Stroke prevention in AF: Insights from Clinical Trials and Real Life Experience

A. John Camm
St. George's University of London
and Imperial College
London, UK

Approval Number G.MA.GM.XA.10.2015.0723

Disclosure Statement: John Camm

- Chairman: ESC Guidelines on Atrial Fibrillation 2012 and Update 2012, ACC/AHA/ESC Guidelines on VAs and SCD; 2012 NICE Guidelines on ACS and NSTEMI; 2008 NICE Guidelines on Heart Failure; 2006 NICE Guidelines on Atrial Fibrillation
- Steering Committees: multiple trials
- DSMBs: multiple trials including AVERROES, SIGNIFY and INOVATE-AF
- Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects
- Consultant/Advisor/Speaker: AstraZeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda

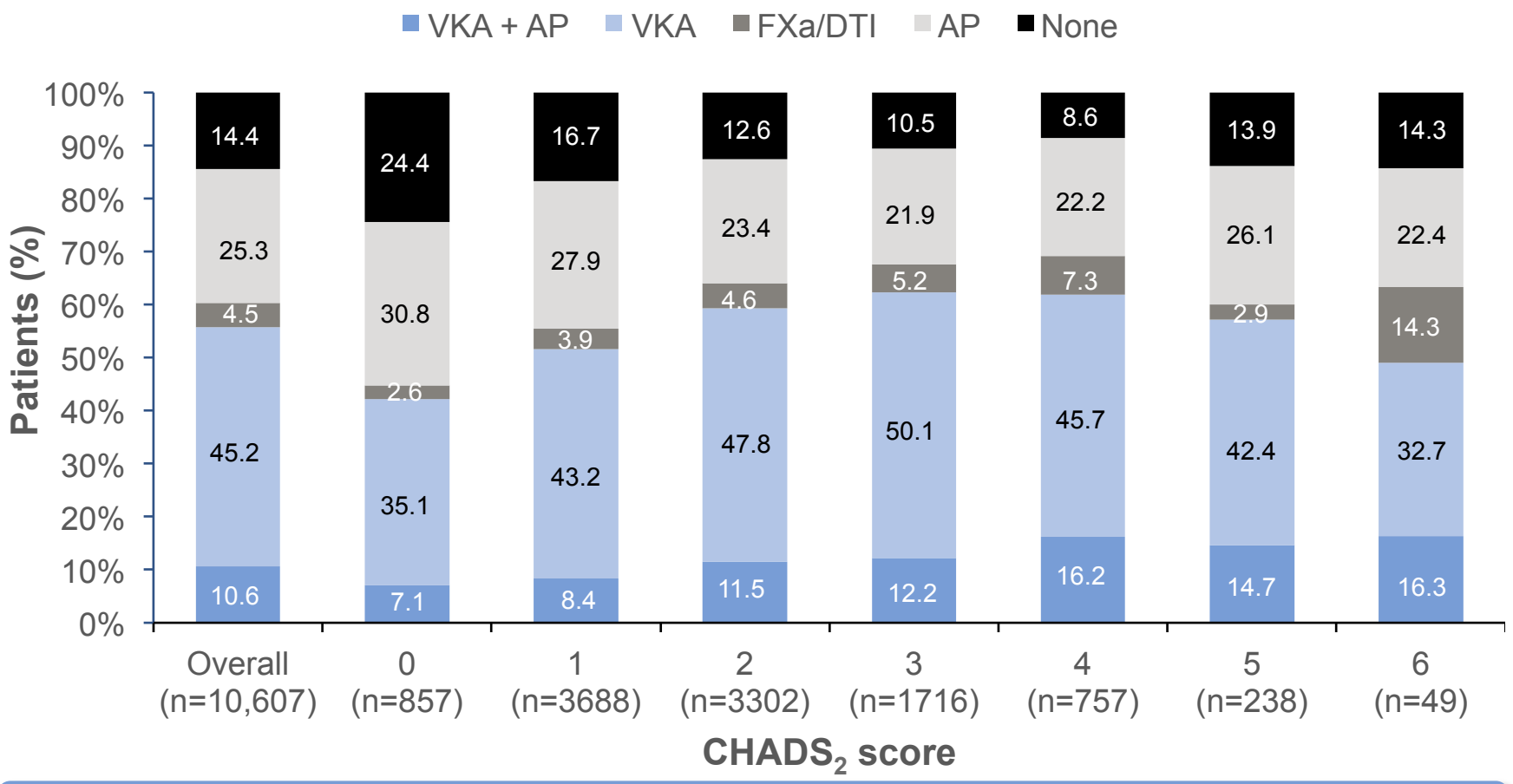
Tolerability of Warfarin During First Year of Therapy: Elderly Patients in the US

$CHADS_2$ score	Major bleeding event	Taken off therapy
	Rate (per 100 person-years)	Rate (per 100 person-years)
0	3.1	15.6
1	4.3	17.1
2	2.0	12.9
3	19.5	32.6
≥4	23.4	35.1

- 58% time in therapeutic range
- Major haemorrhage 7.2%; ICH 2.5%
  - Rates were 2.75× higher in patients ≥80 years
- 28% of patients discontinued warfarin at 1 year

Hylek EM *et al*, *Circulation* 2007;115:2689–2696

GARFIELD AF: AF Patients Are Not Treated According to Current Guidelines



Undertreatment with anticoagulants in 38% of patients with $CHADS_2$ score ≥2

Bayer is supporting GARFIELD AF with an unrestricted educational grant

Kakkar AK *et al*, *PLoS One* 2013;8:e63479

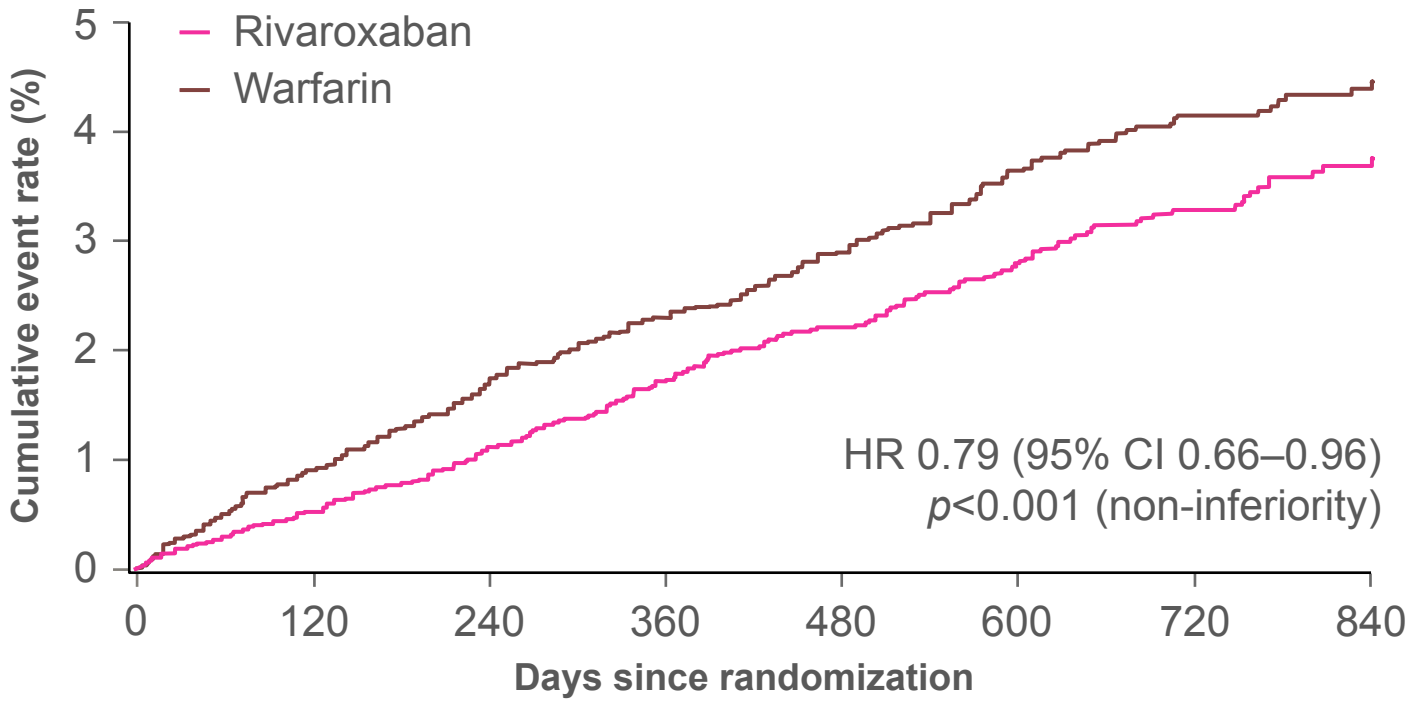
NOACs vs. Warfarin: Overall Outcomes

	Risk ratio (95% CI)	Absolute risk reduction, %	Risk ratio (95% CI) *p*-value
Ischaemic stroke		0.21	0.92 (0.83–1.02) *p*=0.10
Haemorrhagic stroke		0.46	0.49 (0.38–0.64) *p*<0.0001
Myocardial infarction		0.07	0.97 (0.78–1.20) *p*=0.77
All-cause mortality		0.78	0.90 (0.85–0.95) *p*=0.0003

Ruff CT *et al*, *Lancet* 2014;383:955–962

ROCKET AF: Effective Stroke Prevention in Patients With Non-valvular AF vs Warfarin (PPP)

Primary efficacy endpoint: stroke/SE



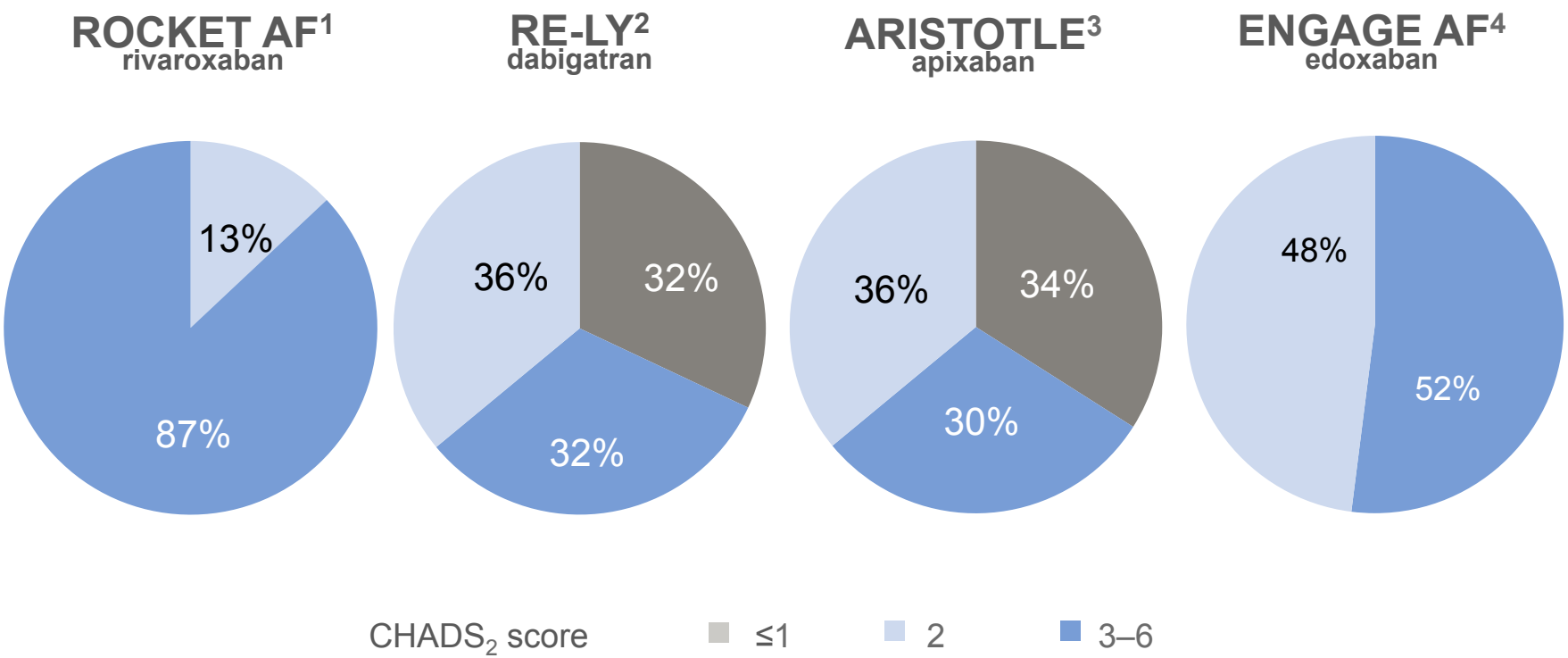
Number of subjects at risk								
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538

PPP, per-protocol population on-treatment (all ITT patients without major predefined protocol violations)

Patel MR *et al*, *N Engl J Med* 2011;365:883–891

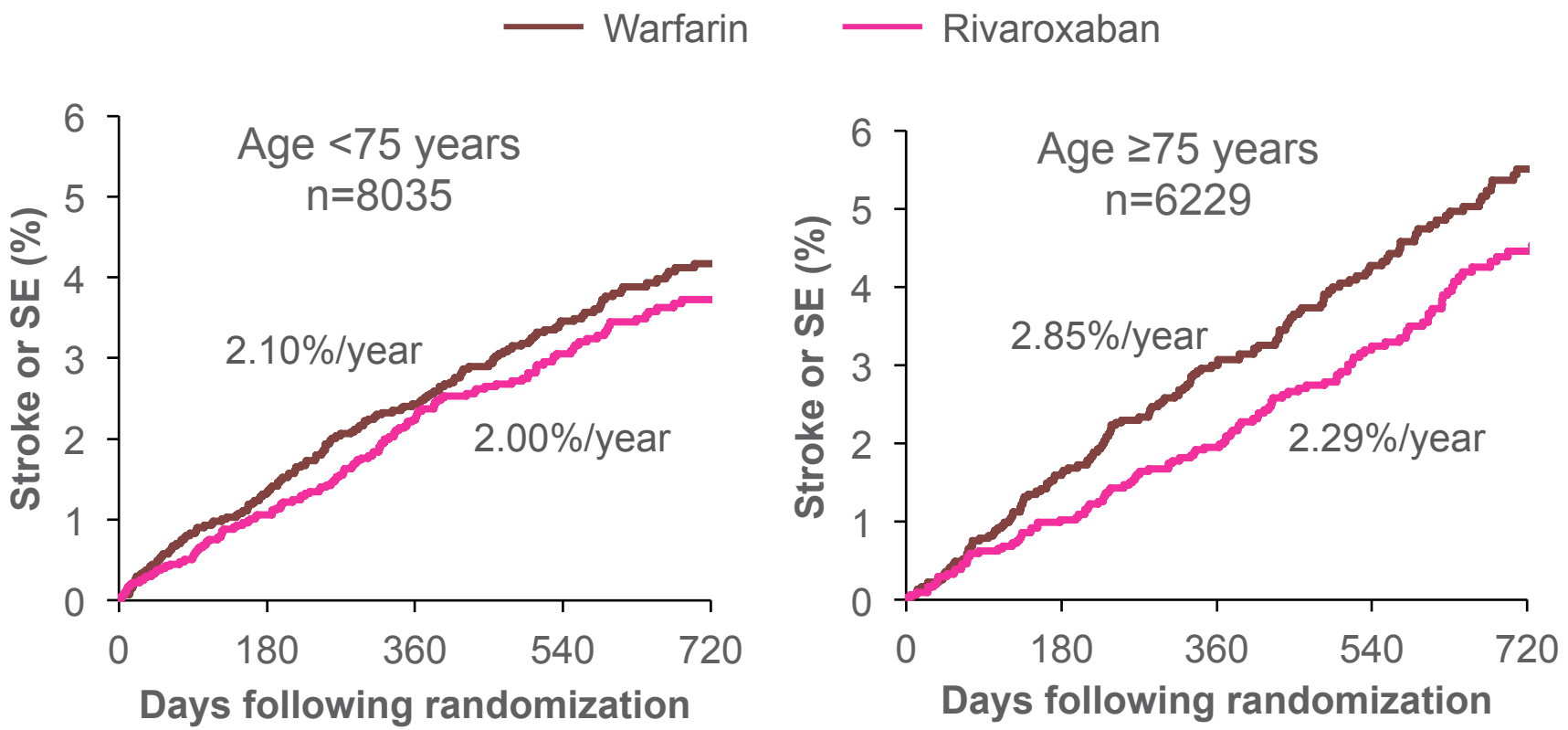
AF Patients in ROCKET AF Had a Higher Risk of Stroke than Patients in Other Phase III Trials

$CHADS_2$ score patient distribution



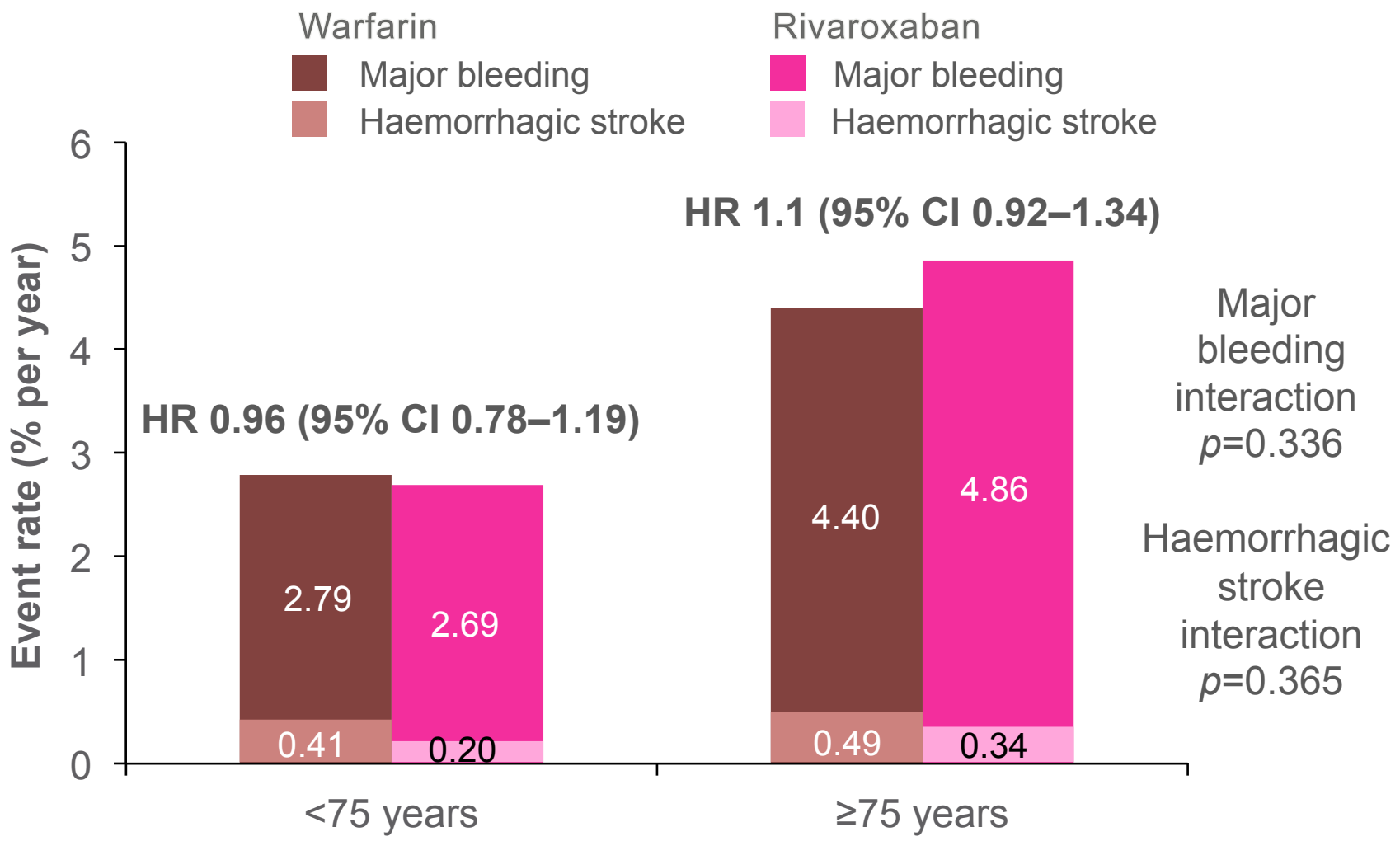
1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Connolly SJ *et al*, *N Engl J Med* 2009;361:1139–1151;
3. Granger CB *et al*, *N Engl J Med* 2011;365:981–992; 4. Giugliano RP *et al*, *N Engl J Med* 2013;369:2093–2104.

Older Age: Stroke and Systemic Embolism Intention-to-Treat Analysis



Halperin JL *et al*, *Circulation* 2014;130:138–146

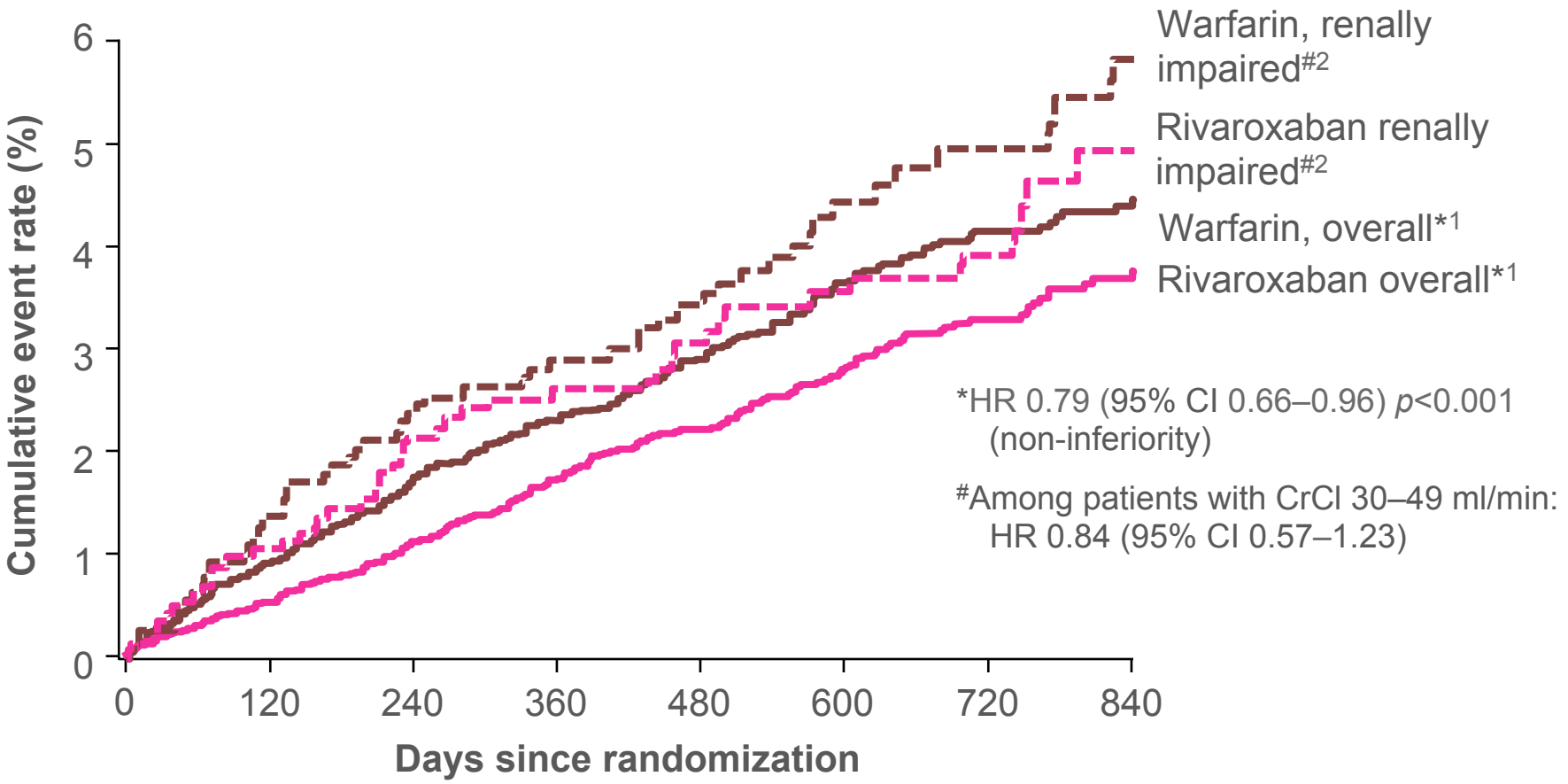
Older Age: Major Bleeding On-Treatment Analysis



Halperin JL *et al*, *Circulation* 2014;130:138–146

ROCKET AF

ROCKET AF: Primary Efficacy Endpoint: Patients with Stroke or non-CNS Embolism and CrCl 30–49 ml/min vs ROCKET AF overall



Per-protocol population on-treatment

1. Fox KA *et al*, *Eur Heart J* 2011;32:2387–2394; 2. Patel MR *et al*, *N Engl J Med* 2011;365:883–891

ROCKET AF

ROCKET AF: Safety Outcomes among AF Patients with CrCl 30–49 ml/min

Clinical endpoint (% per year)	Rivaroxaban (N=7111)	Warfarin (N=7116)	HR (95% CI) rivaroxaban vs warfarin	*p*-value (interaction)
Principal safety outcome*	14.24 17.82	13.67 18.28	1.04 (0.96–1.13) 0.98 (0.84–1.14)	0.45
Major bleeding	3.39 4.49	3.17 4.70	1.07 (0.91–1.26) 0.95 (0.72–1.26)	0.48
Haematocrit or haemoglobin drop	2.54 3.76	2.03 3.28	1.25 (1.03–1.52) 1.14 (0.83–1.58)	0.65
Transfusion	1.49 2.34	1.16 2.00	1.28 (0.99–1.65) 1.17 (0.77–1.76)	0.71
Critical organ	0.83 0.76	1.13 1.39	0.74 (0.55–0.99) 0.55 (0.30–1.00)	0.39
Fatal bleeding	0.23 0.28	0.43 0.74	0.55 (0.32–0.93) 0.39 (0.15–0.99)	0.53
Intracranial haemorrhage	0.44 0.71	0.71 0.88	0.62 (0.42–0.92) 0.81 (0.41–1.60)	0.51
GI bleeding (upper, lower, rectal)	1.79 2.88	1.12 1.77	not reported	

Based on safety population on treatment. *Composite of major plus non-major clinically relevant bleeding; #rivaroxaban 20 mg od; ‡rivaroxaban 15 mg od

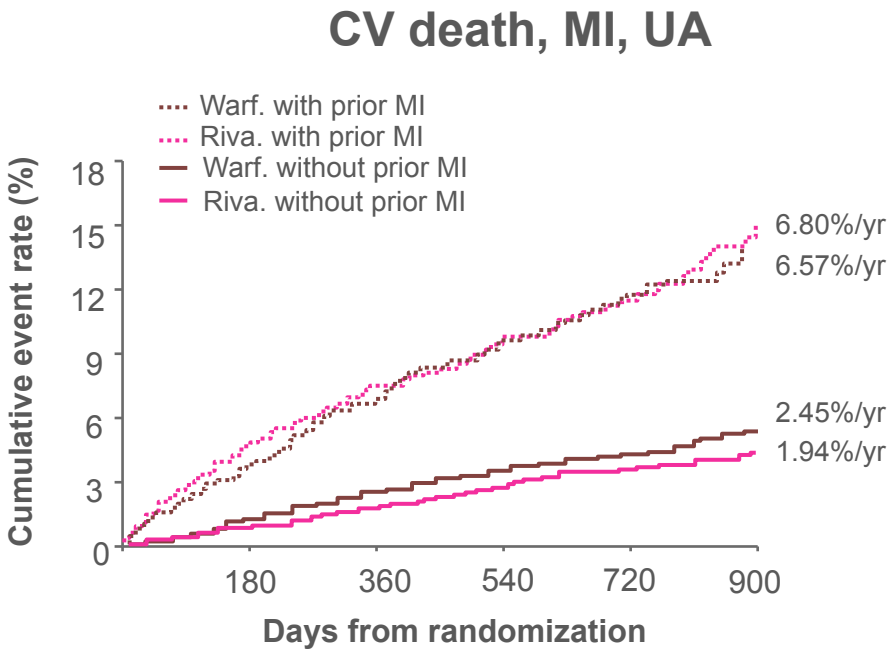
Fox KAA *et al*, *Eur Heart J* 2011;32:2387–2394

ROCKET AF

ROCKET AF: Rivaroxaban in Patients with AF and Prior Myocardial Infarction

Results

- 17% had prior MI
- Primary efficacy and safety outcomes in patients with prior MI were consistent with overall ROCKET AF results
- Overall: 14% reduction in CV death, MI or UA with rivaroxaban vs warfarin (*p*=0.051)



	With prior MI (%/year)		Without prior MI (%/year)		*p*-value (int.)
	Riva.	Warf.	Riva.	Warf.	
Major/NMCR bleeding	18.84	15.51	14.20	14.31	0.035
Major bleeding	4.75	3.61	3.38	3.42	0.112

HR (95% CI) rivaroxaban vs. warfarin:

With prior MI: 1.04 (0.81–1.33);
Without prior MI: 0.79 (0.65–0.96)

Mahaffey KW *et al*, *Eur Heart J* 2014;35:233–241

ROCKET AF

Conclusions

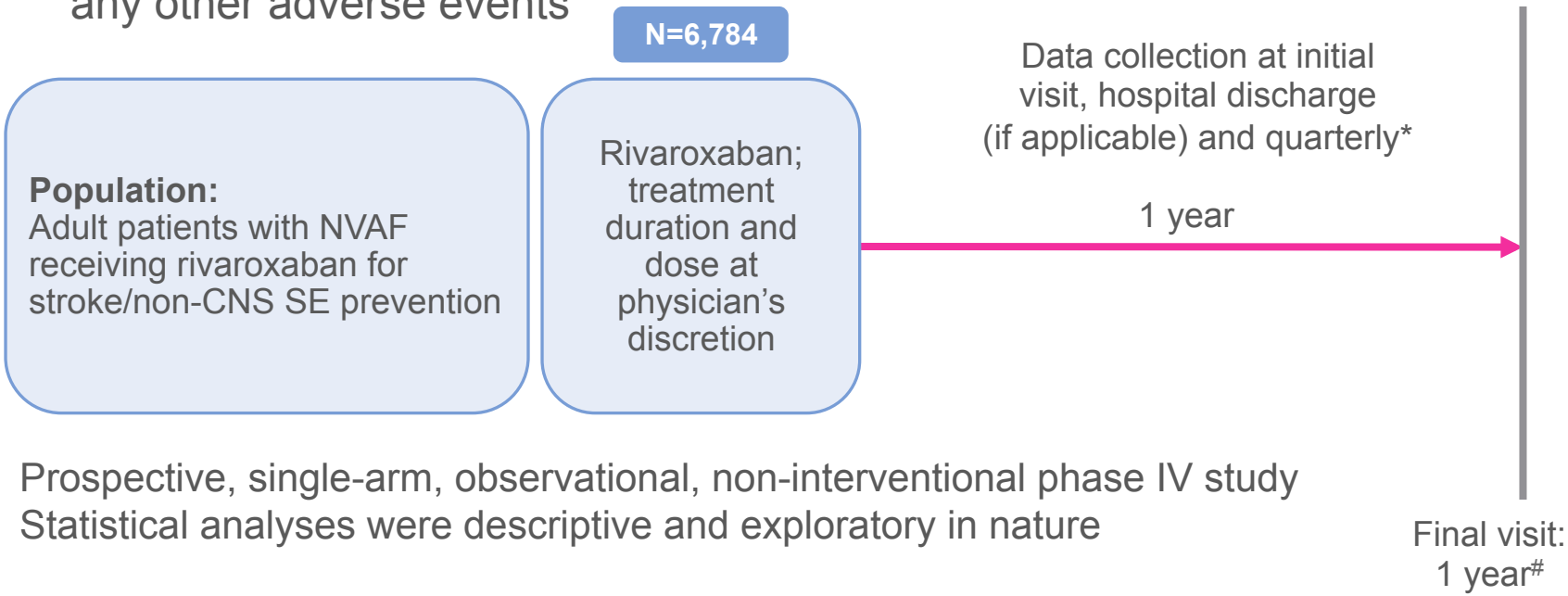
- Many high-risk patients remain untreated or inadequately treated with anticoagulants
- NOACs are recommended by guidelines as they reduce the rate of stroke and intracranial haemorrhage vs. VKAs
- NOACs are effective in high-risk cohorts with favourable benefits compared with risks
- Rivaroxaban once daily is an effective treatment option in many higher-risk cohorts, including in those with moderate renal dysfunction, older age, prior MI etc.

Why is Real World Evidence Needed Given the Positive Outcomes of Phase III trials?

- Phase III studies
  - Gold standard for evaluating efficacy and safety against the current standard of care
  - Support marketing approval by regulatory authorities
- However…
  - Strict protocols and inclusion/exclusion criteria may exclude some patients
    - Limit translation of results from phase III studies to real world populations
    - Event rates, patient characteristics (i.e. co-morbidities), and adherence/ persistence may not fully reflect real world settings
- Real world studies
  - Unselected patient populations typical of those seen in routine clinical practice
  - Observational design with little interference in patient management
  - Provide additional information on rare safety events or routine clinical practice such as management of serious bleeding

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

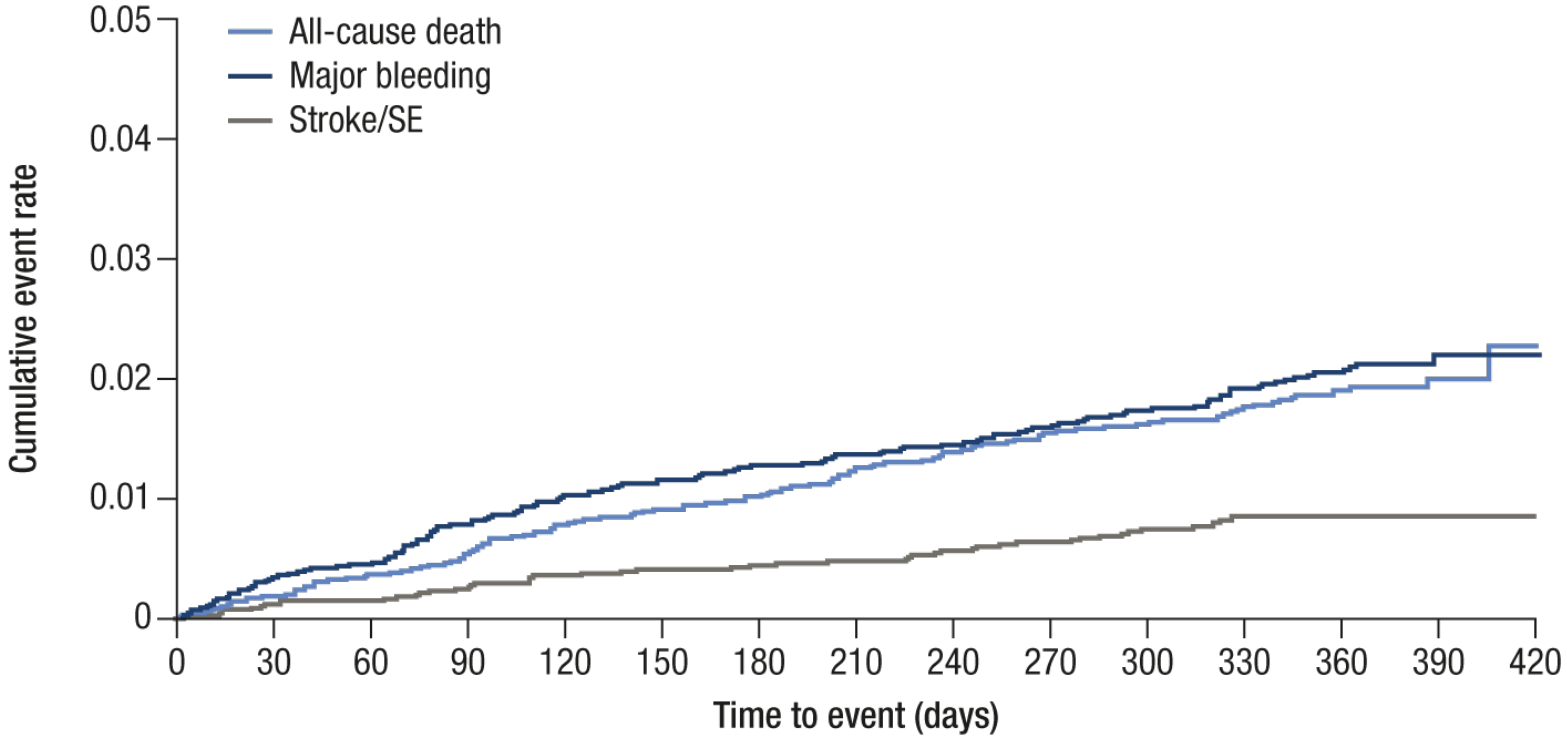
XANTUS: Baseline Demographics – Clinical Characteristics

	Rivaroxaban (N=6784)
Age (years)	
Mean ± SD	71.5±10.0
Age <65, n (%)	1478 (21.8)
Age ≥65–≤75, n (%)	2782 (41.0)
Age >75, n (%)	2524 (37.2)
Gender (male): n (%)	4016 (59.2)
Weight (kg): mean ± SD	83.0±17.3
BMI (kg/m^2): mean ± SD	28.3±5.0
BMI >30 kg/m^2, n (%)	1701 (25.1)
AF, n (%)	
First diagnosed	1253 (18.5)
Paroxysmal	2757 (40.6)
Persistent	923 (13.6)
Permanent	1835 (27.0)
Missing	16 (0.2)

	Rivaroxaban (N=6784)
Creatinine clearance, n (%)	
<15 ml/min	20 (0.3)
≥15–<30 ml/min	75 (1.1)
≥30–<50 ml/min	545 (8.0)
≥50–≤80 ml/min	2354 (34.7)
>80 ml/min	1458 (21.5)
Missing	2332 (34.4)
Existing co-morbidities, n (%)	
Hypertension	5065 (74.7)
Diabetes mellitus	1333 (19.6)
Prior stroke/non-CNS SE/ TIA	1291 (19.0)
Congestive HF	1265 (18.6)
Prior MI	688 (10.1)
Baseline hospitalization, n (%)	1226 (18.1)

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

XANTUS: Cumulative Rates (Kaplan–Meier) for Treatment-Emergent Primary Outcomes



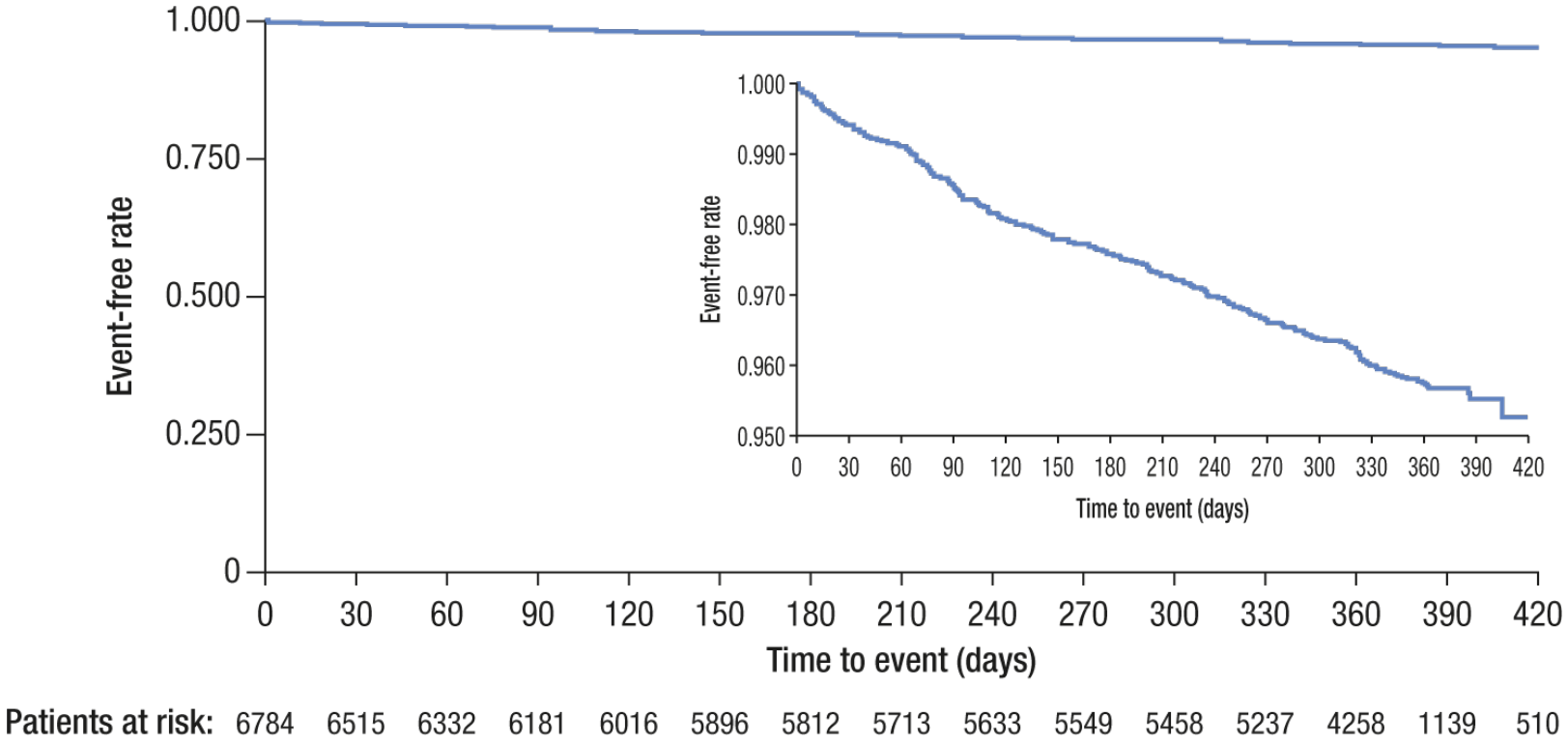
Patients at risk:

All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/SE	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513

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

XANTUS: Event-Free Rate (Kaplan–Meier) for Treatment-Emergent Primary Outcomes

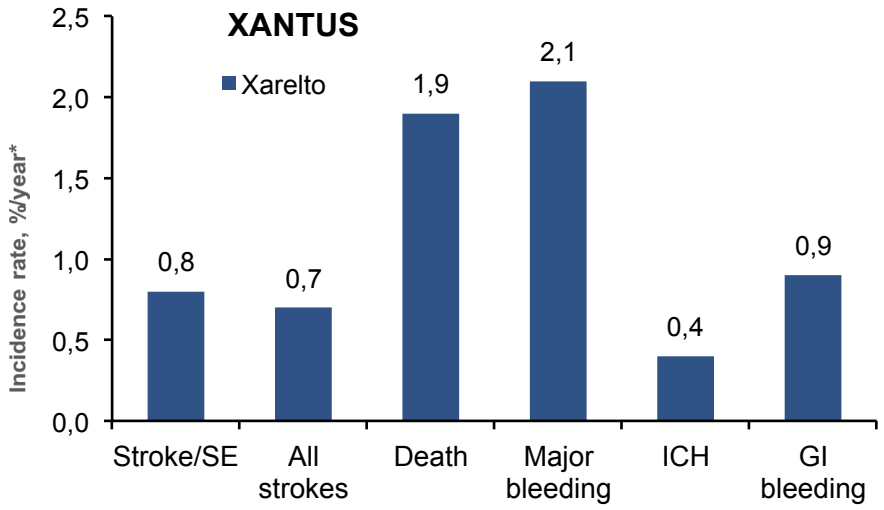
- In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding or stroke/SE

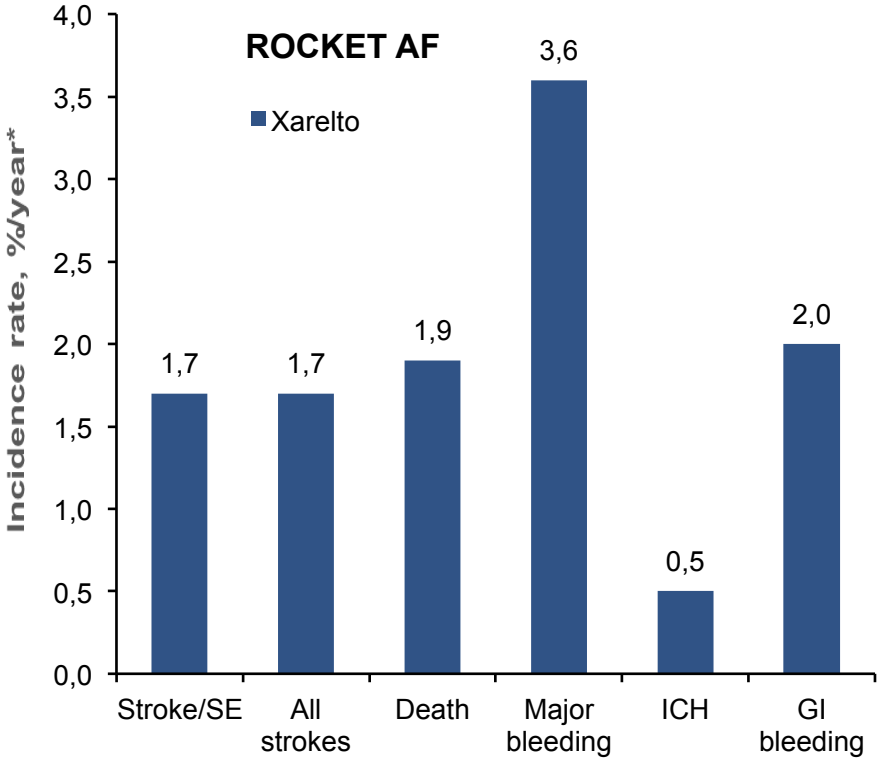


1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	$CHADS_2$	Prior stroke#
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%





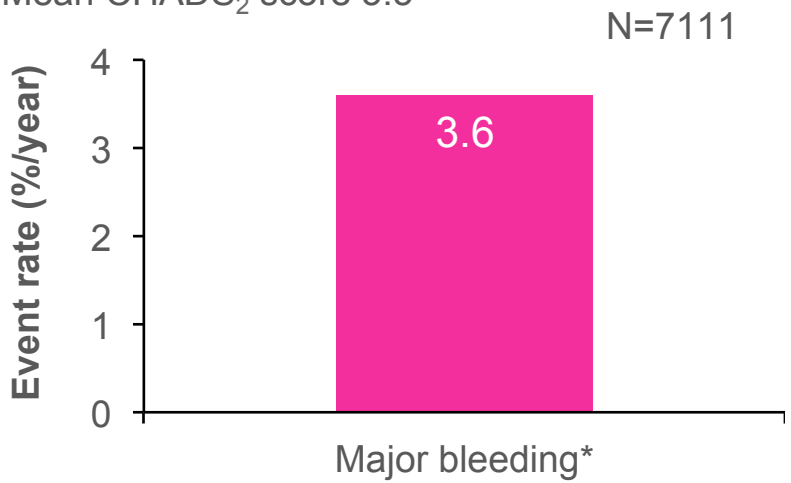
#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

Rivaroxaban Safety Profile in Real Life was Consistent with Findings from ROCKET AF

ROCKET AF[1]

Mean $CHADS_2$ score 3.5

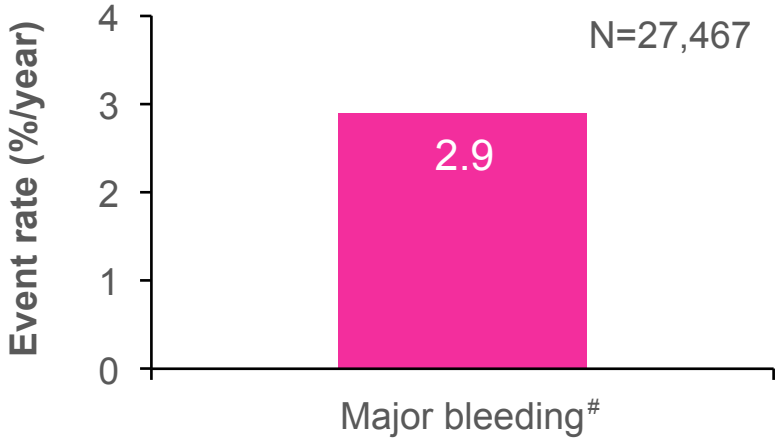


Clinical endpoint	% (n)
ICH	0.8 (55)
Fatal bleeding	0.4 (27)
Major GI bleeding	3.2 (224)

Median duration of treatment exposure was 590 days

US DoD PMSS[2]

Mean $CHADS_2$ score 2.2



Clinical endpoint	% (n)
ICH	0.1 (36)
Fatal bleeding	<0.1 (14)
Major GI bleeding	1.5 (423)

Rivaroxaban users were followed for 455 days

Results are not intended for direct comparison

***Major bleeding definitions according to ISTH; #major bleeding was defined by the Cunningham algorithm[3]**

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Tamayo S *et al*, *Clin Cardiol* 2015;38:63-68;
3. Cunningham A *et al*, *Pharmacoepidemiol Drug Saf* 2011;20:560–566

Similar Risk of Gastrointestinal Bleeding with Novel OACs Compared with Warfarin in Real Life

Population based retrospective cohort study[1]

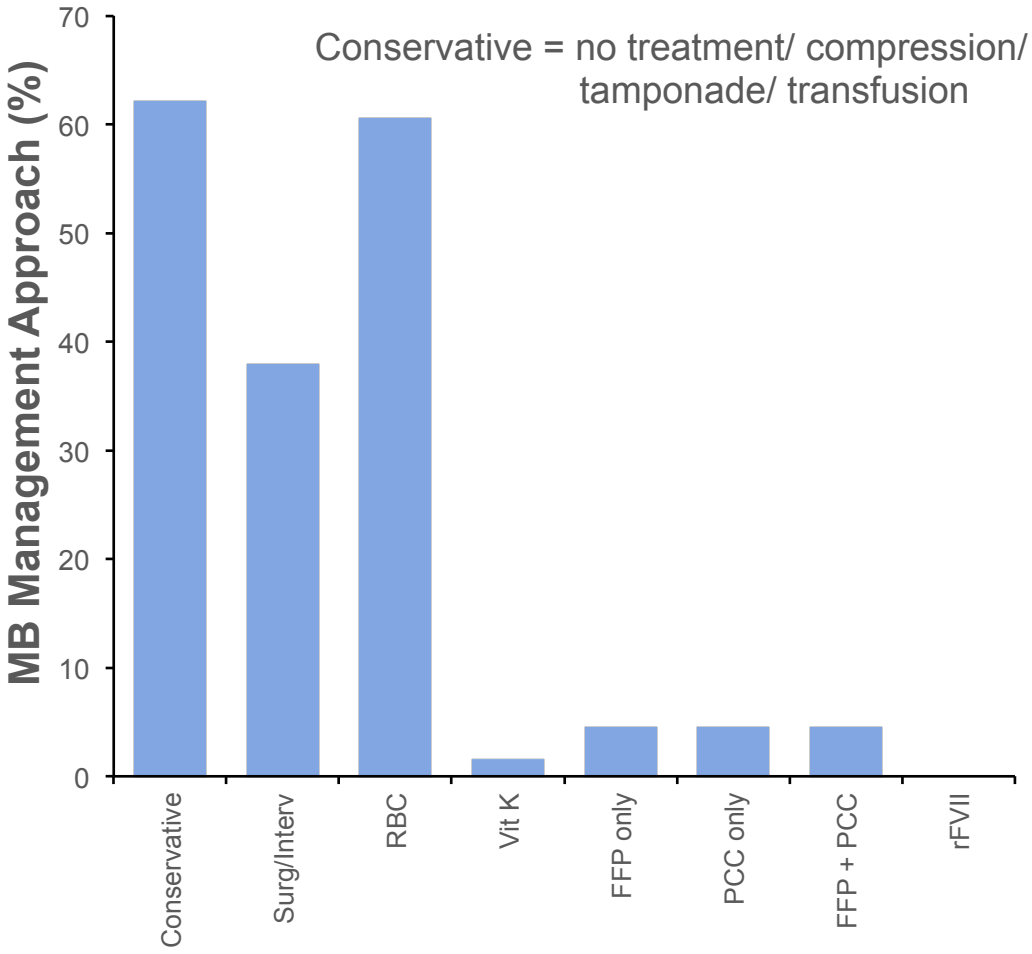
- Patients: 4907 dabigatran, 1649 rivaroxaban, 39,607 warfarin

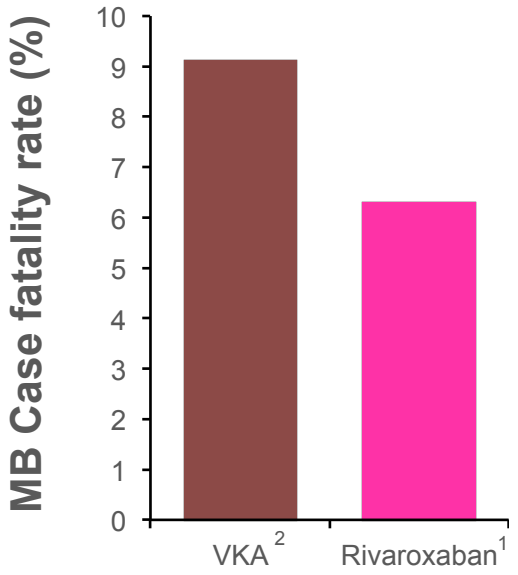
Analysis (reference group warfarin)	Dabigatran	Rivaroxaban
All patients:		
Adjusted HR (95% CI)	1.21 (0.96–1.53)	0.98 (0.36–2.69)
Patients <65 years:		
Adjusted HR (95% CI)	1.34 (0.98–1.83)	1.03 (0.33–3.18)
Patients >65 years:		
Adjusted HR (95% CI)	1.07 (0.75–1.53)	0.62 (0.18–2.08)

- Results are similar to a recent observational study from the US that reported no statistically significant differences in real-life rates of bleeding between rivaroxaban and warfarin (HR for major bleeding 1.08, 95% CI 0.71–1.64)[2]

1. Chang HY *et al*, *BMJ* 2015;350:h1585; 2. Laliberté F *et al*, *Curr Med Res Opin* 2014;30:1317–1325

Dresden NOAC Registry: Outcomes of Major Bleedings May Be Better with Rivaroxaban than Those Reported for VKAs





- Most MB cases could be treated conservatively, rarely requiring procoagulants[1]

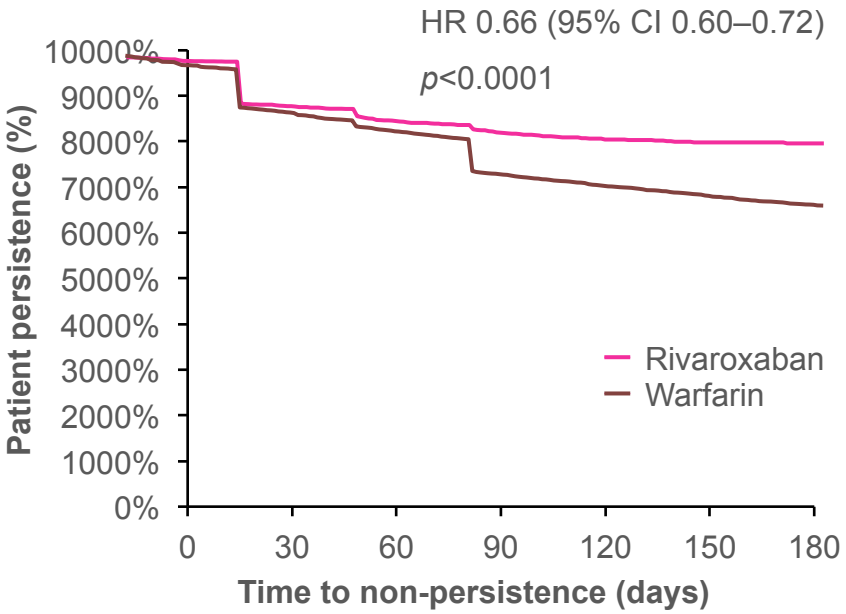
- With Rivaroxaban Case-fatality rate was 6.3% at day 90 after bleeding-related hospitalization compared to 9.1% with VKA
- Different studies report Case fatality rates of VKA-related major bleeding of 15% - 20%[3–5]

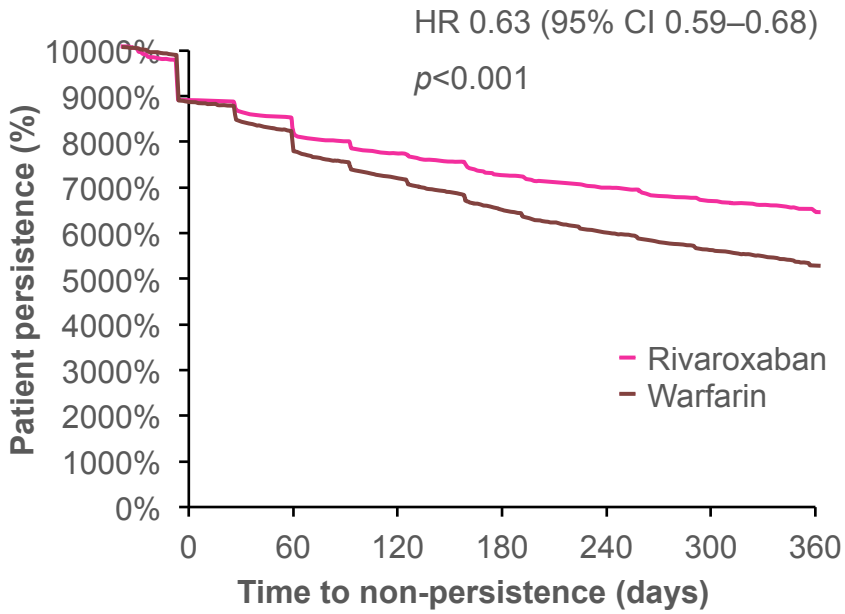
1. Beyer-Westendorf J *et al*, *Blood* 2014;124:955–962; 2. Michalski F *et al, Thromb Haemost* 2015;114 [epub ahead of print]; 3. Gomes *et al*, *CMAJ* 2013;185:E121–E127: 4. Linkins *et al*, *Ann Intern Med* 2003;139:893–900; 5. Halbritter *et al*, *J Thromb Haemost* 2013;11:651–659

In Real Life AF Patients Stayed Longer on Rivaroxaban Than on Warfarin

Two retrospective U.S. database analyses

- Matched sample included 3654 rivaroxaban and 14,616 warfarin patients[1]
- 7259 rivaroxaban patients were matched 1:1 with warfarin patients[2]





Patients were significantly more persistent with Rivaroxaban than with Warfarin

1. Laliberté F *et al*, *Curr Med Res Opin* 2014;30:1317–1325; 2. Nelson WW *et al*, *Curr Med Res Opin* 2014;30:2461–2469

Conclusion

- Real life evidence of novel OACs is important to delineate effectiveness and safety in patients with AF[1-3]
- In XANTUS, rivaroxaban demonstrated low rates of stroke/SE and major bleeding, including intracranial and GI bleeding[4]
- Major bleedings in Real Life can normally be conservatively managed[3]
- Rivaroxaban once daily in real life is associated with higher patient persistence compared with warfarin [5–8]

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68;
3. Beyer-Westendorf *et al*, *Blood* 2014;124;955–962; 4. Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466; 5. Laliberté F *et al*, *Curr Med Res Opin* 2014;30:1317–1325; 6. Nelson WW *et al*, *Curr Med Res Opin* 2014;30:2461–2469; 7. Beyer-Westendorf J *et al*, *Europace* 2015;17:530–538; 8. Beyer-Westendorf J *et al*, *Thromb Haemost* 2015;113:1247–1257