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Dalla "real life" le conferme di rivaroxaban nel paziente anziano

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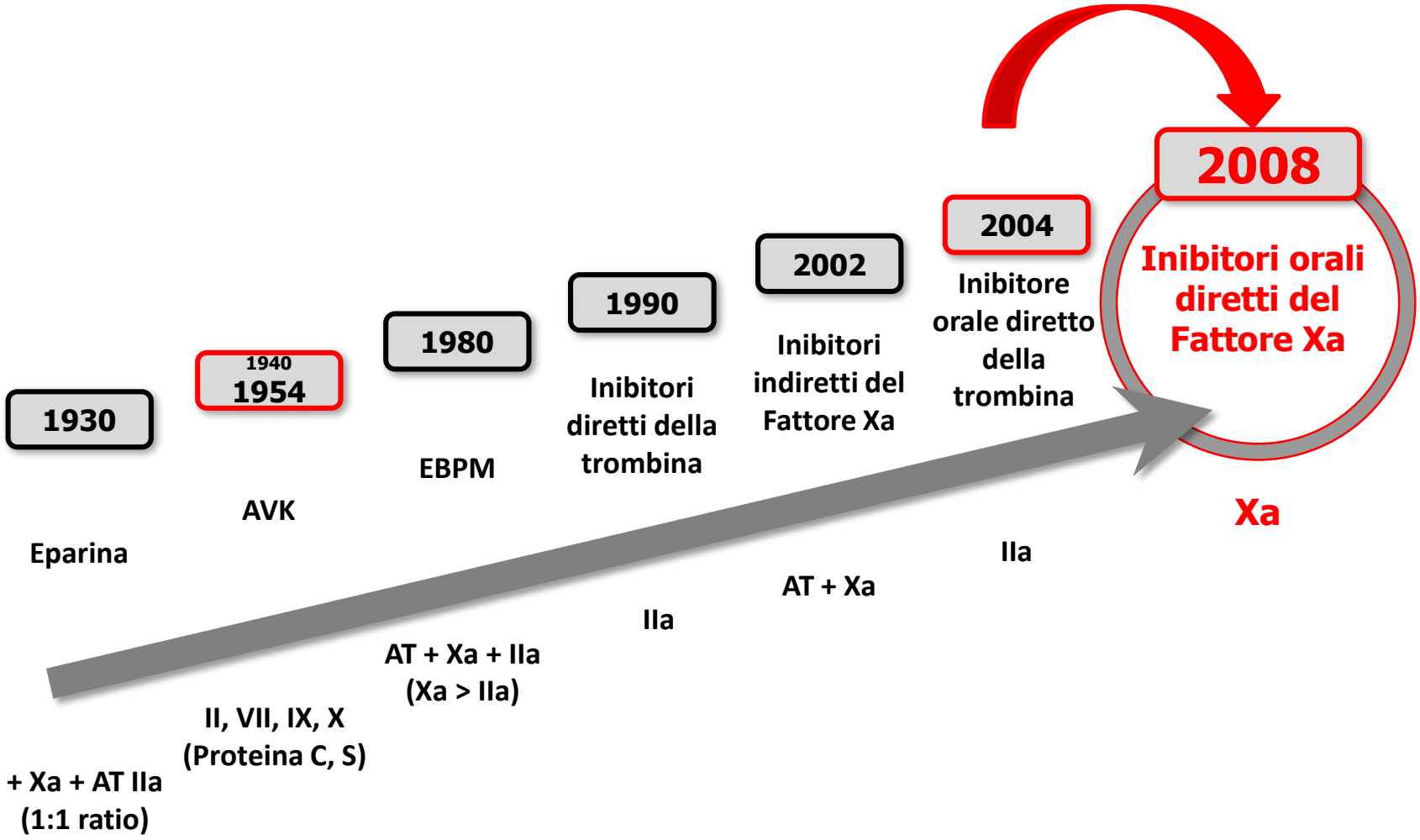
L'evoluzione dei farmaci anticoagulanti



Nat Rev Drug Discov 2011;10:61-75

Nowadays there is substantial clinical evidence to support the use of NOACs for stroke and systemic embolism protection in patients with NVAF (**ESC-2012 guidelines**);

Rivaroxaban has well-established efficacy and safety in challenging patients in a clinical setting (**ROCKET AF study; *NEJM* 2011;365:883–891**). But clinical evidence alone shows us only one part of the picture;

To see the whole picture, there is a need for prospective safety and efficacy data from a large number of unselected patients in everyday clinical practice as well (**EMA requirement**).

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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

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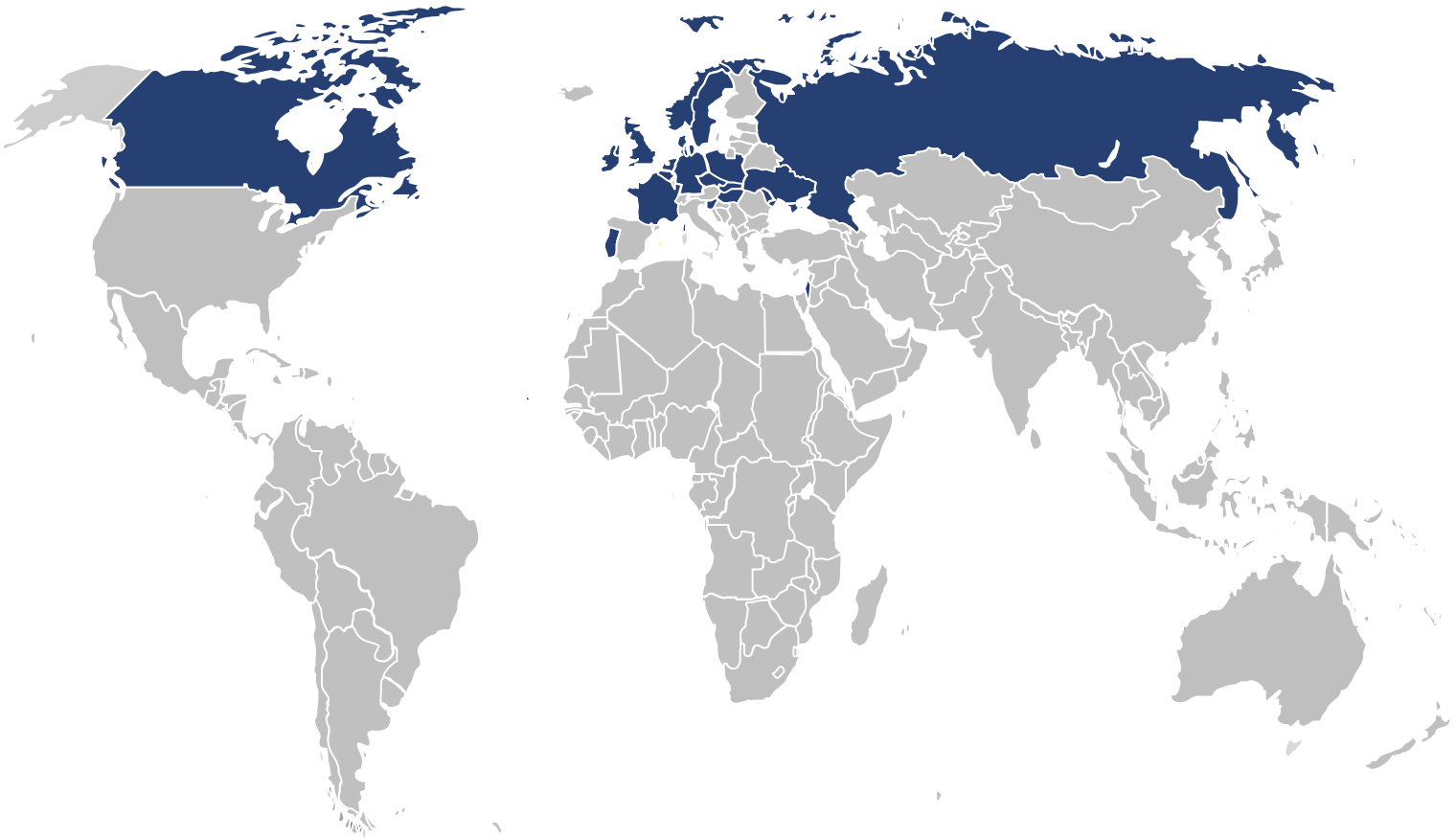
XANTUS: Participating Countries

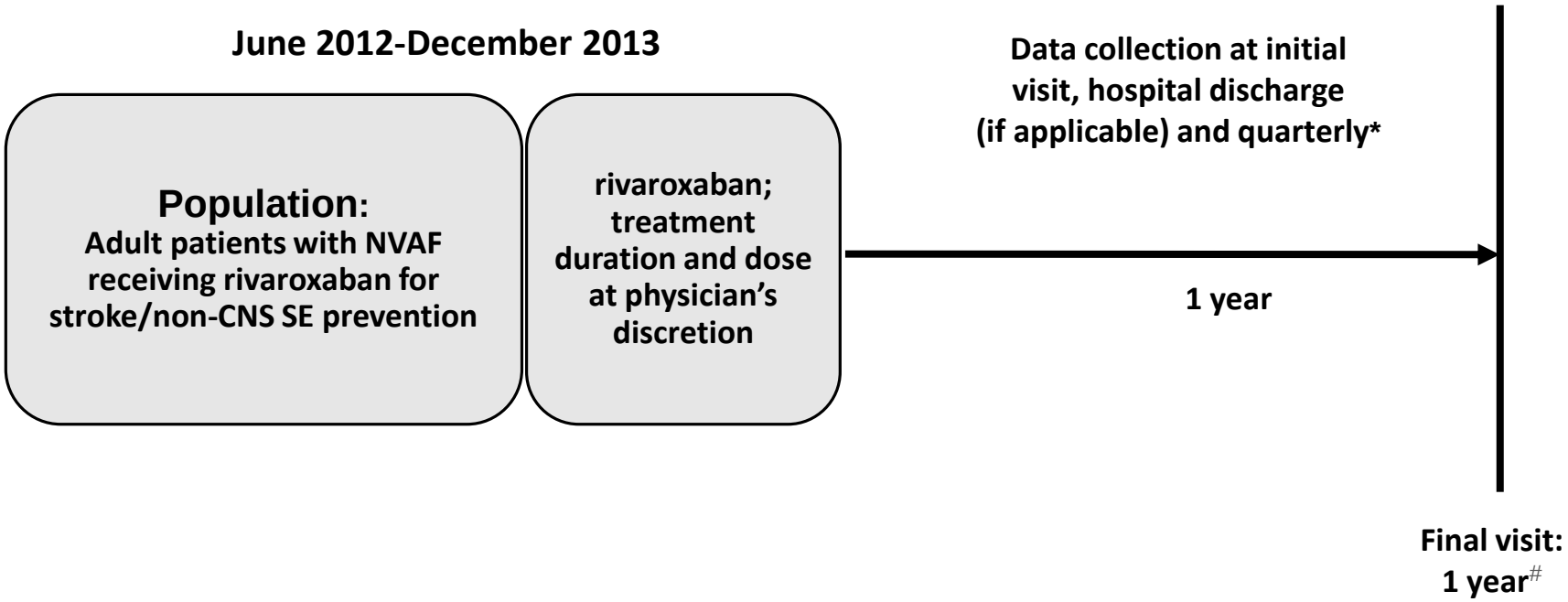


- Patients were enrolled from June 2012 to December 2013 from 311 centres in Europe and Canada
- Participating countries included: Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Israel, Moldova, The Netherlands, Norway, Poland, Portugal, Russia, Slovakia, Slovenia, Sweden, Ukraine, UK

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

XANTUS: Study Design

Prospective, single-arm, observational, non-interventional phase IV study



***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: Medication and Follow-up

Decisions about rivaroxaban prescription were at the discretion of the treating physician, including dose and duration of therapy.

Label-recommended rivaroxaban doses for stroke prevention in NVAF are 20 mg once daily (od) for patients with normal renal function or mild impairment (creatinine clearance [CrCl] ≥50 mL/min) and 15 mg od for patients with moderate or severe renal impairment (CrCl 15–49 mL/min; e.g. in Europe).

XANTUS: Outcomes to be captured

Primary outcomes

- Major bleeding (ISTH definition)
- All-cause mortality
- Any other serious AEs
- Any other AEs

Secondary outcomes

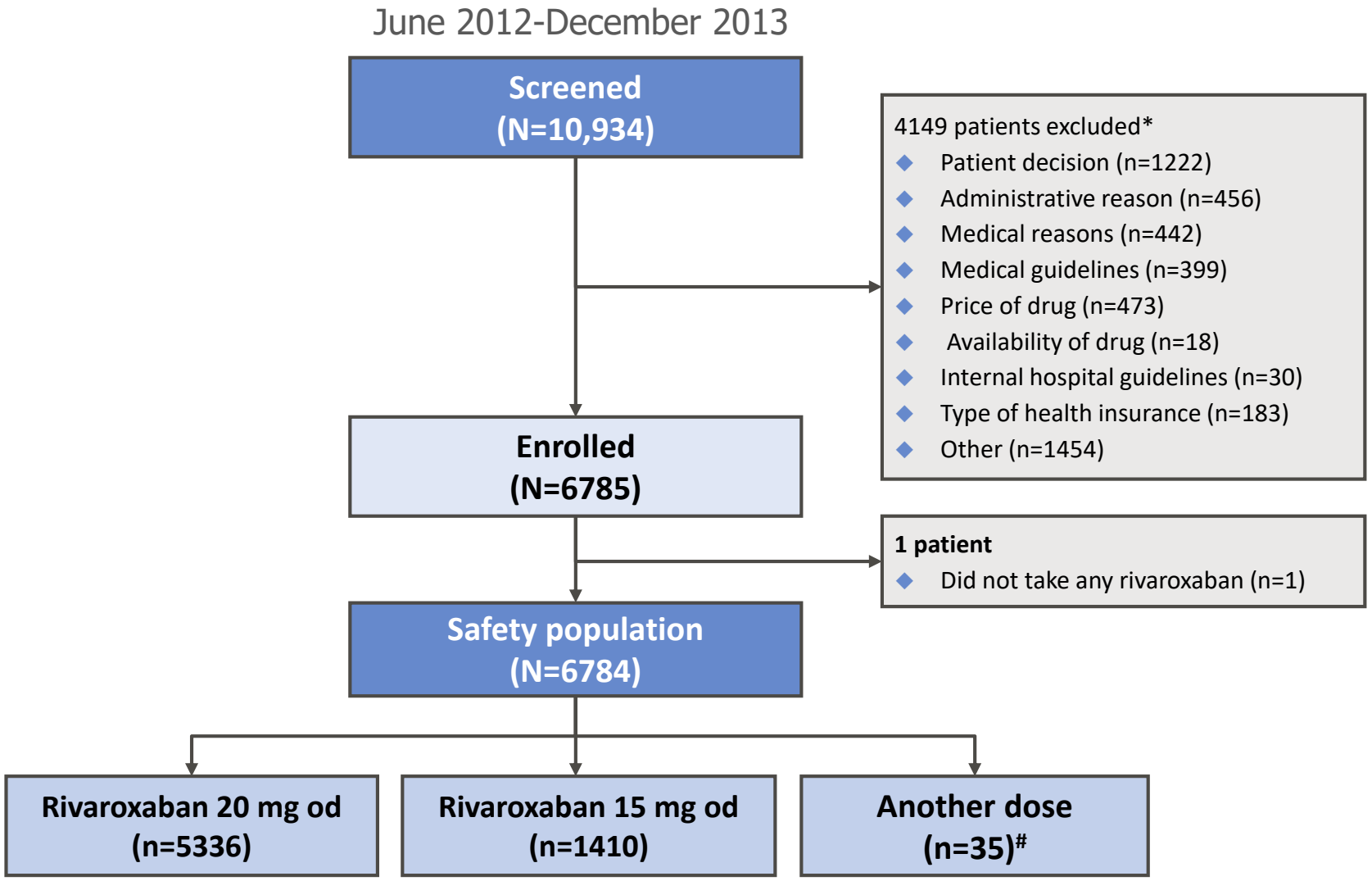
- Symptomatic thromboembolic events
- Non-major bleeding events
  - AEs and serious AEs across risk scores
  - AEs and serious AEs in subgroups

Other outcomes

- Patient treatment satisfaction
- Persistence with therapy
- Healthcare resource use
- Concomitant medication use
- Reasons for switching/interrupting rivaroxaban therapy

Camm AJ et al, Vasc Health Risk Manag 2014;10:425–434

XANTUS: Patient Disposition



***Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion; #other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)**

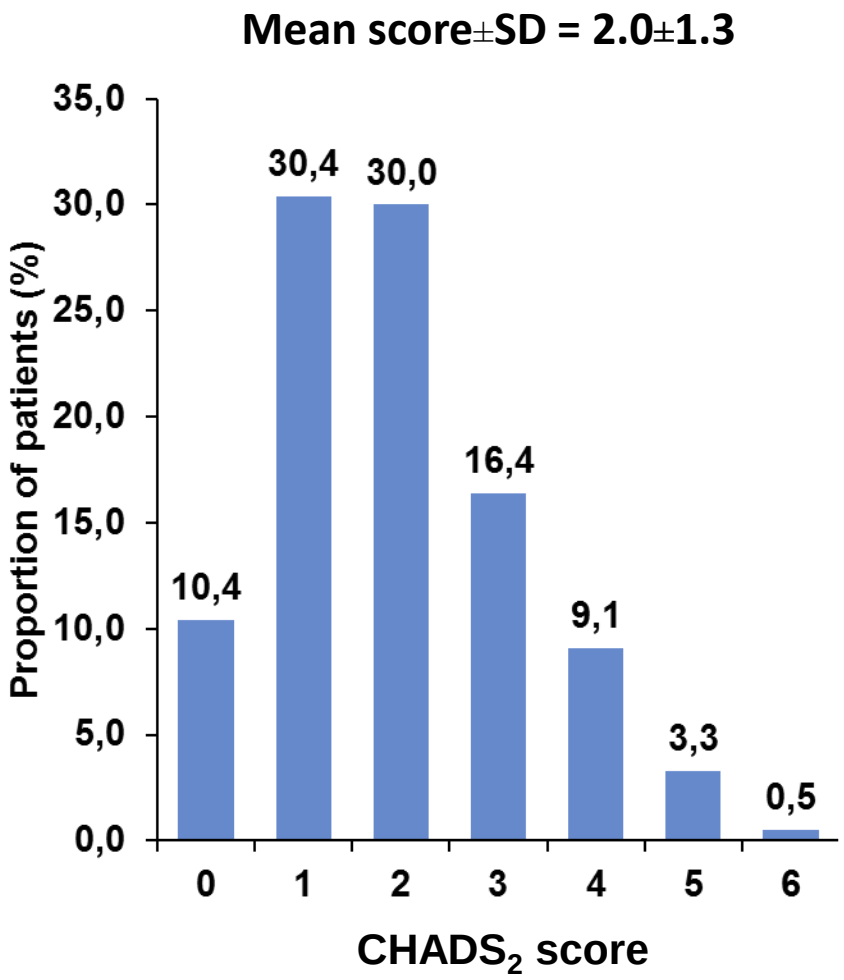
Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466

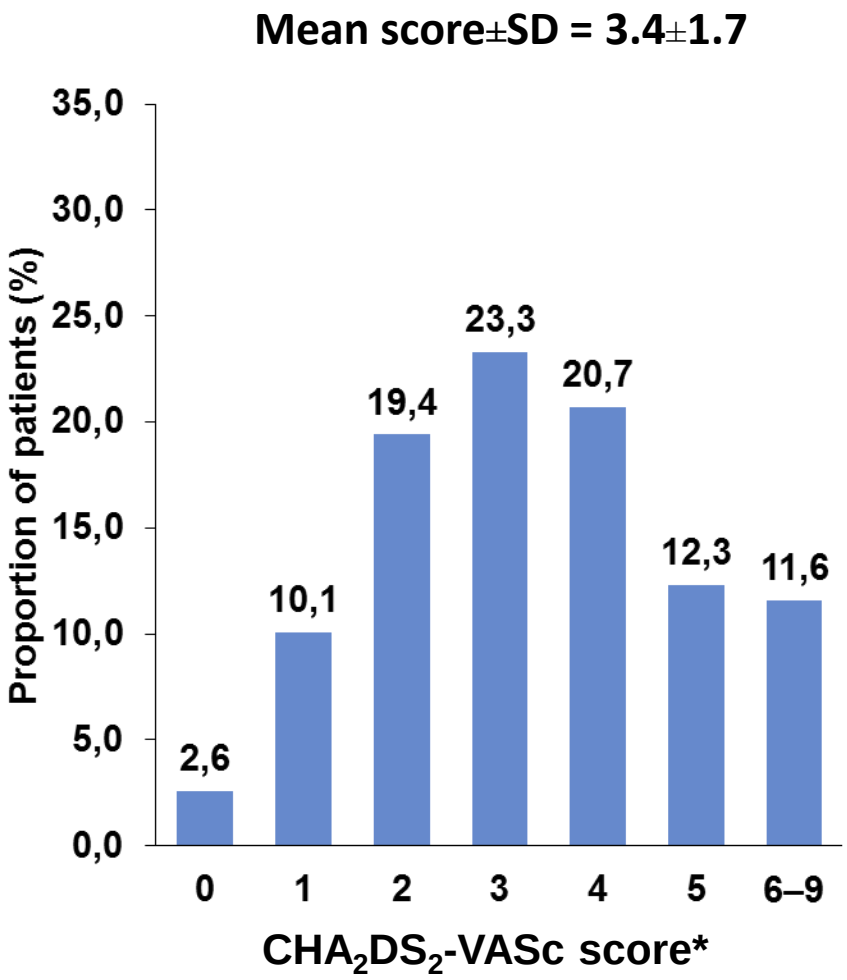
XANTUS: Baseline Demographics - Clinical Characteristics

	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)

XANTUS: Baseline Demographics - Distribution of Stroke Risk Factors





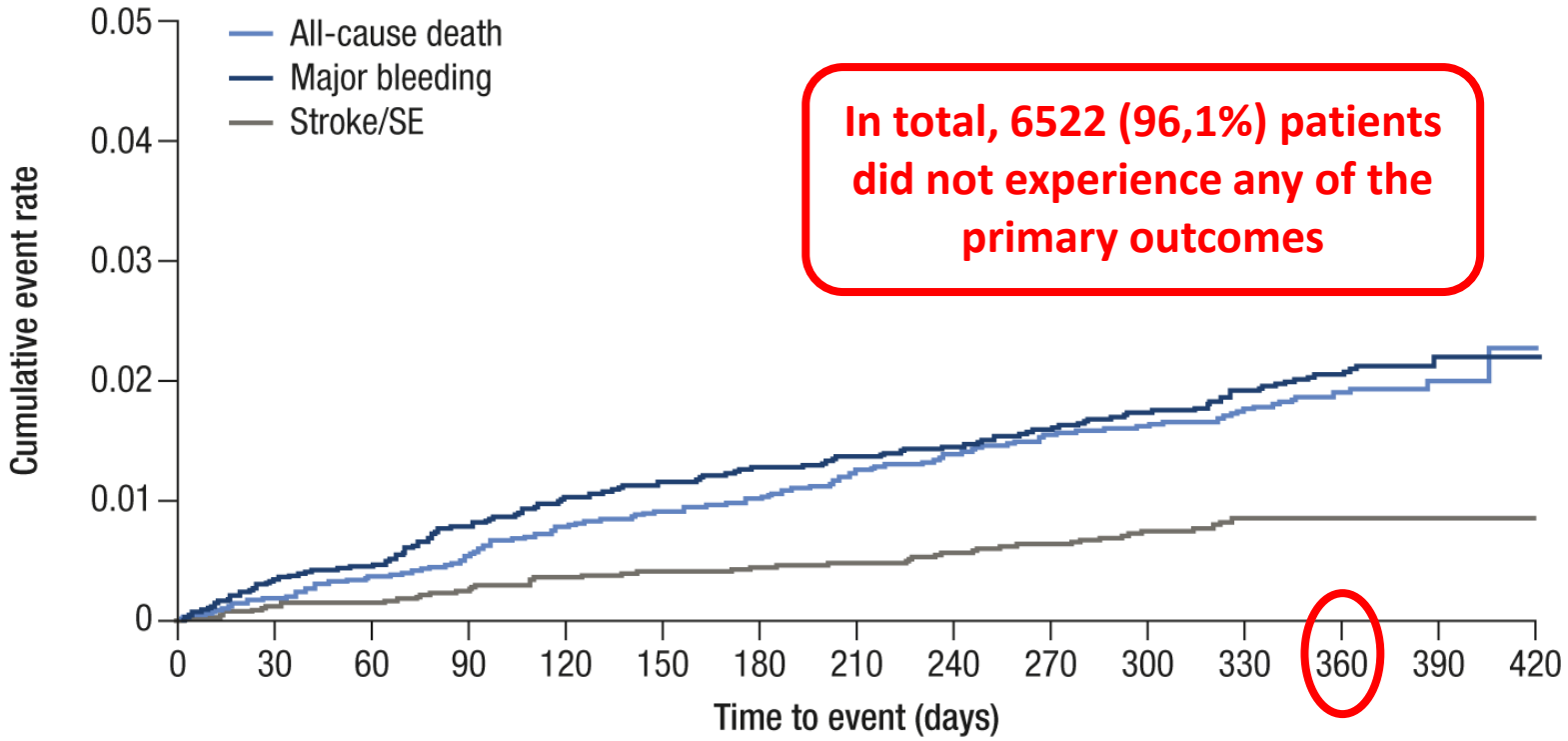
*3 patients had missing CHA_2DS_2-VASc scores

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

XANTUS: Baseline Demographics - Prior Antithrombotic Use

	Rivaroxaban (N=6784)
VKA	
Experienced	3089 (45.5)
Naïve	3695 (54.5)
Prior use of antithrombotics, n (%)	
VKA alone	2767 (40.8)
Direct thrombin inhibitor	208 (3.1)
Acetylsalicylic acid (excluding dual antiplatelet therapy)	1224 (18.0)
Dual antiplatelet therapy	68 (1.0)
Factor Xa inhibitor (excluding rivaroxaban)	10 (0.1)
Heparin group	217 (3.2)
Other	55 (0.8)
Multiple	410 (6.0)

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



In total, 6522 (96,1%) patients did not experience any of the 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

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

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

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

XANTUS: Adjudicated Causes of Death

	Number of patients (N=118* 1,7%), n (%)
Cardiovascular	49 (41.5)
Cardiac decompensation, heart failure	24 (20.3)
Sudden or unwitnessed death	14 (11.9)
MI	6 (5.1)
Non-haemorrhagic stroke	4 (3.4)
Dysrhythmia	1 (0.8)
Cancer	23 (19.5)
Other	16 (13.6)
Bleeding	12 (10.2)
Extracranial haemorrhage	5 (4.2)
Intracranial bleeding	7 (5.9)
Infectious disease	10 (8.5)
Unexplained	9 (7.6)

**Multiple reasons were recorded for the cause of treatment-emergent adjudicated death of some patients

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

XANTUS: Treatment-Emergent Thromboembolic Events

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
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

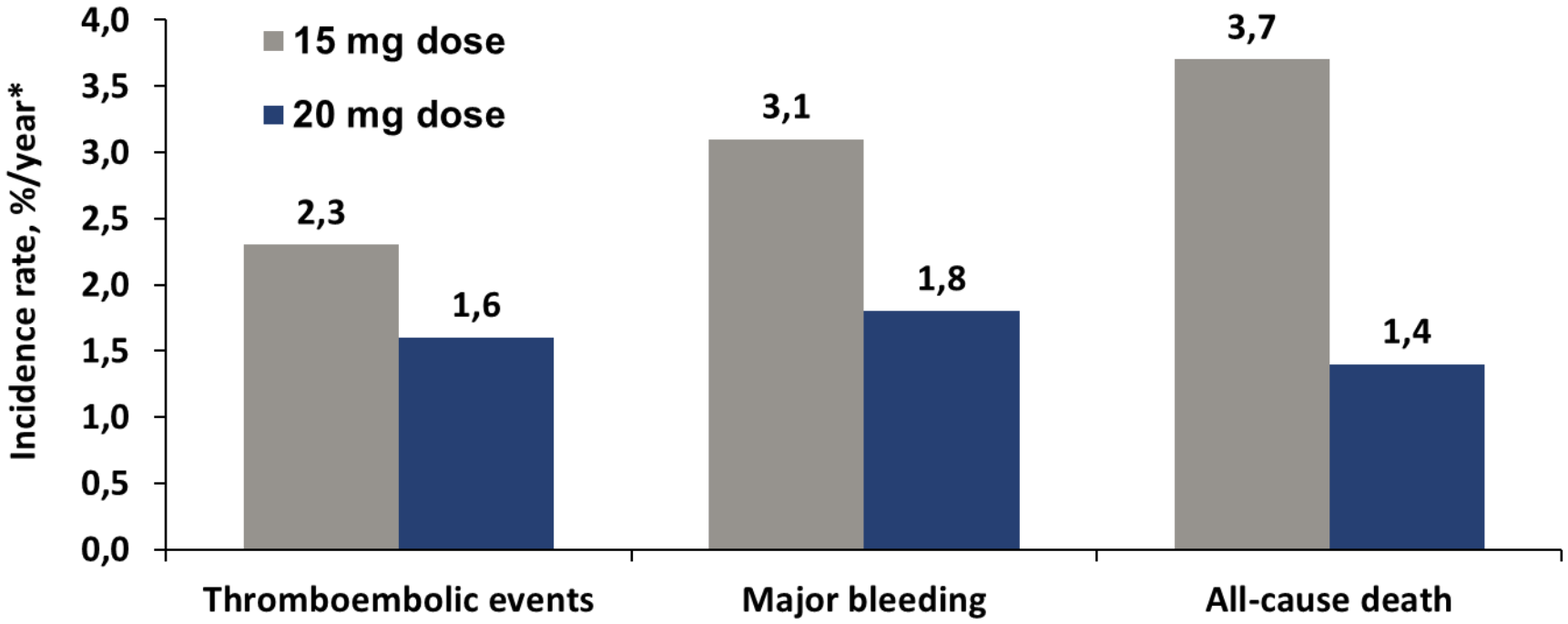
Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466

Xantus: Incidence Rate for Treatment- Major Bleeding and Symptomatic Thromboembolic Events in Different Age Groups

Age (years)	Major bleeding events (per 100 patient-years)	Symptomatic thromboembolic events (per 100 patient-years)
<65	0.9	0.8
65-75	1.7	1.8
>75	3.2	2.3

XANTUS: Outcomes According to Dosing (20/15 mg od)

- **Major bleeding, all-cause death and thromboembolic events (stroke/SE/TIA/MI) occurred at higher incidence rates for the 15 mg od versus the 20 mg od dose**

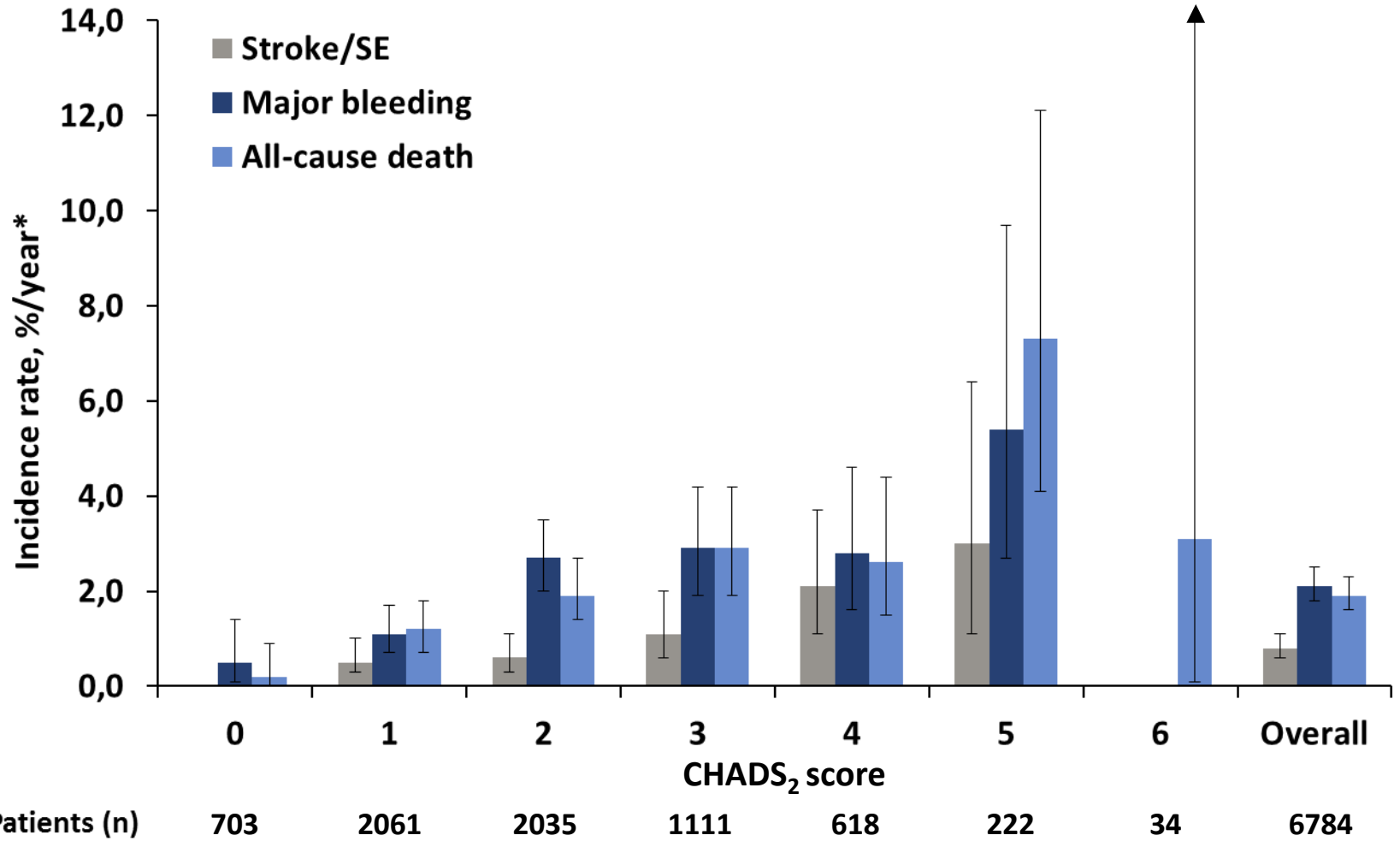


- **Dosing decisions may have been based on other clinical considerations besides impaired renal function**

***Events per 100 patient-years**

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

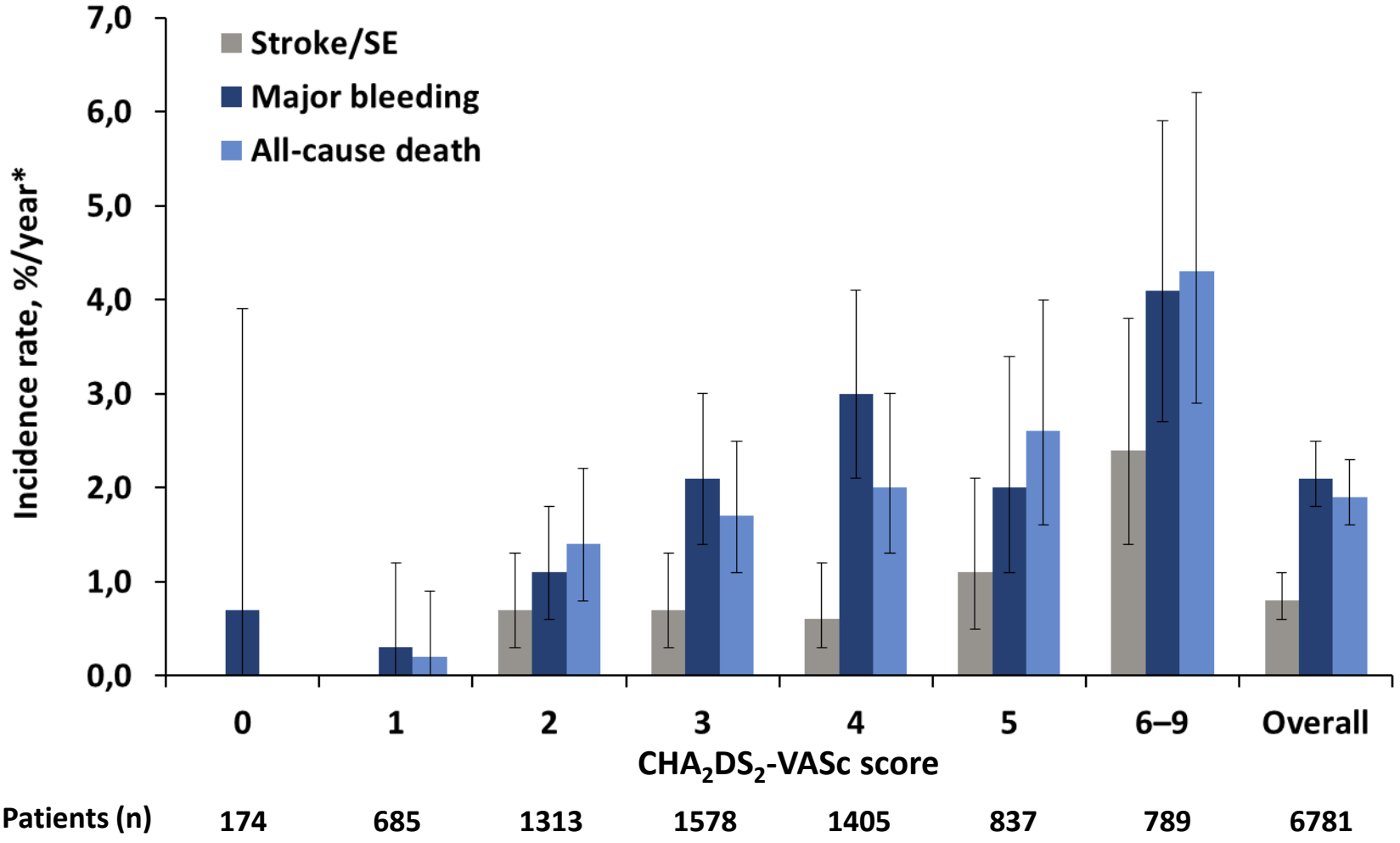
XANTUS: Incident Rate for Treatment-Emergent Stroke/SE, Major Bleeding and All-Cause Death by $CHADS_2$ Score



Events were centrically adjudicated *Events per 100 patient-years

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

XANTUS: Incident Rate for Treatment-Emergent Stroke/SE, Major Bleeding and All-Cause Death by CHA_2DS_2-VASc Score



Events were centrically adjudicated *Events per 100 patient-years

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

What we have learned from Xantus study?

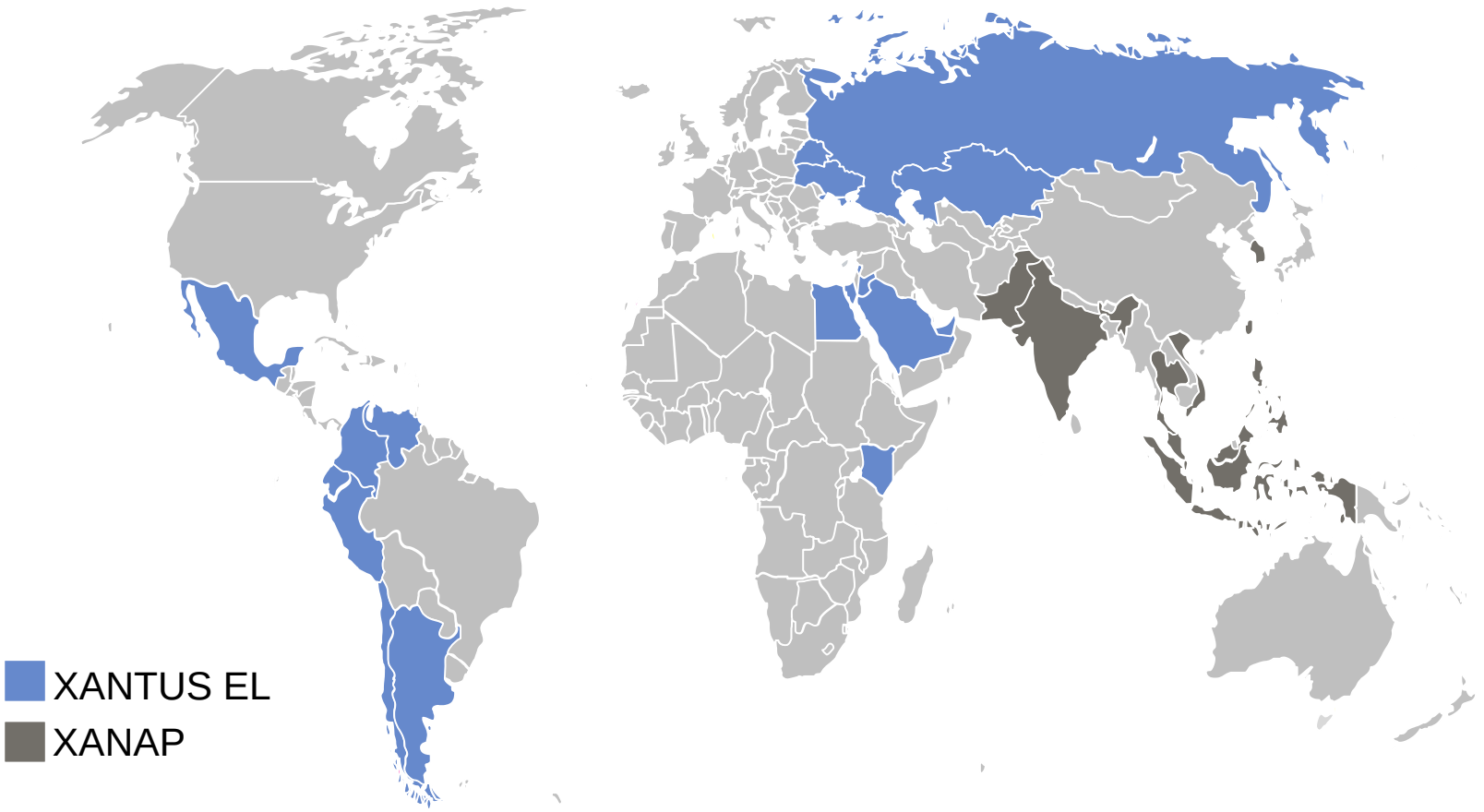
XANTUS showed reassuring safety results with low rates of 2.1%/yr for major bleeding including critical organ bleeding, ICH and fatal bleeding in the real world, consistent with ROCKET AF (3.6%);

The study also showed effective stroke and systemic embolism protection in the real world (0.8%/yr), again, consistent with ROCKET AF (1.7%);

In XANTUS, 96% of patients did not experience any of the outcomes of treatment-emergent stroke or systemic embolism, major bleeding or all-cause death whilst receiving Rivaroxaban;

And finally, persistence rates were at 80% and 75% of patients were satisfied or very satisfied with Rivaroxaban over the one year observational period, giving the confidence of simple dosing for the patients.

Regional Studies Following XANTUS Protocol: XANTUS EL and XANAP



- XANTUS EL study in Eastern EU, Middle East, Africa and Latin America (NCT01800006)[1]

  Argentina, Belarus, Chile, Colombia, Ecuador, Egypt, Jordan, Kazakhstan, Kenya, Lebanon, Mexico, Peru, Russia, Saudi Arabia, Ukraine, United Arab Emirates, Venezuela

- XANAP study in Asia (NCT01750788)[2]

  Planned recruitment: India, Indonesia, Korea, Malaysia, Pakistan, Philippines, Singapore, Taiwan, Thailand, Vietnam

1. www.clinicaltrials.gov/ct2/show/NCT01800006; 2. www.clinicaltrials.gov/ct2/show/NCT01750788