 months	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg		Rivaroxaban 5 mg bid vs aspirin 100 mg	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Modified ISTH major bleeding	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Non-fatal ICH*	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Non-fatal other critical organ*	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06

The use of the standard ISTH major bleeding definition would have led to approximately one third fewer major bleeding events than with the use of the modified ISTH definition

Each event is counted in the most severe hierarchical category (fatal; critical organ bleeding; bleeding into surgical site requiring re-operation; bleeding leading to hospitalization) only. For each outcome, the first event experienced per patient is considered. Subsequent events of the same type are not shown. Therefore subcategories do not necessarily sum up to overall category. *Symptomatic

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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Net Clinical Benefit: 20% RRR with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin

- **Definition:** composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ
  - **In other words, net clinical benefit represented the composite of fatal and non-fatal events of irreversible harm**

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
Net clinical benefit	431 (4.7%)	534 (5.9%)	0.80 (0.70–0.91)	<0.001

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Approval Number: L.IT.MA.09.2017.2889

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Approval Number: L.IT.MA.09.2017.2889

Dual Pathway Inhibition with Rivaroxaban 2.5 mg bid + Aspirin Significantly Reduced MACE by 28% and MALE by 46% Versus Aspirin

Outcome	Rivaroxaban 2.5 mg bid + aspirin N=2492	Rivaroxaban 5 mg bid N=2474	Aspirin N=2,504	Rivaroxaban 2.5 mg bid + aspirin vs. aspirin		Rivaroxaban 5 mg bid vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACE	126 (5.1)	149 (6.0)	174 (6.9)	0.72 (0.57–0.90)	0.005	0.86 (0.69–1.08)	0.19
CV death	64 (2.6)	66 (2.7)	78 (3.1)	0.82 (0.59–1.14)	-	0.86 (0.62–1.19)	-
Stroke	25 (1.0)	43 (1.7)	47 (1.9)	0.54 (0.33–0.87)	-	0.93 (0.61–1.40)	-
MI	51 (2.0)	56 (2.3)	67 (2.7)	0.76 (0.53–1.09)	-	0.84 (0.59–1.20)	-
MALE	30 (1.2)	35 (1.4)	56 (2.2)	0.54 (0.35–0.84)	0.005	0.63 (0.41–0.96)	0.03
Major amputation	5 (0.2)	8 (0.3)	17 (0.7)	0.30 (0.11–0.80)	0.01	0.46 (0.20–1.08)	0.07

Rivaroxaban 2.5 mg bid + aspirin significantly reduced major amputation by 70% versus aspirin

Anand SS *et al*. ESC 2017, Abs 1157; Available at: http://spo.escardio.org/SessionDetails.aspx?eevtid=1220&sessId=22247&subSessId=0;
Anand SS *et al*. *Lancet* 2017;In Press

COMPASS

Approval Number: L.IT.MA.09.2017.2889

Rivaroxaban Has Shown Improved Outcomes for Patients with High Need for Increased Vascular Protection

In patients with chronic CAD or PAD, dual pathway inhibition with rivaroxaban vascular dose 2.5 mg bid plus aspirin, versus aspirin alone:

- Significantly reduced the combined risk of stroke, CV death and MI by 24%
- Demonstrated 42% reduction in stroke, 22% reduction in CV death, and 18% reduction in all-cause mortality
- As expected, resulted in increased major bleeding, however bleeding rates were low and notably, there was no significant increase in intracranial, critical organ or fatal bleeding
- Showed a substantial improvement in net clinical benefit of 20%

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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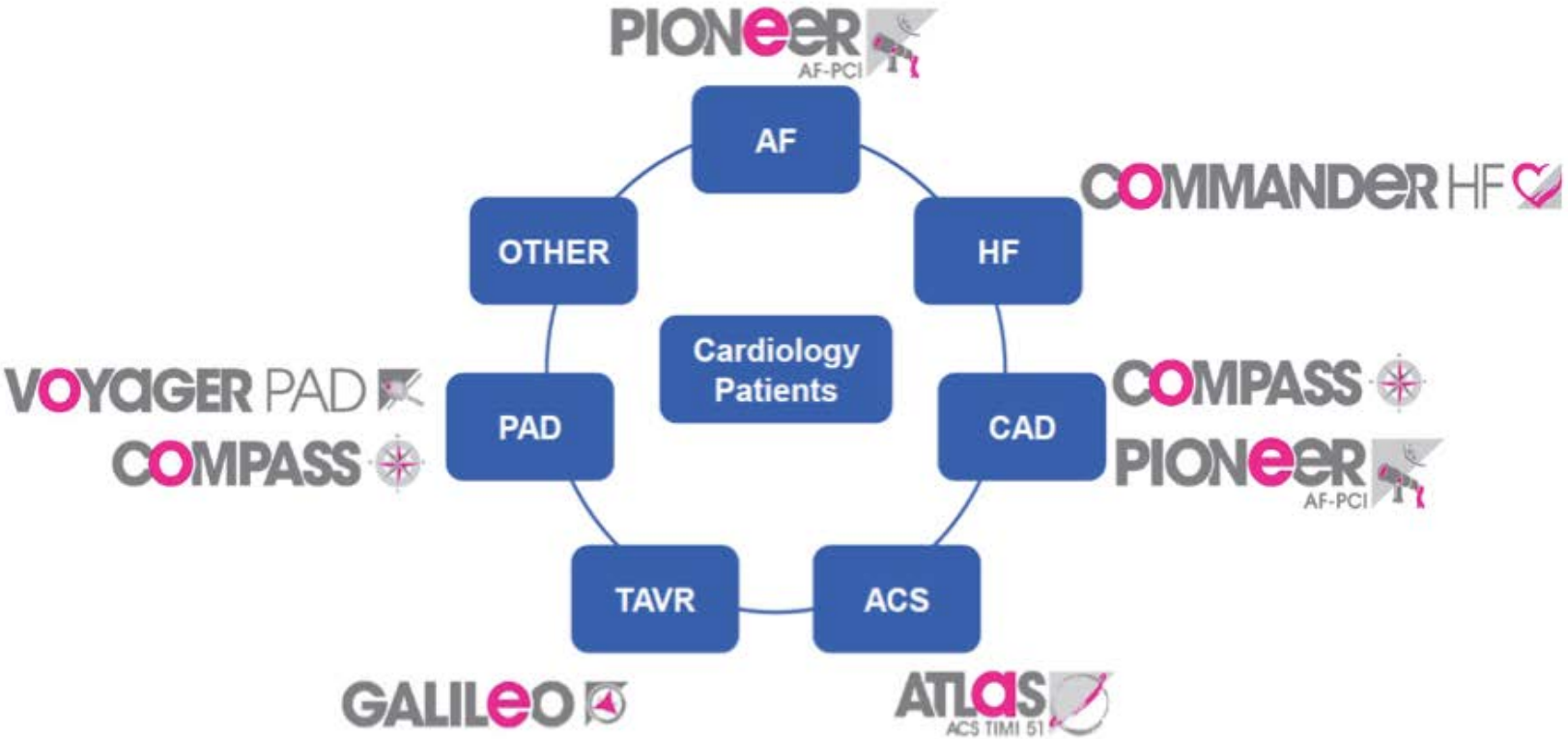
Rivaroxaban Is Committed to Advancing Thrombosis Management…Today and Tomorrow



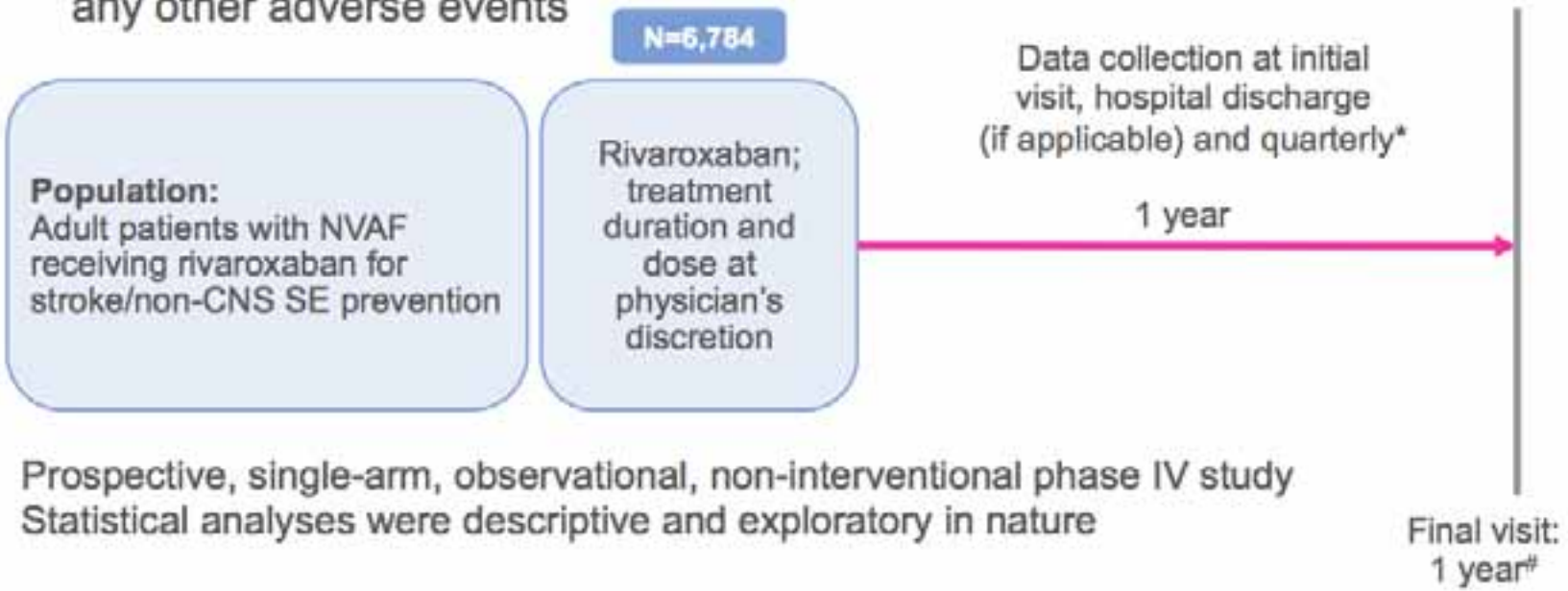
Risk-Benefit Profile of NOACs vs Warfarin in the Elderly

	Stroke/Systemic Thromboembolism, %/y		Major Bleeding	
	Age < 75 y	Age > 75 y	Age < 75 y	Age > 75 y
RE-LY				
Dabigatran 150 mg	0.9	1.4	2.1	5.1
Warfarin	1.4	2.1	3.0	4.4
ROCKET-AF				
Rivaroxaban	2	2.3	2.7	4.9
Warfarin	2.1	2.9	2.8	4.4
ARISTOTLE				
Apixaban	1.2	1.6	2.0	3.3
Warfarin	1.7	2.2	2.8	5.2
ENGAGE-TIMI 48				
Edoxaban -- higher dose	1.7	1.9	2.5	4.0
Warfarin	1.8	2.3	3.3	4.8

Turagam et al. *Clin Interv Aging*. 2015;10:1431–44

XANTUS: Study Objective and Design

- To collect real world data on adverse events in patients with NVAF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice
  - Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events



Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

*Exact referral dates for follow-up visits not defined (every 3 months recommended); #for rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

1. Camm AJ *et al*, *Vasc Health Risk Manag* 2014;10:425–434; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

XANTUS: Treatment-Emergent Thromboembolic Events and All-Cause Death

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
All-cause death	118 (1.7)	1.9 (1.6–2.3)
Thromboembolic events (stroke, SE, TIA, and MI)	108 (1.6)	1.8 (1.5–2.1)
Stroke/SE	51 (0.8)	0.8 (0.6–1.1)
Stroke	43 (0.6)	0.7 (0.5–0.9)
Primary haemorrhagic	11 (0.2)	
Primary ischaemic	32 (0.5)	
SE	8 (0.1)	0.1 (0.1–0.3)
TIA	32 (0.5)	0.5 (0.4–0.7)
MI	27 (0.4)	0.4 (0.3–0.6)

*Events per 100 patient-years

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

XANTUS: Treatment-Emergent Bleeding Events

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
Major bleeding	128 (1.9)	2.1 (1.8–2.5)
Fatal	12 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	43 (0.6)	0.7 (0.5–0.9)
Intracranial haemorrhage	26 (0.4)	0.4 (0.3–0.6)
Mucosal bleeding#	60 (0.9)	1.0 (0.7–1.3)
Gastrointestinal	52 (0.8)	0.9 (0.6–1.1)
Haemoglobin decrease ≥2 g/dl‡	52 (0.8)	0.9 (0.6–1.1)
Transfusion of ≥2 units of packed RBCs or whole blood‡	53 (0.8)	0.9 (0.6–1.1)
Non-major bleeding events	878 (12.9)	15.4 (14.4–16.5)

Patients could experience multiple bleeding events in different categories. *Events per 100 patient-years; #numbers are for major mucosal and gastrointestinal bleeding events; ‡representing major bleeding

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

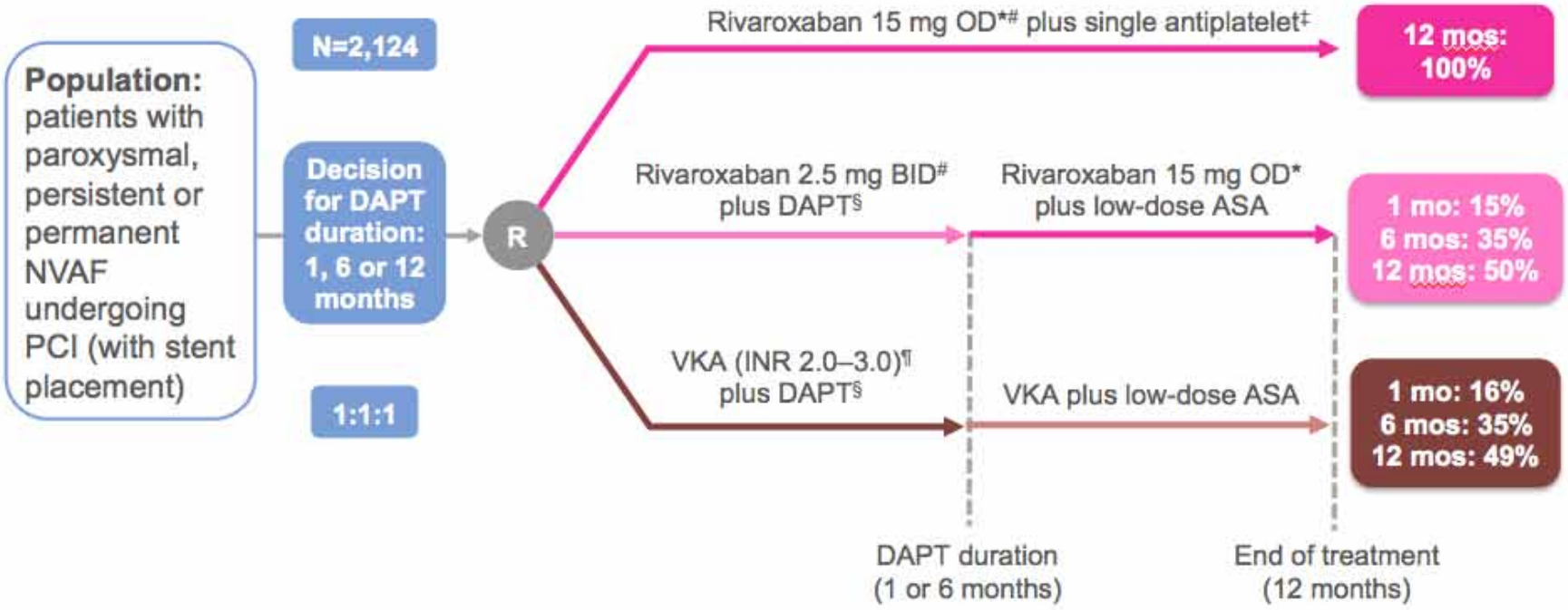
XANTUS

XANTUS: Module Summary

- XANTUS is the first large, international prospective study to describe rivaroxaban use in a broad patient population with NVAF
  - Patients were at lower overall risk than in the phase III ROCKET AF trial
- Over 96% patients receiving rivaroxaban did not experience any of the outcomes of stroke/SE, treatment-emergent major bleeding or all-cause death
- In XANTUS, rivaroxaban demonstrated low rates of stroke/SE and major bleeding, including intracranial and GI bleeding
  - Incidences of these outcomes generally increased with higher stroke risk scores
  - Major bleeding was mostly treated conservatively; reversal agents were rarely used
- Treatment persistence and patient satisfaction were high
  - 80% of patients remained on rivaroxaban
  - 75% reported they were satisfied with their treatment at 1 year

Rivaroxaban is the First & Currently Only NOAC to Provide Data From a Dedicated RCT in AF-PCI

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



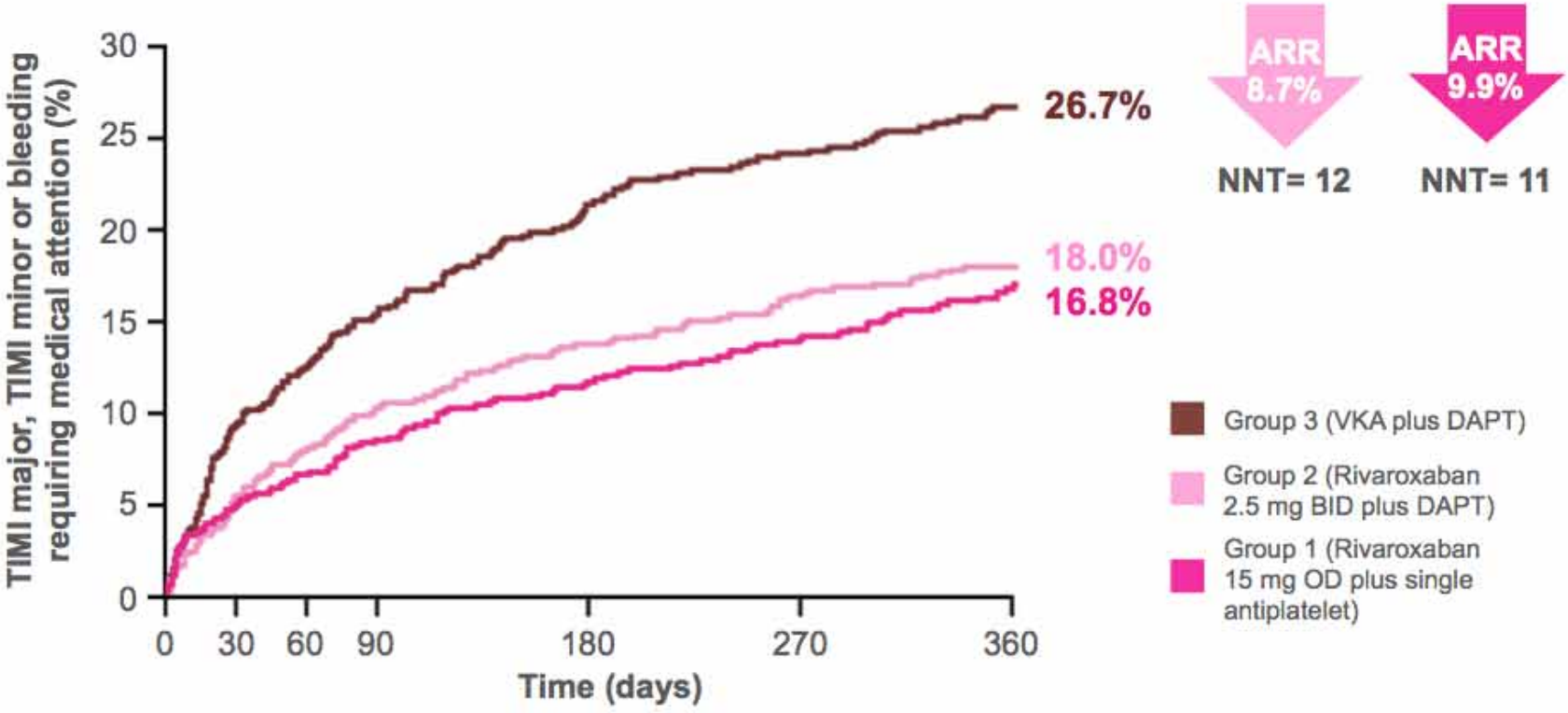
*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶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, *New Engl J Med* 2016;375:2423-2434

Both Rivaroxaban Strategies was Associated With Significantly Improved Safety vs the VKA Strategy

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); *p*<0.001

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); *p*<0.001



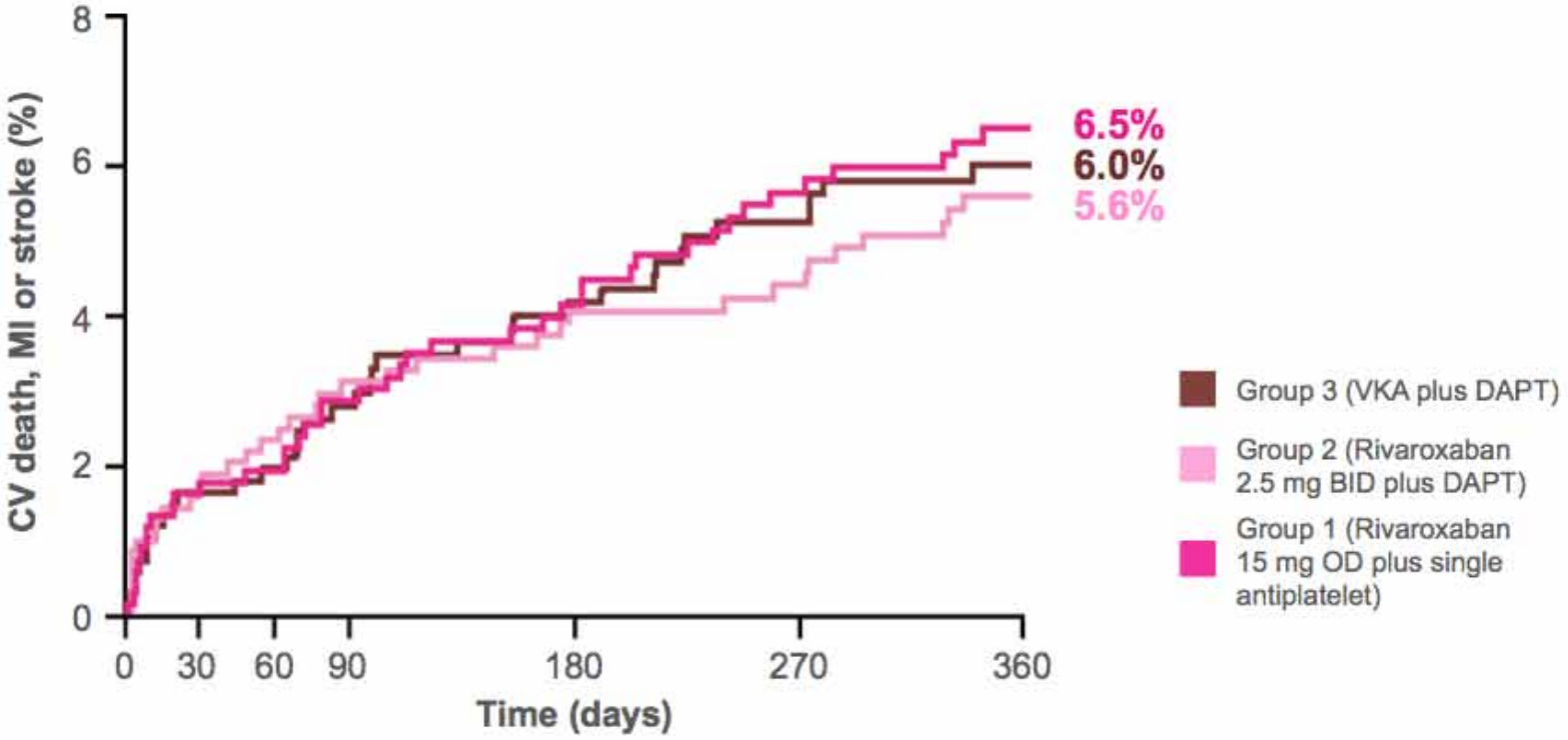
Gibson CM et al, *New Engl J Med* 2016;375:2423-2434

The tested dosing regimens with rivaroxaban in PIONEER AF-PCI are currently not approved

Efficacy was Comparable Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); *p*=0.75

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); *p*=0.76

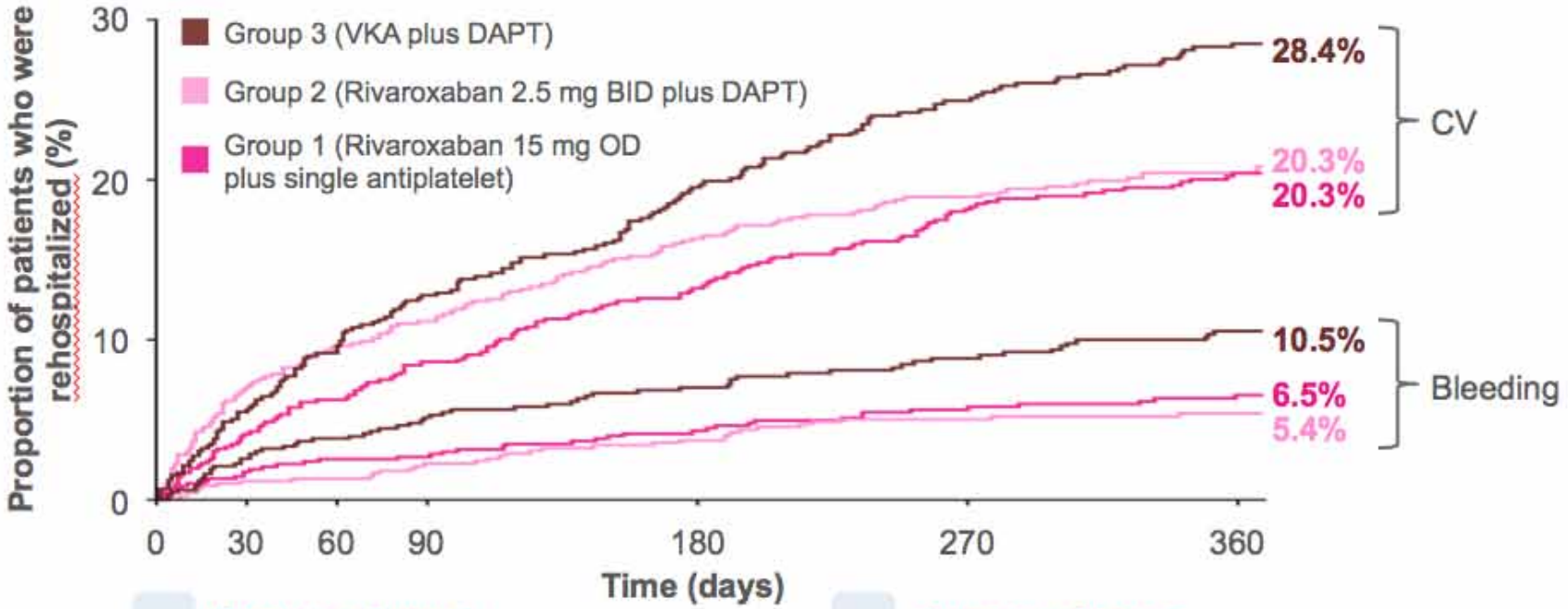


*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints

The tested dosing regimens with rivaroxaban in PIONEER AF-PCI are currently not approved

Gibson CM et al, *New Engl J Med* 2016;375:2423-2434

Re-hospitalization Due to CV Events and Bleeding Were Both Reduced with the Rivaroxaban Strategies



CV

Group 1 vs Group 3:
HR=0.68; (95% CI 0.54–0.85); $p<0.001$
ARR=8.1%; NNT=13

Group 2 vs Group 3:
HR=0.73 (95% CI 0.58–0.91); $p=0.005$
ARR=8.1%; NNT=13

Bleeding

Group 1 vs Group 3:
HR=0.61; (95% CI 0.41–0.90); $p=0.012$
ARR=4.0%; NNT=25

Group 2 vs Group 3:
HR=0.51 (95% CI 0.34–0.77); $p=0.001$
ARR=5.1%; NNT=20

Gibson CM *et al*, *Circulation* 2016; pii: CIRCULATIONAHA.116.025783. [Epub ahead of print]

The tested dosing regimens with rivaroxaban in PIONEER AF-PCI are currently not approved

COMPASS Design

Stable CAD or PAD

2,200 with a primary outcome event