Consistent safety outcome of Xarelto from RCT to RWE

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이 종영

NOACs approved for risk reduction of stroke or systemic embolism in patients with non-valvular AF

	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
Action	Activated factor Xa (FXa) inhibitor	Direct thrombin inhibitor	Activated factor Xa (FXa) inhibitor	Activated factor Xa (FXa) inhibitor
Dose	20 mg QD 15 mg QD*	150 mg BID 110 mg BID	5 mg BID 2.5 mg BID	60 mg QD 30 mg QD
Phase III clinical trial	**ROCKET-AF** [5]	RE-LY [1]	ARISTOTLE [2] AVERROES [3]	ENGAGE-AF [4]

Please note this information is not from head-to-head Randomized Control Trial. Therefore should be carefully interpreted

*중등도의 신장애 환자(크레아티닌 청소율 30-49 mL/min) 및 중증의 신장애 환자(크레아티닌 청소율 15-29 mL/min)에서의 권장용량은 1일 1회, 1회 15 mg입니다. 자렐토는 '비판막성 심방세동 환자에서 뇌졸중 및 전신 색전증의 위험감소'로 국내에서 허가를 받았습니다. 바이엘코리아는 국내에서 허가 받지 않은 사항으로 의약품을 사용하는 것을 권장하지 않으며, 각 해당 제품의 제품설명서를 참고해 주시기 바랍니다.

1. Connolly et al, N Engl J Med 2009; 361:1139-51
2. Granger et al, N Engl J Med 2011; 365:981-92
3. Connolly et al, N Engl J Med 2011; 364:806-17
4. Ruff et al, Am Heart J 2010; 160:635-41
5. Patel et al, N Engl J Med 2011;365:883-91

Angiology. 2005;90:840–4.

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

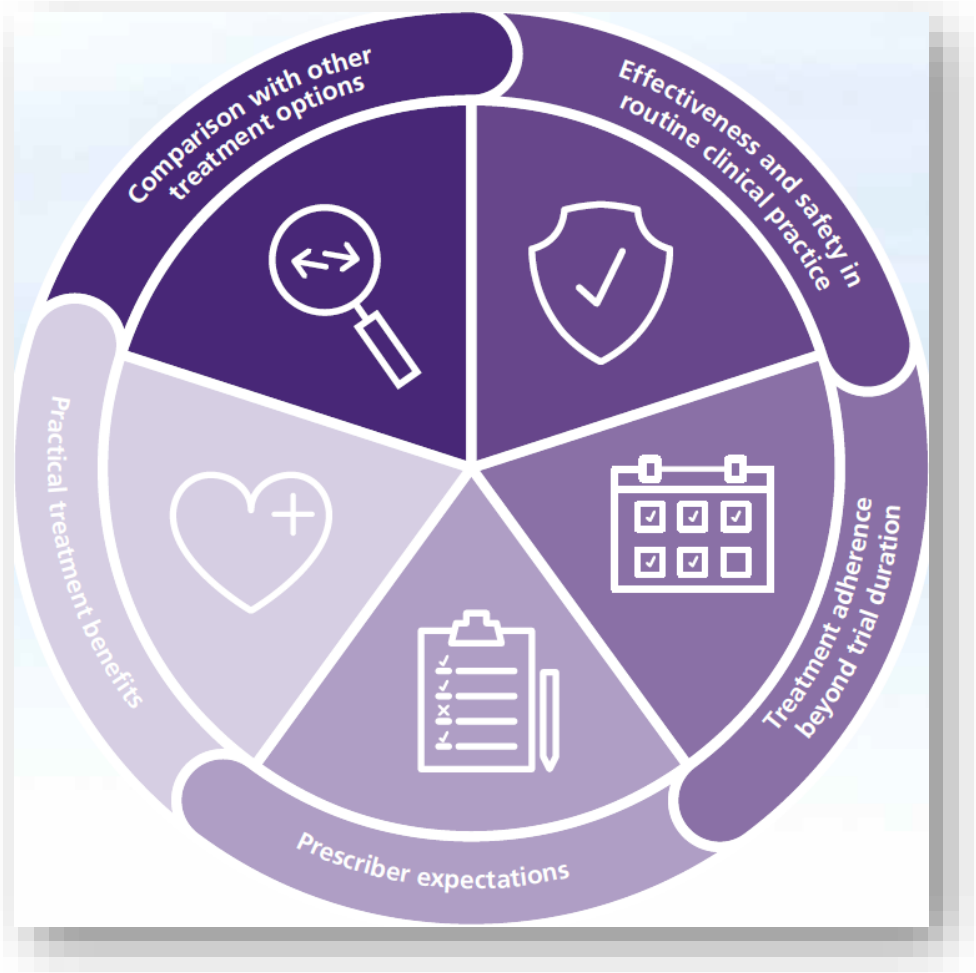
- **Phase III studies**
  - Gold standard for evaluating efficacy and safety against the current standard of care
  - Support marketing approval by regulatory authorities

- **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

Akobeng A.K. Arch Dis Child. 2005;90:840–4.

RWE can demonstrate effectiveness, safety, persistence, adherence and dosing for a treatment in patients in routine clinical practice



- RWE is generated from wide and diverse patient populations to test the effectiveness and safety of a treatment in an uncontrolled setting that is reflective of routine clinical practice
- When analyzed correctly, RWE complements the data from RCTs and supports better-informed decisions around the use of medicines in response to individual patients' needs

ISPOR. Market access and reimbursement: the increasing role of real-world evidence. Available at: https://www.ispor.org/research_pdfs/48/pdffiles/PHP280.pdf

RWE is Not All the Same:
Different Methodologies Have Their Own Strengths & Limitations

	Strengths/Can support	Caveats/Limitations
Prospective registries/ non-interventional studies	◆ Understanding of treatment patterns, adherence/ persistence, safety, comparative effectiveness resource use and patient reported outcomes	◆ Choice of comparator vs sample size and selection/ reporting bias
Retrospective comparative clinical or claims database studies	◆ Understanding of treatment patterns, persistence, safety, effectiveness, healthcare resource use	◆ No clinical meaningful guidance for management of clinical situations; single country experience, selection bias ◆ All databases are not equal; some are better for some analyses than others
Case series	◆ Identify specific case-based lessons for practice	◆ Usually driven by a set of specific factors with limited application in a wider setting

ISPOR., 2007. Accessed online: https://www.ispor.org/workpaper/RWD_TF/

XANTUS Pooled Analysis

Prospective Real-World Evidence on Rivaroxaban in Patients with Atrial Fibrillation

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Rationale for the XANTUS Programme: Differences in Clinical Characteristics of Patients with AF Worldwide

XANTUS POOLED

Latin America

AF-related stroke and associated morbidity is increasing, partly due to poor control of key risk factors[1]

Asia

Higher overall stroke risk in Asian patients compared with Caucasian populations[4]

Middle East

Patients are ~10 years younger than in Western countries but the incidence of diabetes and obesity is higher[2,3]

Africa

Patients have higher rates of heart failure and left ventricular systolic dysfunction than Western patients[2]

1. Massaro AR, Lip GYH, *Arq Bras Cardiol* 2016:doi: 10.5935/abc.20160116; 2. Healey JS *et al*, *Lancet* 2017:388:1161–1169;
3. Zubaid M *et al, Circ Cardiovasc Qual Outcomes* 2011:4:477–482; 4. Sabir I *et al, Nat Rev Cardiol* 2014;11:290–303

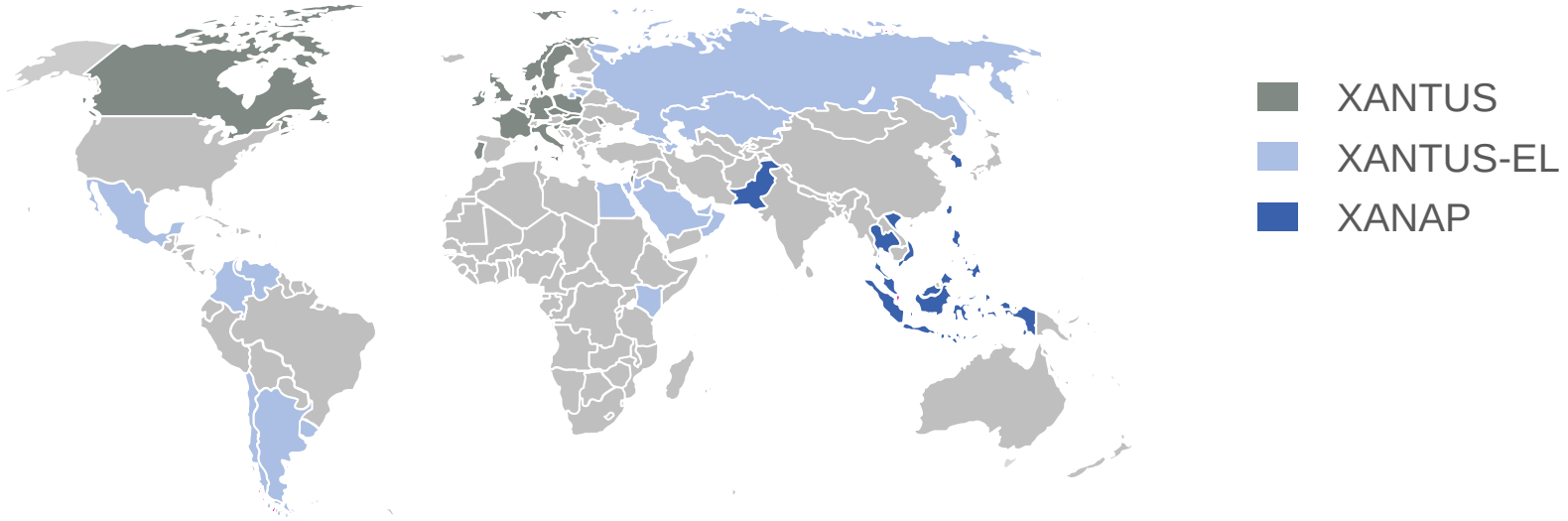
First Prospective NOAC Real-World study, XANTUS Programme: >11,000 Patients Receiving Rivaroxaban Globally

XANTUS POOLED

XANTUS
Europe, Israel and Canada

XANTUS-EL
Middle East, Eastern Europe, Africa and Latin America

XANAP
Asia Pacific

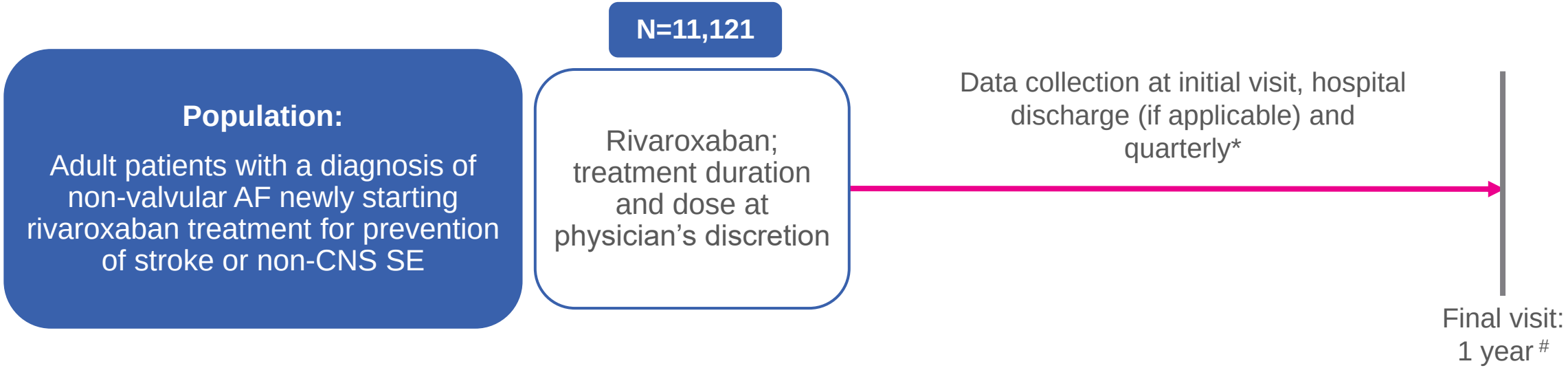


- XANTUS pooled is the largest pre-planned, prospective, observational analysis of a single NOAC, rivaroxaban, used for stroke prevention in patients with AF
  - The analysis uses combined data from three multicentre non-interventional studies enrolling >11,000 patients from 47 countries worldwide

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

XANTUS Programme Study Design

- **XANTUS, XANTUS-EL and XANAP study protocols were aligned**
- Prospective, single-arm, non-interventional studies
  - Major outcomes adjudicated by an **independent Central Adjudication Committee**

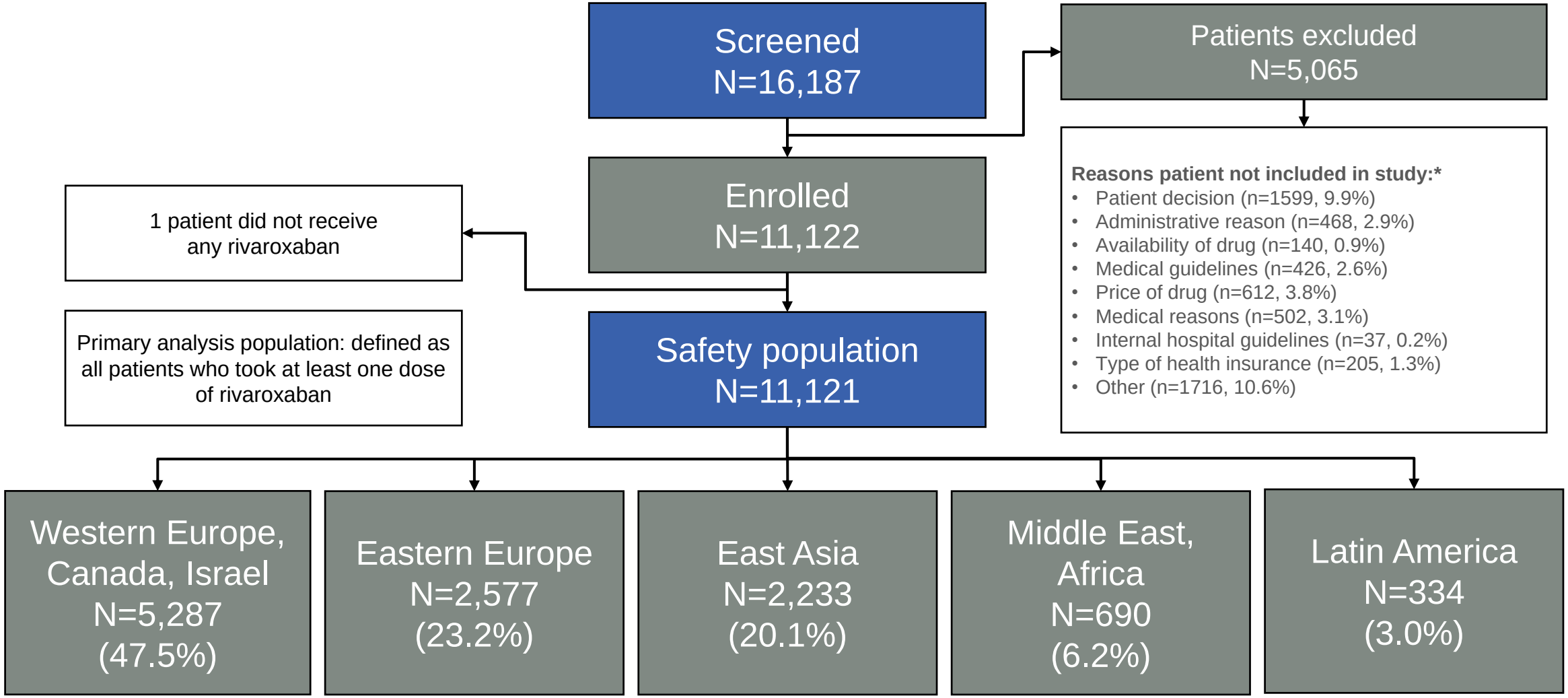


Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events

*Exact referral dates for follow-up visits were not defined (every 3 months recommended); #for rivaroxaban discontinuation after ≤1 year, the observation period ended 30 days after the last dose

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

XANTUS Global Pooled Analysis



*Some patients could have > 1 reason for exclusion

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Baseline Demographics and Clinical Characteristics of XANTUS Pooled Safety Population

XANTUS POOLED

	Rivaroxaban (N=11,121)
Age, years, mean ± SD	70.5±10.5
Male, n (%)	6345 (57.1)
Weight, kg, mean ± SD	80.0±17.8
BMI, kg/m^2, mean ± SD	28.0±5.2
>30, n (%)	2523 (22.7)
$CHADS_2$ score, mean ± SD	**2.0±1.3**
CHA_2DS_2-VASc score, mean ± SD	**3.5±1.7**
HAS-BLED score, mean ± SD	2.0±1.1
AF, n (%)	
First diagnosed	2049 (18.4)
Paroxysmal	4147 (37.3)
Persistent	1798 (16.2)
Permanent	3084 (27.7)
Missing	43 (0.4)
Prior anticoagulation therapy, n (%)	8048 (72.4)

	Rivaroxaban (N=11,121)
First available CrCl, ml/min, n (%)	
<15	47 (0.4)
≥15 to <30	166 (1.5)
≥30 to <50	1061 (9.5)
≥50 to ≤80	3478 (31.3)
>80	2320 (20.9)
Missing	4049 (36.4)
Co-morbidities, n (%)	
Hypertension	8476 (76.2)
Diabetes mellitus	2484 (22.3)
Prior stroke/non-CNS SE/TIA	**2372 (21.3)**
Congestive heart failure	2359 (21.2)
Prior MI	994 (8.9)
Hospitalization at baseline, n (%)	2072 (18.6)

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Baseline Demographics and Clinical Characteristics: Main Differences in XANTUS by Region

XANTUS POOLED

Western Europe/Canada/Israel and Middle East/Africa
Lowest stroke risk scores

Eastern Europe
Highest prevalence of hypertension, heart failure and prior MI

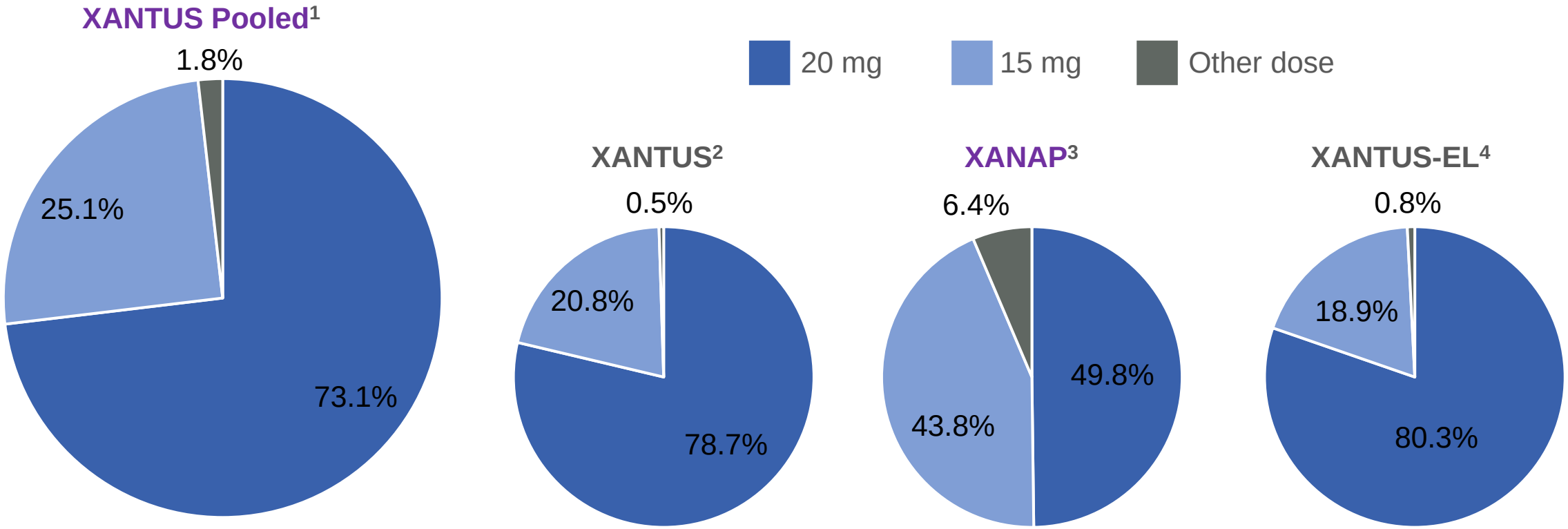
East Asia
Highest prevalence of prior stroke/TIA/non-CNS SE

Middle East, Africa and Latin America
Lowest bleeding risk scores

Eastern Europe and Middle East/Africa
Youngest patients

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

XANTUS Programme: Rivaroxaban Treatment Profile



- Treatment Duration (mean ± SD) was 324.5±117.80 days, with a median of 366 days*
- Treatment Persistence at 1 year was 77.4%

*Interquartile range 330–379 days

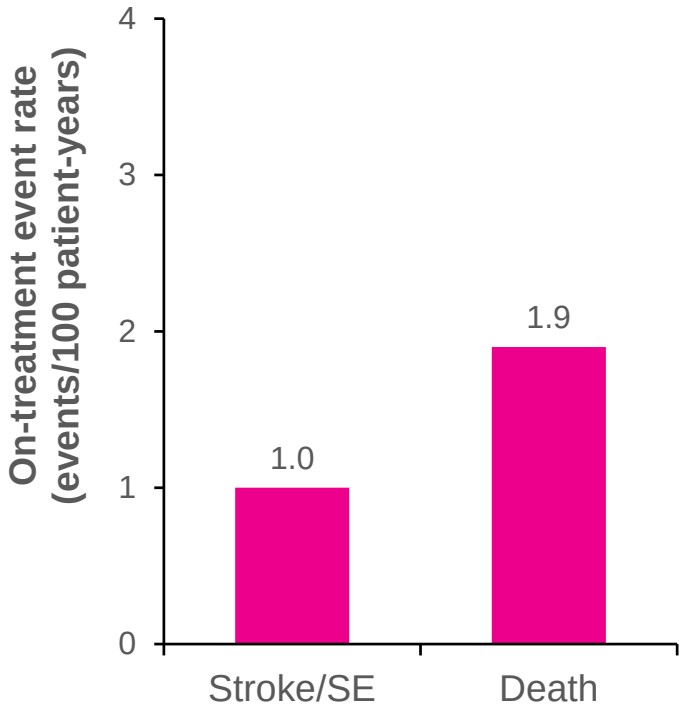
1. Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058; 2. Camm AJ *et al*, *Eur Heart J* 2016;37:1145–1153; 3. Kim YH *et al*, presented at *APHRS* 2016, poster number 2–116; 4. Turpie AGG *et al*, presented at *Cardioalex* 2017, Day 1, Hall A, Session 2

Rivaroxaban Is Highly Effective and Provides a Beneficial Safety Profile in the Real World

XANTUS POOLED

XANTUS Pooled

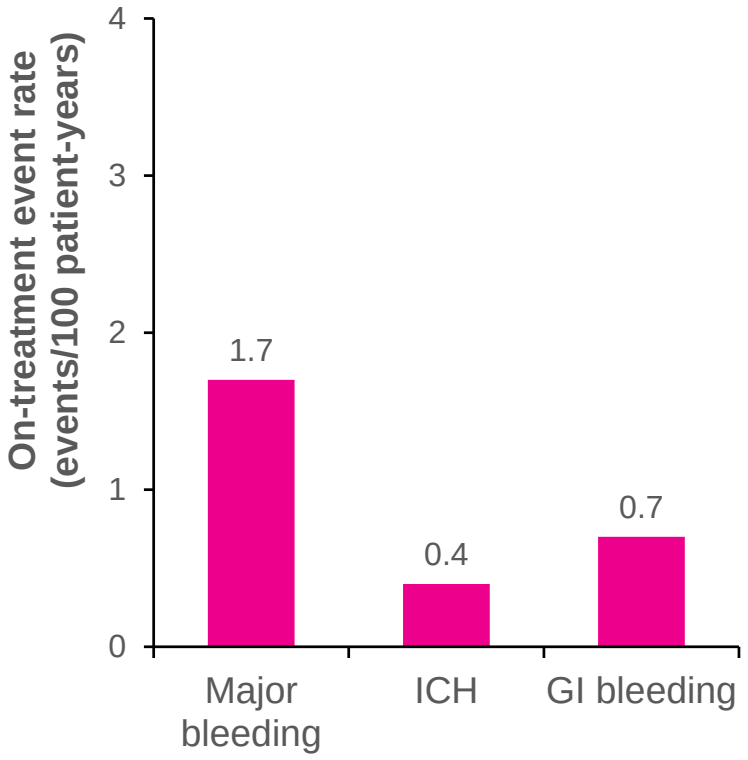
Effectiveness*



Baseline	XANTUS Pooled*
$CHADS_2$, mean	2.0
Age, years, mean	70.5
Heart failure	21%
Hypertension	76%
Diabetes	22%
Prior stroke#	21%
Prior MI	9%

XANTUS Pooled

Safety*

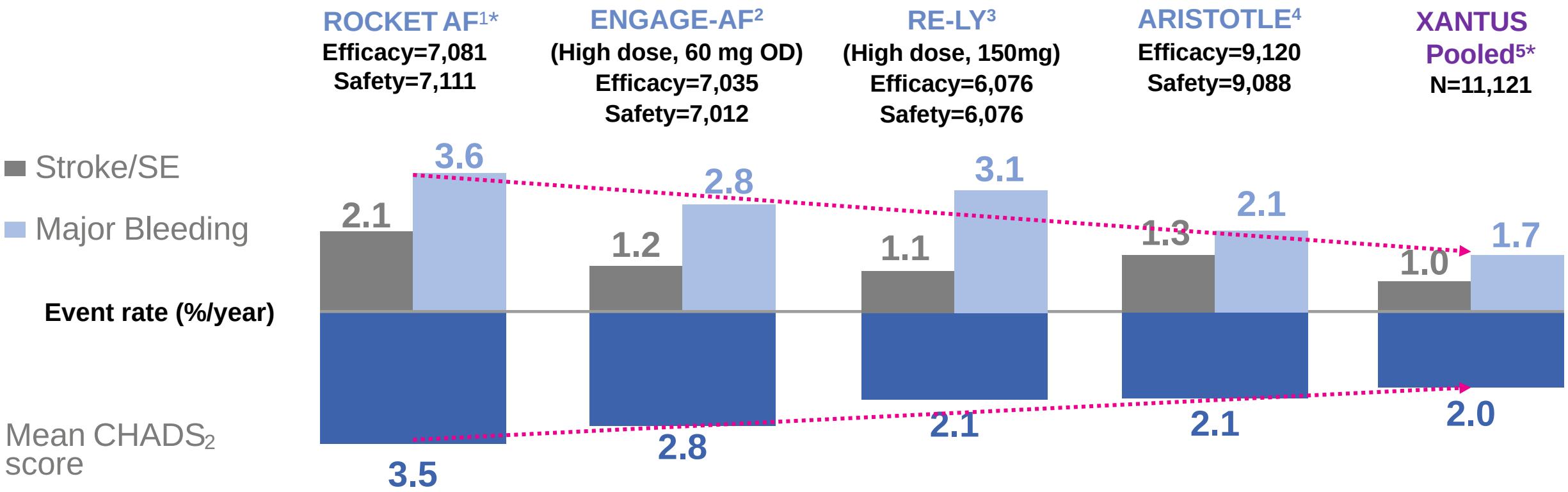


*Results based on safety population n=11,121; #includes prior stroke, SE or TIA

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Risk of stroke/SE and major bleeding are relative to patient's $CHADS_2$ score

XANTUS POOLED



Results are not intended for direct comparison

SE, systemic embolism

Please note this information is from separate, Independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

*Major bleeding definition according to ISTH

1. Patel M.R., et al. *N Engl J Med*. 2011;365(10):883–91. 2. Giugliano R.P., et al. *N Engl J Med*. 2013;369(22):2093-104. 3. Proietti M, et al. J Intern Med. 2018;283(3):282-92. 4. Lopes R.D., et al. *Lancet*. 2012;380(9855):1749–58.
5. Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Adjudicated Treatment-Emergent Bleeding Events in Safety Population

	Incidence proportion, n (%)	Incidence rate, events/ 100 patient-years (95% CI)
Major bleeding	172 (1.5)	1.7 (1.5–2.0)
Fatal*	17 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	62 (0.6)	0.6 (0.5–0.8)
ICH	42 (0.4)	0.4 (0.3–0.6)
Mucosal bleeding	80 (0.7)	0.8 (0.6–1.0)
Gastrointestinal bleeding	71 (0.6)	0.7 (0.6–0.9)
Haemoglobin decrease in ≥2 g/dl	58 (0.5)	0.6 (0.4–0.8)
Transfusion in ≥2 units of packed RBCs or whole blood	73 (0.7)	0.7 (0.6–0.9)
Non-major bleeding events	1195 (10.7)	12.8 (12.1–13.5)

Rates of fatal bleeding and ICH were low in patients treated with rivaroxaban[#]

*Fatal bleeding using narrow definitions (the patient experienced a treatment-emergent major bleeding event and died within 30 days of the major bleeding event and the adjudicated primary cause of death was either ICH or extracranial bleeding; [#]Analyses based on 11,121 patients in the safety population

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Adjudicated Treatment-Emergent Thromboembolic Events in Safety population

XANTUS POOLED

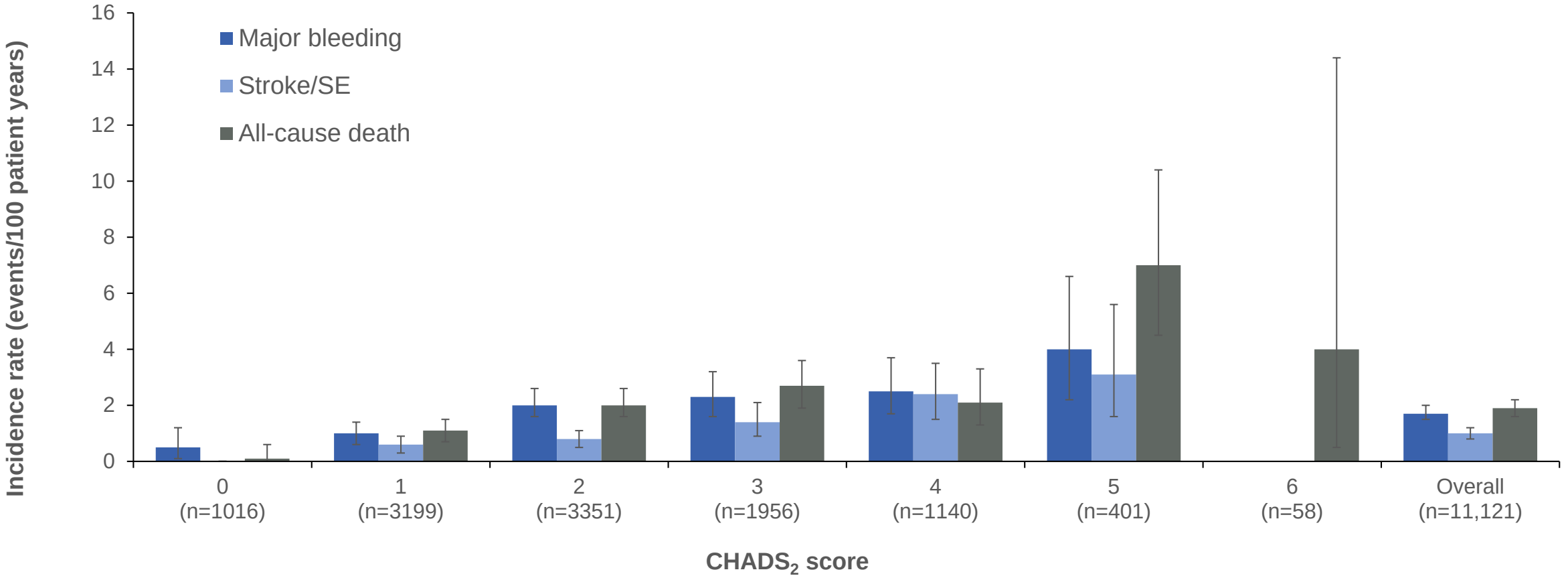
	Incidence proportion, n (%)	Incidence rate, events/ 100 patient-years (95% CI)
Thromboembolic events (stroke, TIA, non-CNS SE and MI)	179 (1.6)	1.8 (1.6–2.1)
Stroke/non-CNS SE	98 (0.9)	1.0 (0.8–1.2)
Stroke	87 (0.8)	0.9 (0.7–1.1)
Primary ischaemic	64 (0.6)	0.6 (0.5–0.8)
Primary haemorrhagic*	20 (0.2)	0.2 (0.1–0.3)
Non-CNS SE	11 (0.1)	0.1 (0.1–0.2)
TIA	41 (0.4)	0.4 (0.3–0.6)
MI	42 (0.4)	0.4 (0.3–0.6)

Rates of stroke/non-CNS SE were low in patients treated with rivaroxaban[#]

*Haemorrhagic strokes and haemorrhagic transformations of ischaemic stroke were reported as both stroke and major bleeding (multiple reasons for major bleedings were possible); [#]Analyses based on 11,121 patients in the safety population

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Key Outcomes in Safety Population Stratified by $CHADS_2$ Score



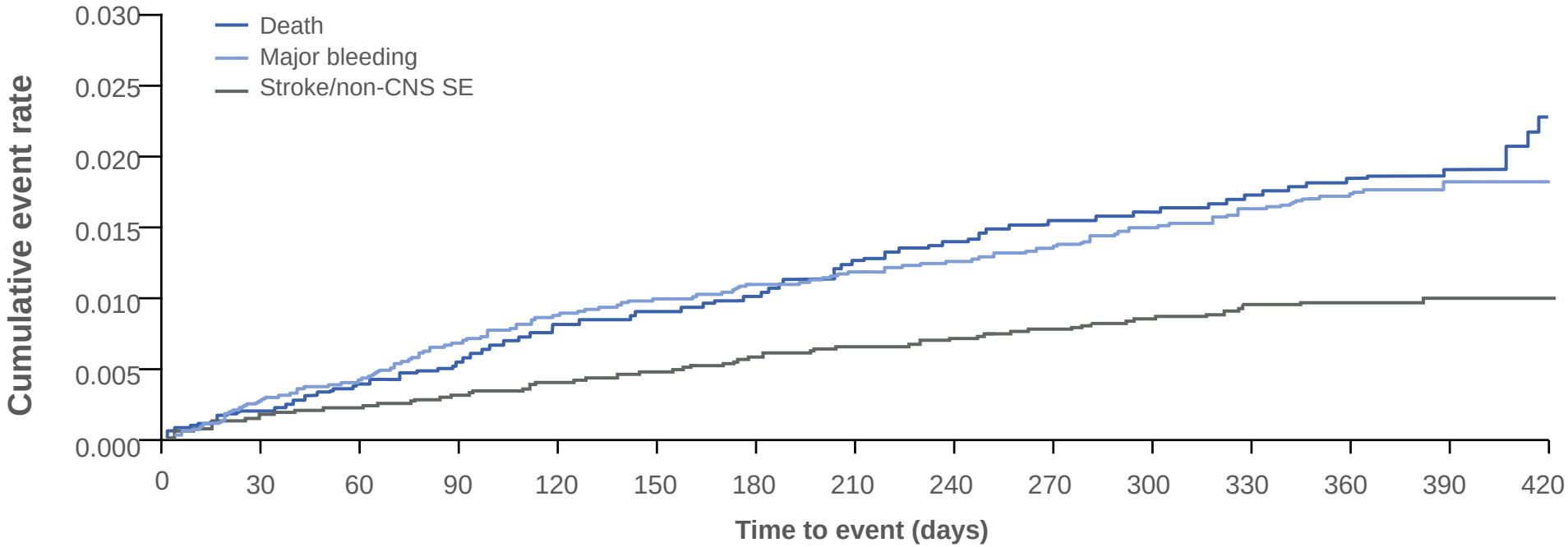
In general, rates of major outcomes increased with higher $CHADS_2$ scores*

*Analyses based on 11,121 patients in the safety population

Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Cumulative Rates for Treatment-Emergent Major Bleeding, Stroke/non-CNS SE and Death in Safety Population

XANTUS POOLED



Number of patients at risk															
Major bleeding	11121	10720	10394	10138	9823	9618	9439	9239	9091	8917	8703	8313	6734	1862	844
Stroke/SE*	11121	10729	10404	10155	9842	9637	9456	9257	9108	8939	8724	8332	6748	1864	843
Death	11121	10726	10403	10153	9847	9648	9471	9272	9125	8961	8751	8361	6772	1871	845

Over 96% of the XANTUS pooled safety population[#] did not experience any of the events
of treatment-emergent major bleeding, stroke/non-CNS SE or all-cause death

*Non-CNS SE; [#]Safety population n=11,121

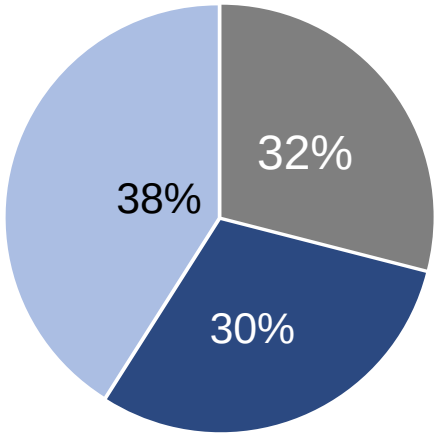
Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058

Rivaroxaban studied in different populations in Randomized Clinical Trial and the Real World

XANTUS POOLED

XANTUS Pooled

Rivaroxaban[1]

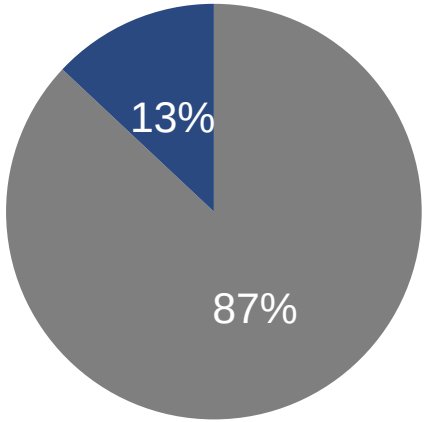


XANTUS[1]	Baseline	ROCKET AF[2]
2.0	$CHADS_2$	3.5
38%	0–1	0%
30%	2	13%
32%	≥3	87%
19%	Heart failure	63%
76%	Hypertension	91%
35%	Age >75 years	44%[3]
22%	Diabetes	40%
21%	Prior stroke#	55%
9%	Prior MI	17%

Results are not intended for direct comparison

ROCKET AF

Rivaroxaban[2,3]



Please note this information is from separate, Independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

$CHADS_2$ score ≤1 2 3–6

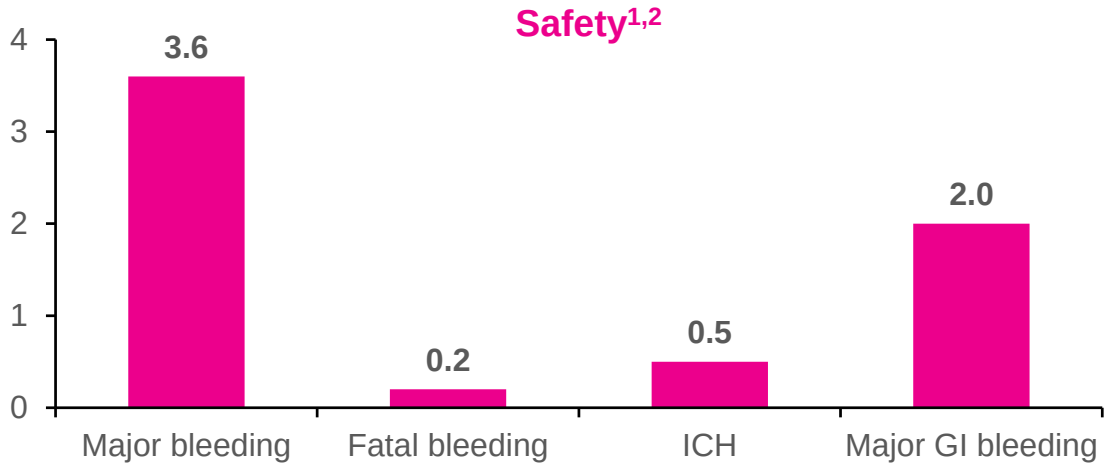
SE, systemic embolism; TIA, transient ischemic attack; MI, Myocardial infarction
#includes prior stroke, SE or TIA

1. Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058, 2. Patel M.R., et al. *N Engl J Med*. 2011;365(10):883–91. 3. Halperin J.L., et al. *Circulation*. 2014;130(2):138-46.

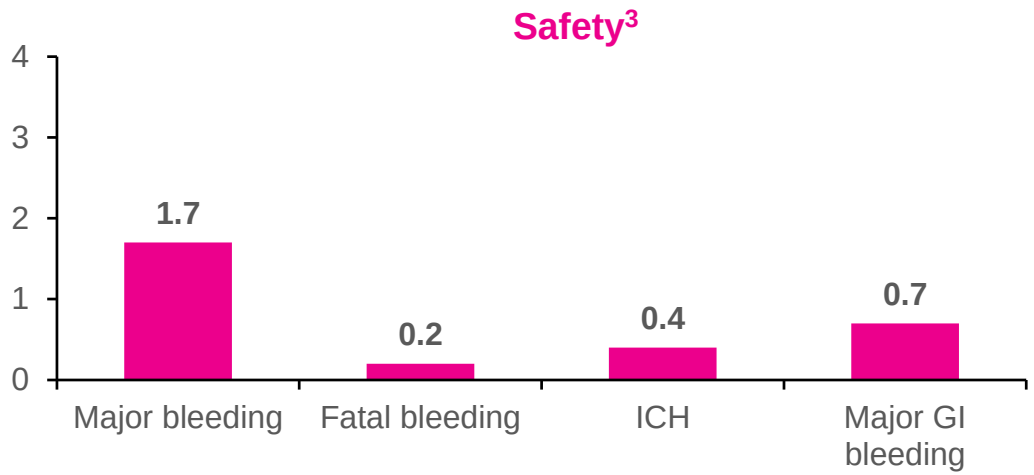
Rivaroxaban Is Highly Effective and Has a Good Safety Profile in Clinical Trials and Real World

XANTUS POOLED

ROCKET AF



XANTUS Pooled



Please note this information is from separate, Independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

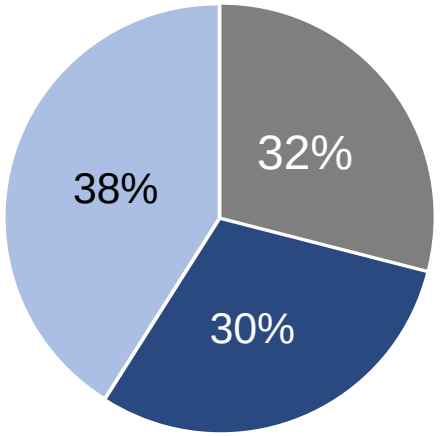
SE, systemic embolism; ICH, Intracranial haemorrhage; GI, gastrointestinal

*Events per 100 patient-years, ** Intention-to-treat population

1. Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058, 2. Sherwood M.W., et al. *JACC*. 2015;66(21):2271–81. 3. Camm A.J., et al. *Eur Heart J.* 2016 Apr 7;37(14):1145-53.

Baseline Characteristics from XANTUS and ARISTOTLE

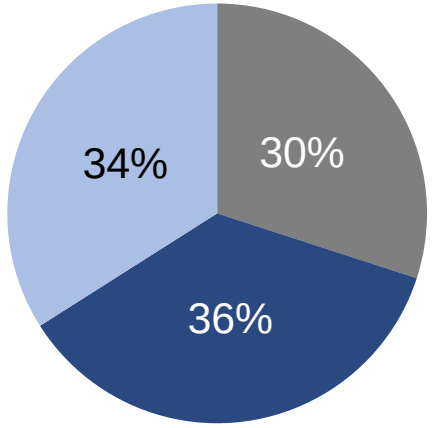
XANTUS Pooled
Rivaroxaban[1]



XANTUS[1]	Baseline	ARISTOTLE[2]
2.0	$CHADS_2$	2.1
38%	0–1	34%
30%	2	36%
32%	≥3	30%
19%	Heart failure	35%
76%	Hypertension	87%
35%	Age >75 years	31%
22%	Diabetes	25%
21%	Prior stroke#	19%
9%	Prior MI	14%

Results are not intended for direct comparison

ARISTOTLE
Apixaban[2]



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$CHADS_2$ score ≤1 2 3–6

SE, systemic embolism; TIA, transient ischemic attack; MI, Myocardial infarction
#includes prior stroke, SE or TIA

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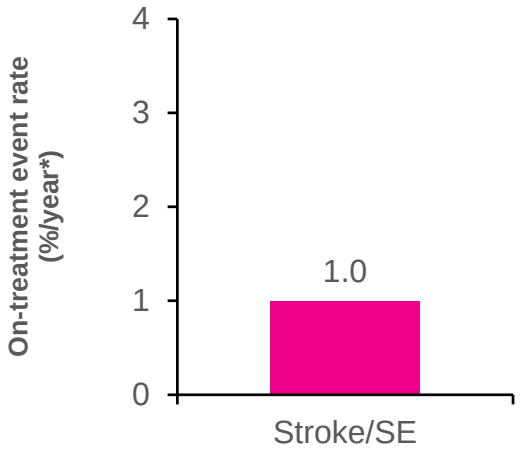
Rivaroxaban Is Highly Effective and Has a Good Safety Profile in Clinical Trials and Real World

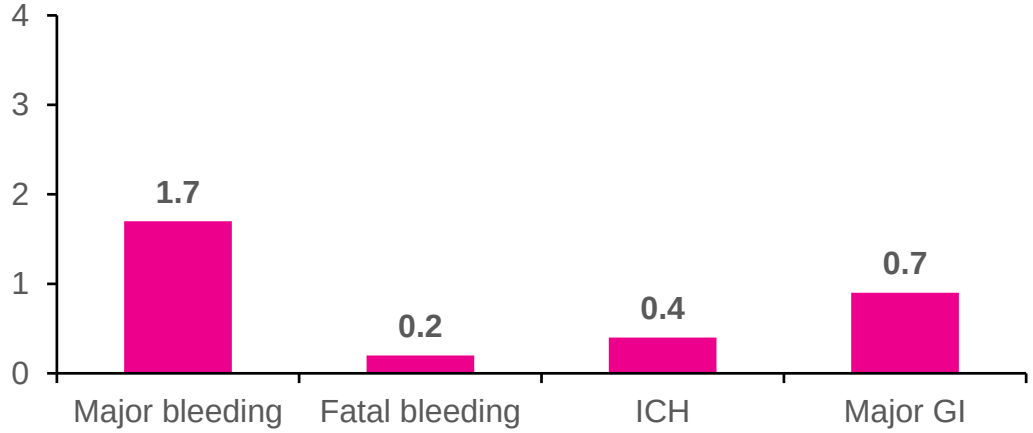
XANTUS POOLED

XANTUS Pooled

Effectiveness[1]

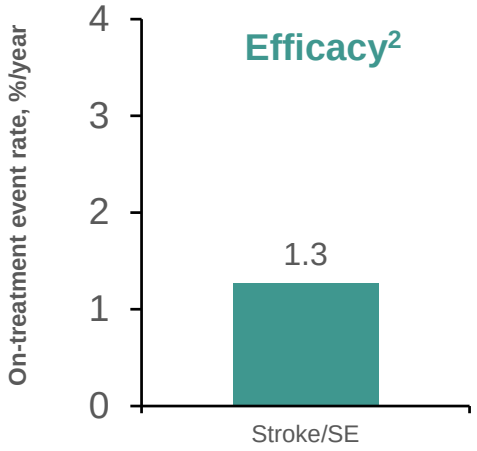


Safety[1]

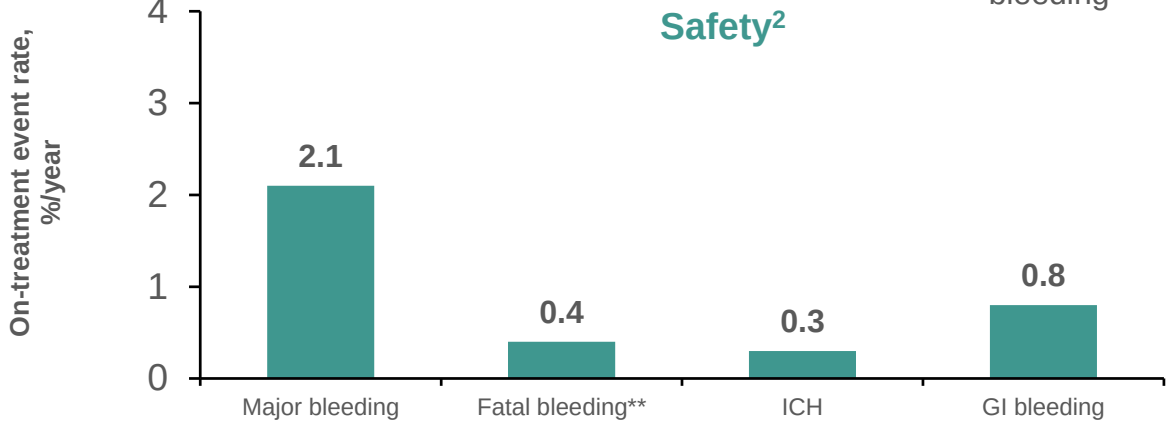


ARISTOTLE

Efficacy[2]



Safety[2]



Please note this information is from separate, Independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

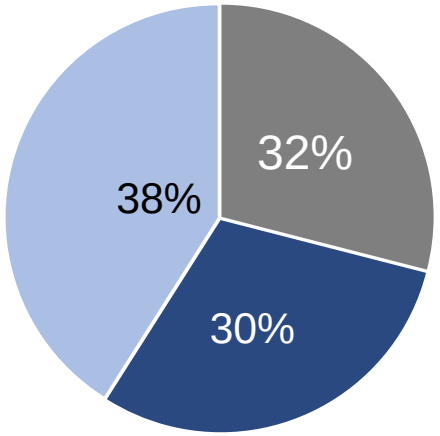
*Events per 100 patient-years; SE, systemic embolism; ICH, Intracranial haemorrhage; GI, gastrointestinal

**Fatal bleeding (including fatal hemorrhagic stroke), as evaluated in the intention-to-treat analysis, occurred in 34 patients in the apixaban group and 55 patients in the warfarin group.

1. Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058. 2. Granger C.B., et al. *N Engl J Med*. 2011;365(11):981–92.

Baseline Characteristics from XANTUS and ENGAGE-AF

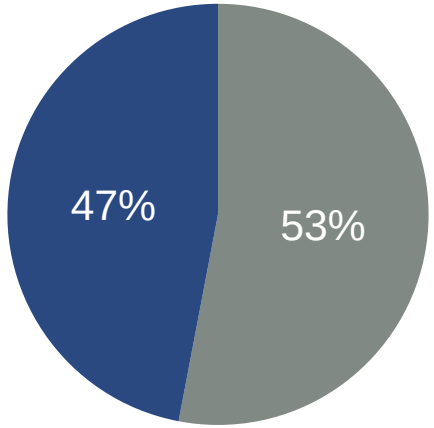
XANTUS Pooled
Rivaroxaban[1]



XANTUS[1]	Baseline	ENGAGE-AF[2]
2.0	$CHADS_2$	2.8
19%	Heart failure	57%
76%	Hypertension	94%
35%	Age >75 years	40%
22%	Diabetes	36%
21%	Prior stroke*	28%

Results are not intended for direct comparison

ENGAGE-AF
Edoxaban[2,3]



Please note this information is from separate, Independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

SE, systemic embolism; TIA, transient ischemic attack

*Prior stroke: Xantus includes prior stroke, SE or TIA, ENGAGE-AF includes prior stroke or TIA

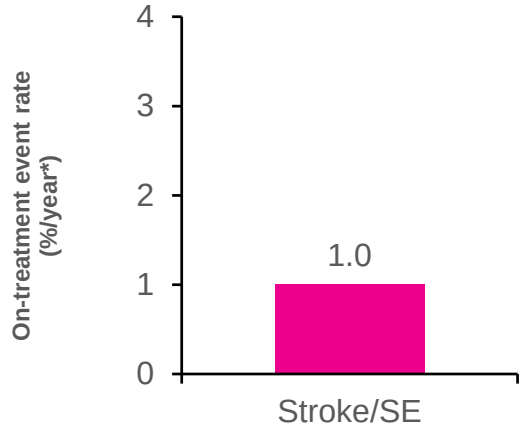
1. Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058, 2. Giugliano R.P., et al. *N Engl J Med*. 2013;369(22):2093-104. 3. FDA. Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee. Available at: https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Pink%20Sheet%20DAILY/2014/October/Edoxaban_AC_FDA_brfg.pdf (accessed in May 2018)

Rivaroxaban Is Highly Effective and Has a Good Safety Profile in Clinical Trials and Real World

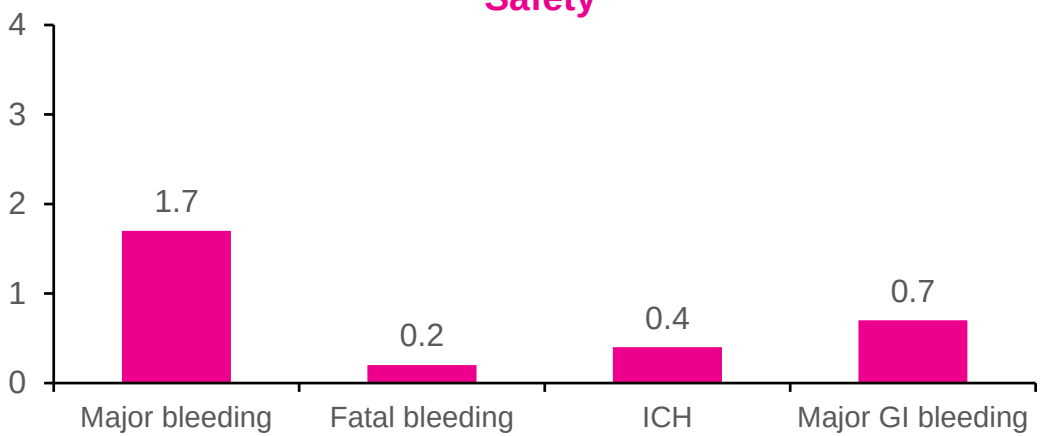
XANTUS POOLED

XANTUS Pooled

Effectiveness[1]



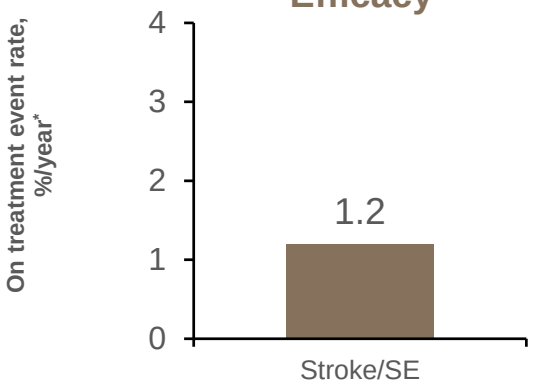
Safety[1]



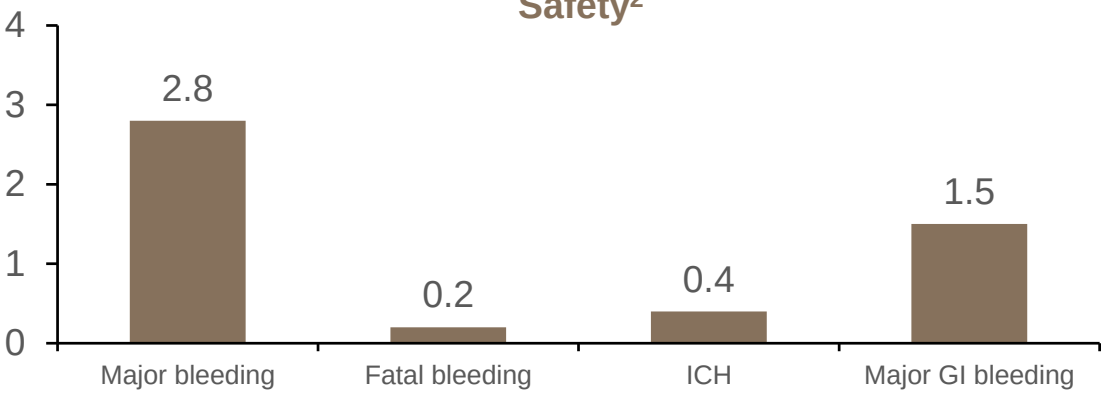
ENGAGE-AF

(High dose, 60mg OD)

Efficacy[2]



Safety[2]



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Conclusion

- Phase III studies are the gold standard for evaluating efficacy and safety against the current standard of care However, Strict protocols and inclusion/exclusion criteria may exclude some patients
- Real world studies provides additional information on rare safety events or routine clinical practice such as management of serious bleeding
- According to result from the XANTUS, the first international, prospective, observational study, the benefits from rivaroxaban were consistent across different patient population worldwide[1]
- The XANTUS international study programme offers a unique RWE dataset
  - Results were consistent with the phase III ROCKET AF study[2]

1. Kirchhof P et al, J Am Coll Cardiol. 2018 Jul 10;72(2):141-153. doi: 10.1016/j.jacc.2018.04.058; 2. Patel MR *et al*, *N Engl J Med* 2011:365:883–891; 3. Kim YH *et al*, presented at *APHRS* 2016, poster number 2–116;