Anticoagulation Management
Update in Atrial Fibrillation: New Evidence and Practical Tips

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Disclosures for Dr A G G Turpie

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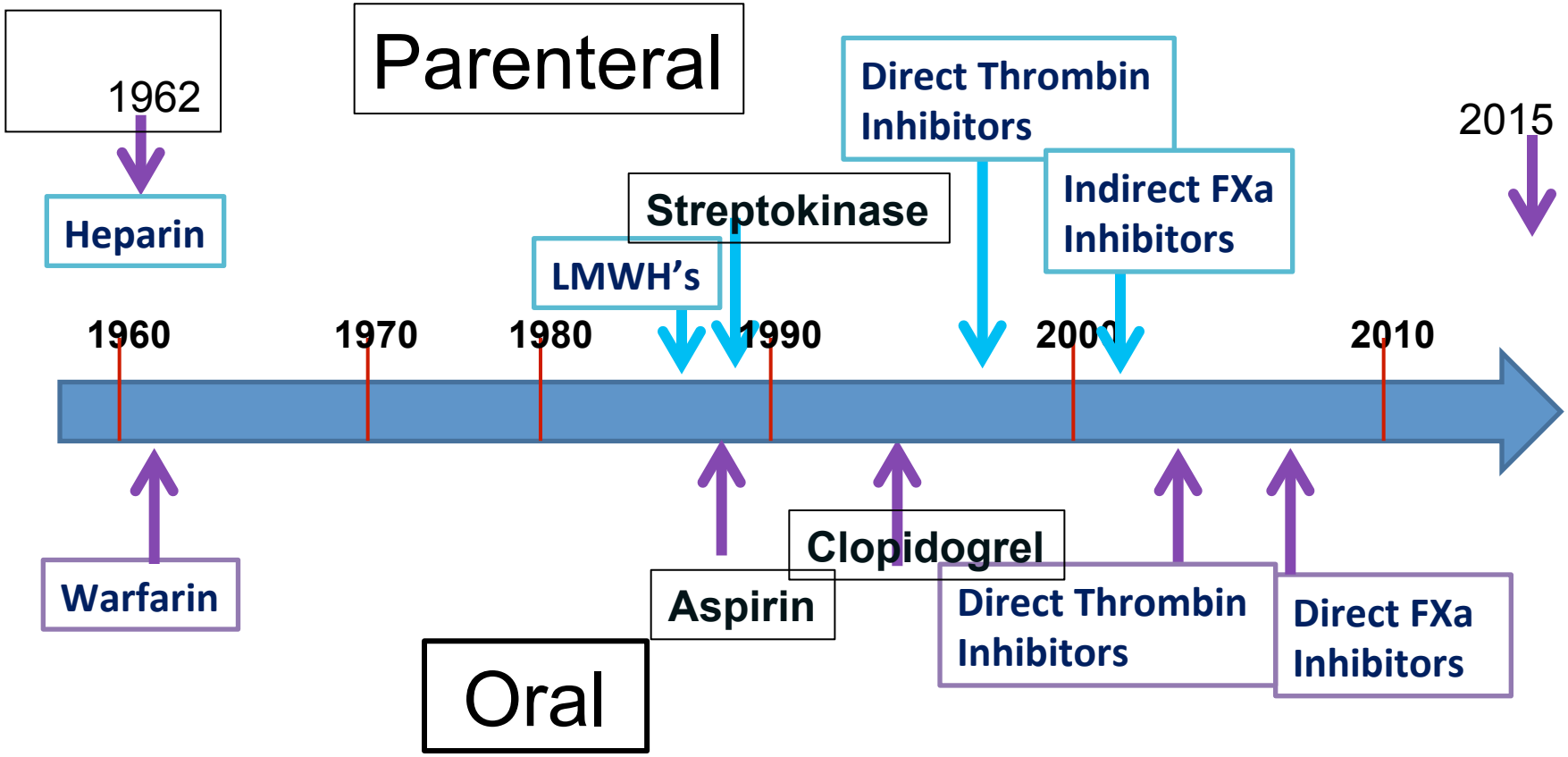
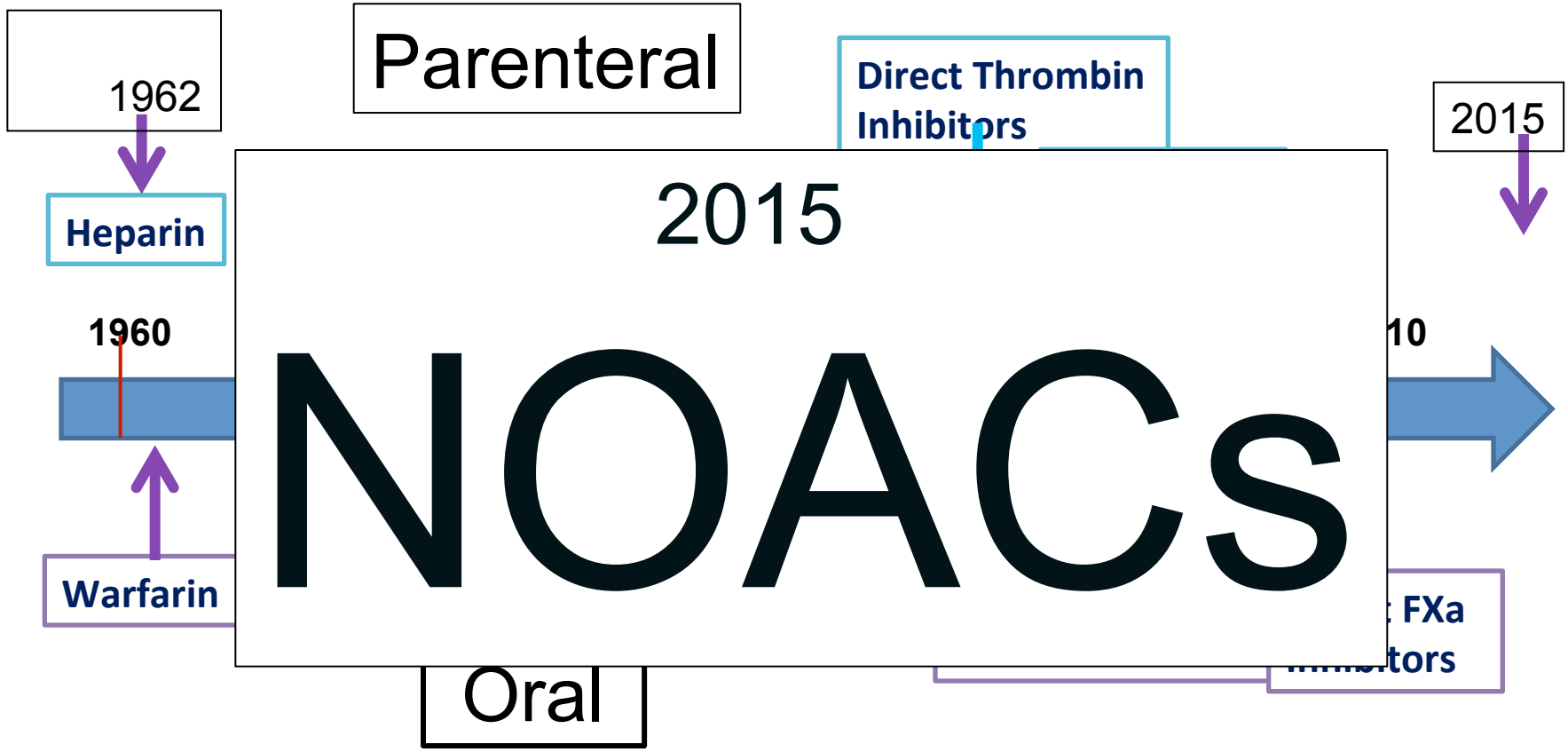
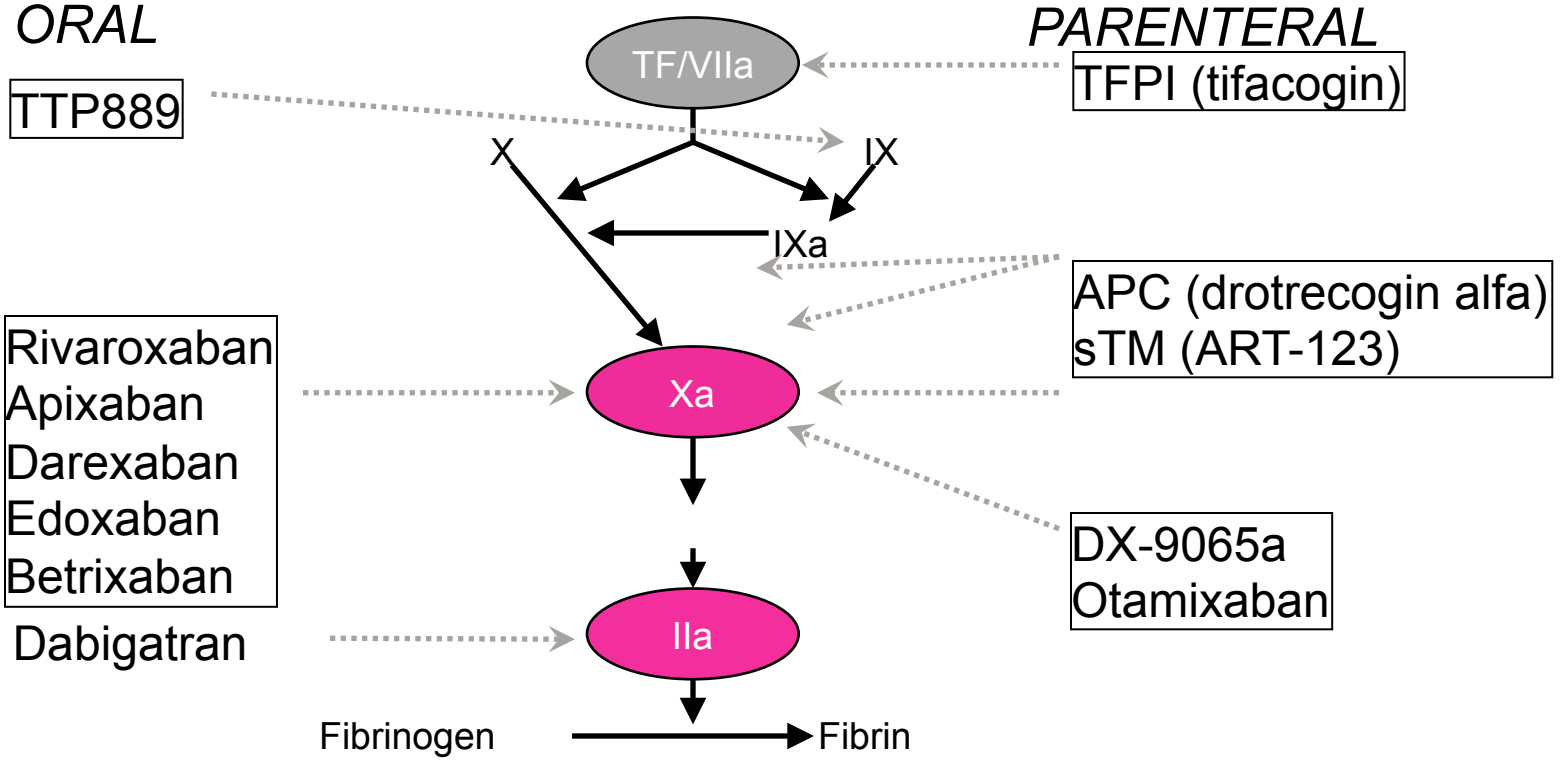
EVOLUTION OF ANTITHROMBOTICS



EVOLUTION OF ANTITHROMBOTICS



New anticoagulants



New Anticoagulants

Direct Thrombin Inhibitors

- Dabigatran

Factor Xa Inhibitors

- Rivaroxaban
- Apixaban
- Edoxaban

New Anticoagulants

- VTE Prevention
- VTE Treatment
- Stroke Prevention in AF
- Secondary Prevention of ACS

Phase III Clinical Trials

- Registration trials
- Support marketing approval by the regulatory authorities
- Strict design to ensure well -defined inclusion and exclusion criteria
- Strict protocol adherence, appropriate clinical endpoints and statistical validity

However...

- Event rates and patient characteristics may not fully reflect those observed in the patients seen in routine care
- Adherence, persistence and co-morbidities may vary between the strict environment of a clinical trial and that of ‘real-world’ therapy

Post-authorization Studies

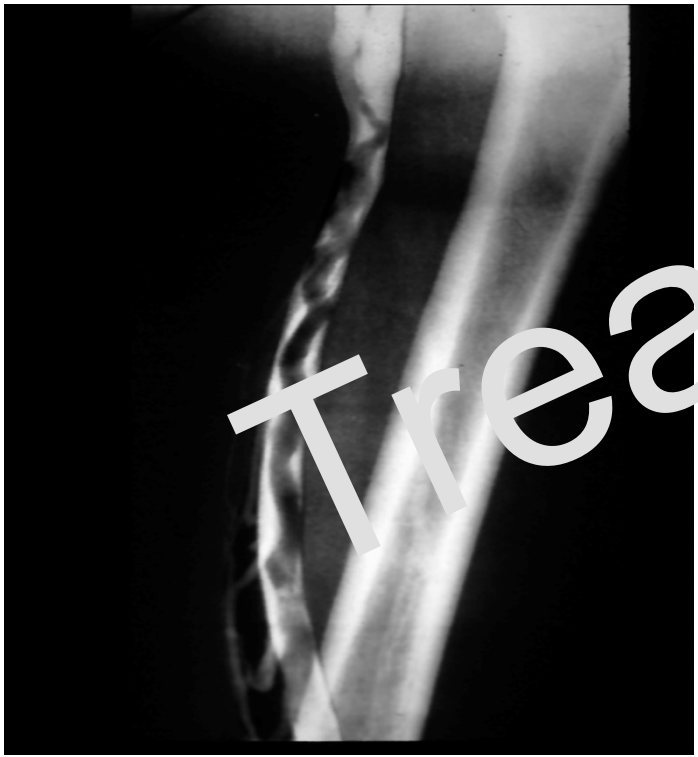
- Post-marketing surveillance studies (PMSS)
- Non-interventional studies
- Registries

Non-interventional Studies: Rivaroxaban

Study	Description
XAMOS (VTE prevention in MOS)	Non-interventional phase IV comparison of rivaroxaban vs SOC for VTE prophylaxis in MOS (NCT00831714)
XALIA (DVT treatment in clinical practice)	Non-interventional cohort study to assess long-term safety of rivaroxaban vs SOC for the treatment of acute DVT in routine clinical practice (NCT01619007)
XANTUS (XANAP, XANTUS-EL) (Stroke prevention in patients with AF in clinical practice)	Non-interventional cohort study to determine safety of rivaroxaban under clinical practice conditions for stroke prevention in patients with non-valvular AF (NCT01606995)

AF, atrial fibrillation; DVT, deep vein thrombosis; MOS, major orthopaedic surgery; SOC, standard of care; VTE, venous thromboembolism

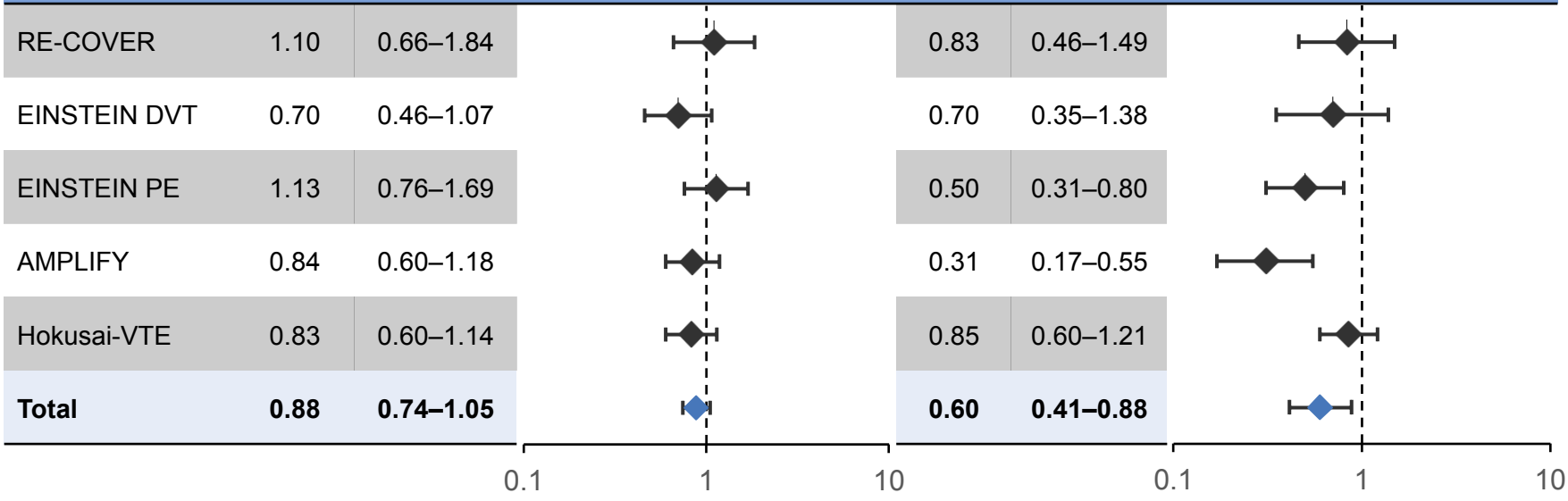
Venous Thromboembolism



Treatment

Meta-analysis of Phase III Trials of Novel OACs for VTE Treatment

Trial	Recurrent VTE				Major bleeding			
	Risk ratio	95% CI	RR (95% CI) Favours novel OAC	Favours SOC	Risk ratio	95% CI	RR (95% CI) Favours novel OAC	Favours SOC
RE-COVER	1.10	0.66–1.84			0.83	0.46–1.49		
EINSTEIN DVT	0.70	0.46–1.07			0.70	0.35–1.38		
EINSTEIN PE	1.13	0.76–1.69			0.50	0.31–0.80		
AMPLIFY	0.84	0.60–1.18			0.31	0.17–0.55		
Hokusai-VTE	0.83	0.60–1.14			0.85	0.60–1.21		
Total	**0.88**	**0.74–1.05**			**0.60**	**0.41–0.88**		



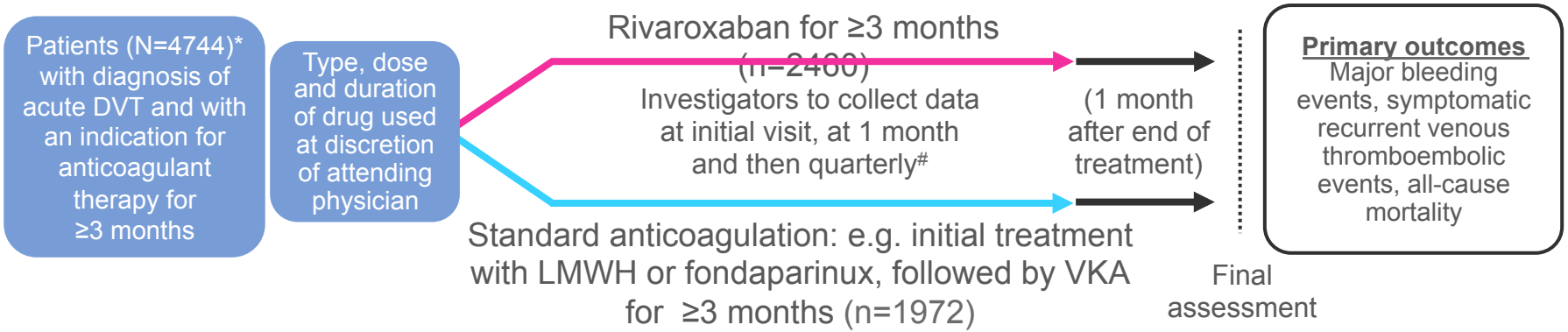
Van der Hulle T *et al*. *J Thromb Haemost* 2014;12:320–328

Treatment of Acute DVT

XALIA: Study Design

Prospective, non-interventional cohort field study

Objective: To collect real-life data on adverse events (AEs), bleeding, thromboembolic events and mortality in patients diagnosed with acute DVT treated with rivaroxaban or standard therapy



Study start date: June 2012
Estimated study completion date: June 2015

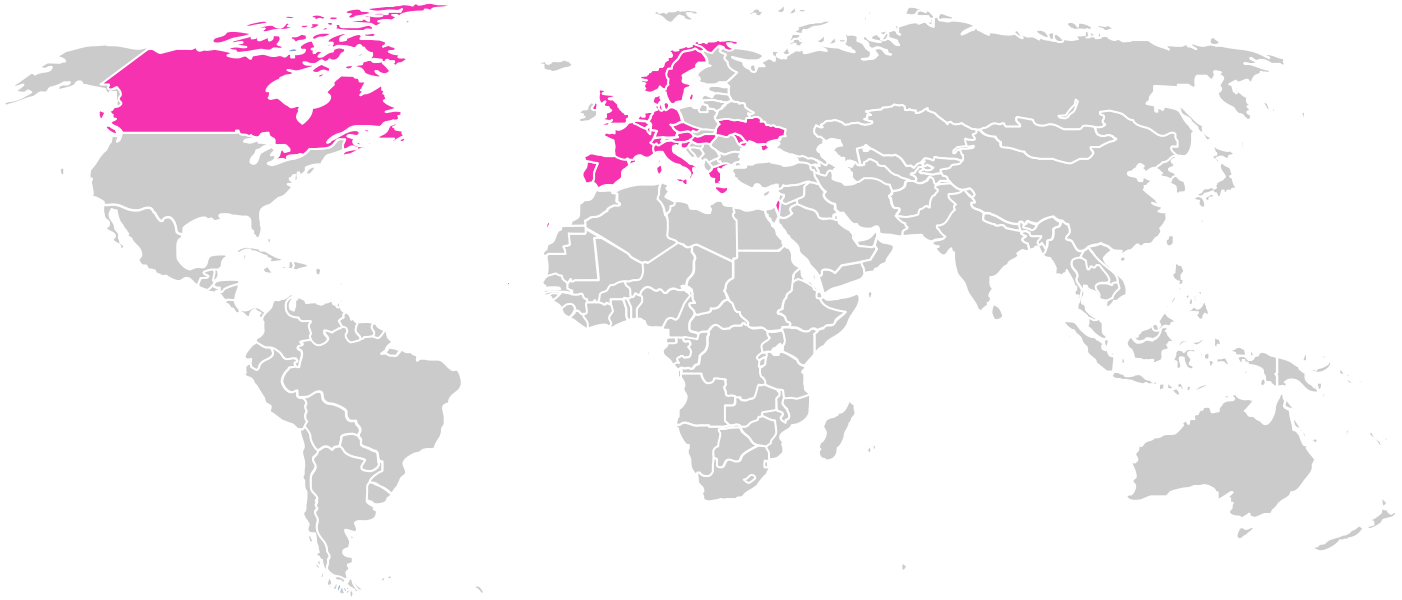
*Includes 312 early switchers, defined as patients who received parenteral anticoagulation and/or VKA for >2–14 days before being switched to rivaroxaban, and excludes 414 patients had no treatment assigned (n=377) or were not included in the analysis for other reasons (n=37); #protocol does not define exact referral dates for follow-up visits

Ageno W *et al*, *Thromb J* 2014;12:16; Turpie A *et al*. ISTH 2015 (Poster PO607-TUE)

XALIA

XALIA: Participating Countries

- Recruitment began in 2012; database closed in 2015
  - 5158 patients from 21 countries



Turpie A *et al*. ISTH 2015 (Poster PO607-TUE)

XALIA: Patients Receiving Rivaroxaban

	Rivaroxaban (n=2460)		Early switchers (n=312)
	Rivaroxaban alone, n (%)	Other anticoagulation for ≤2 days before first rivaroxaban dose, n (%)	Other anticoagulation for >2–14 days ('early switchers'), n (%)
Patients enrolled	1985 (80.7)	475 (19.3)	312 (100)
Patients switching from parenteral anticoagulant*	–	475 (100)	271 (86.9)
Patients switching from a VKA#	–	–	41 (13.1)

*Low molecular weight heparin, unfractionated heparin or fondaparinux; #0–14 days for VKA

Turpie A *et al*. ISTH 2015 (Poster PO607-TUE)

XALIA: Baseline Demographics

	Rivaroxaban		Standard anticoagulation (n=1972)
	No or other prior anticoagulant* (n=2460)	Early switchers# (n=312)	
Age, years, mean (SD)	57.4 (16.8)	59.0 (17.2)	63.0 (16.9)
<65 years, n (%)	1512 (61.5)	180 (57.7)	949 (48.1)
≥65–<75 years, n (%)	528 (21.5)	66 (21.2)	450 (22.8)
≥75 years, n (%)	420 (17.1)	66 (21.2)	572 (29.0)
Male sex, n (%)	1349 (54.8)	177 (56.7)	1025 (52.0)
Weight, kg, mean (SD)	82.5 (18.2)	82.7 (19.4)	80.8 (18.1)
BMI, kg/m^2, mean (SD)	28.0 (5.2)	28.1 (5.6)	28.4 (7.0)
Index diagnosis, n (%)			
DVT without PE	2259 (91.8)	249 (79.8)	1758 (89.1)
DVT with PE	201 (8.2)	63 (20.2)	214 (10.9)

*For ≤2 days before first dose of rivaroxaban; #other anticoagulation >2–14 days; some demographic parameters have some data missing (not shown)

Turpie A *et al*. ISTH 2015 (Poster PO607-TUE)

XALIA

XALIA: Baseline Demographics

	Rivaroxaban		Standard anticoagulation (n=1972)
	No or other prior anticoagulant* (n=2460)	Early switchers† (n=312)	
Creatinine clearance, n (%)			
≥80 ml/min	691 (28.1)	68 (21.8)	422 (21.4)
≥50–<80 ml/min	339 (13.8)	40 (12.8)	295 (15.0)
≥30–<50 ml/min	58 (2.4)	8 (2.6)	93 (4.7)
<30 ml/min	5 (0.2)	3 (1.0)	38 (1.9)
Missing	1367 (55.6)	193 (61.9)	1124 (57.0)
Previous VTE	597 (24.3)	69 (22.1)	437 (22.2)
Recent hospitalization	314 (12.8)	48 (15.4)	390 (19.8)
Active cancer	137 (5.6)	25 (8.0)	373 (18.9)
Thrombophilia	146 (5.9)	22 (7.1)	105 (5.3)

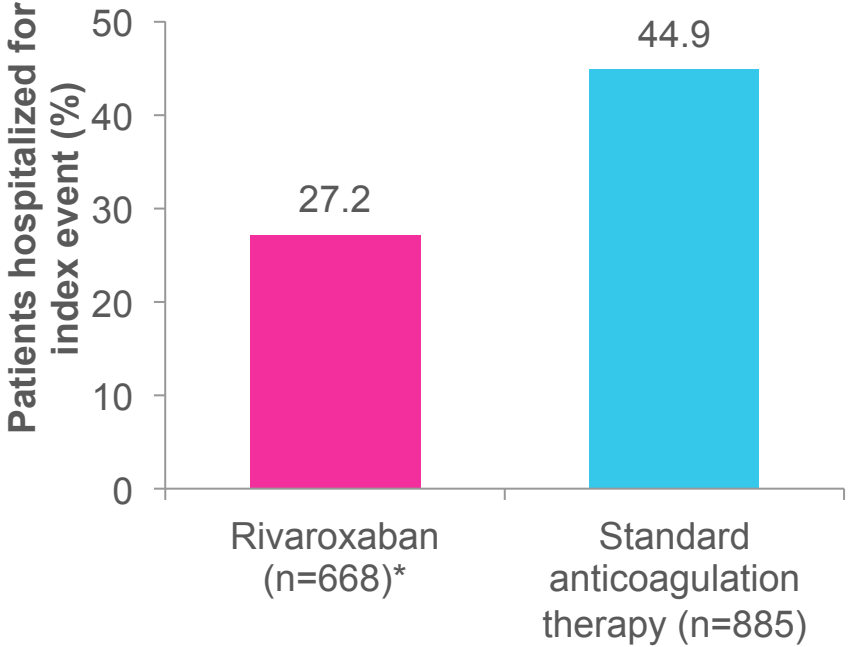
*For ≤2 days before first dose of rivaroxaban; †other anticoagulation >2–14 days; n (%) of missing data are included for creatinine clearance groups; other demographic parameters also have some data missing

Turpie A *et al*. ISTH 2015 (Poster PO607-TUE)

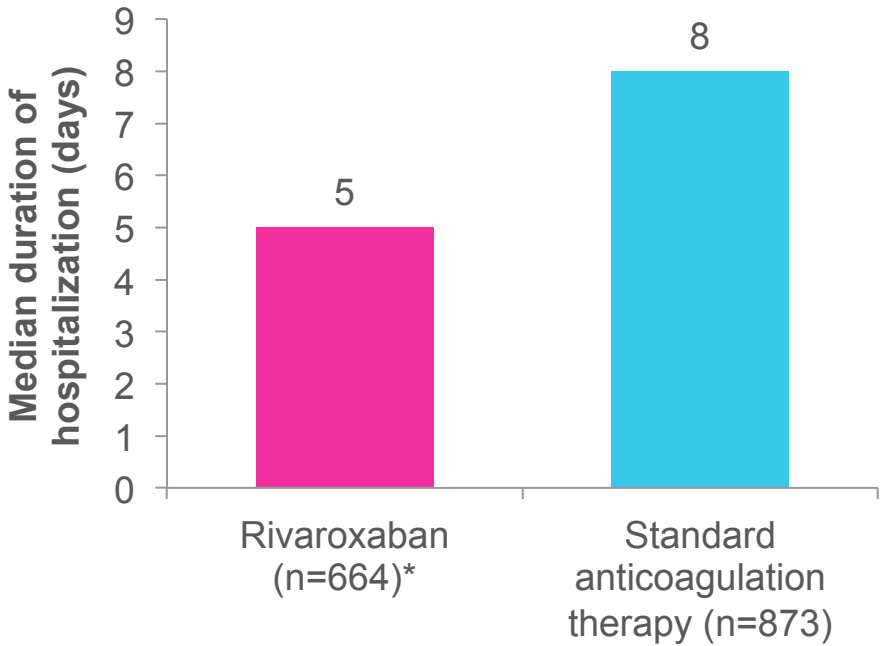
XALIA

XALIA: Hospitalizations

Proportion of patients hospitalized



Median duration of hospitalization



*Patients received rivaroxaban alone or had parenteral anticoagulation for ≤2 days before the first dose of rivaroxaban was administered

Turpie A *et al*. ISTH 2015 (Poster PO607-TUE)

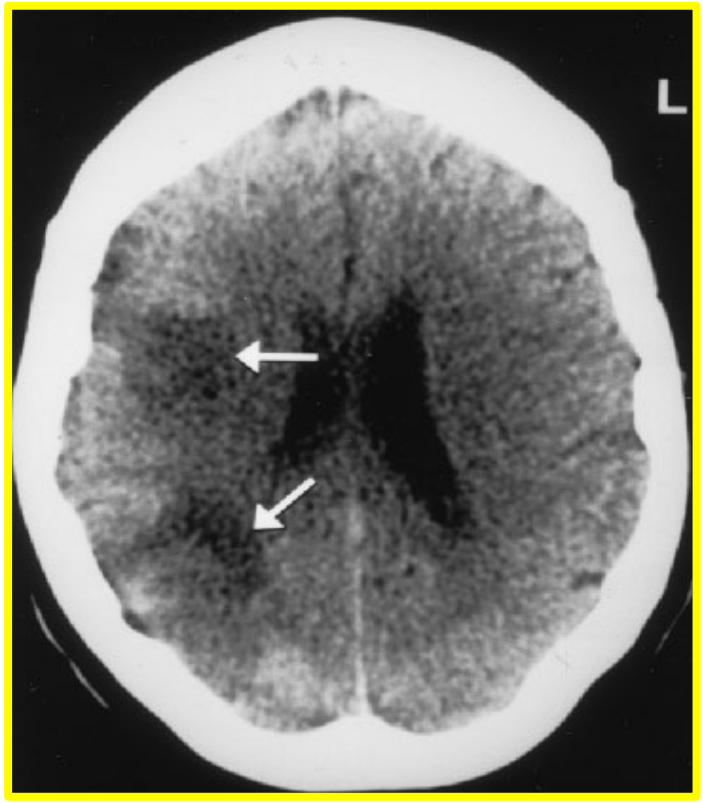
Summary and Conclusions

- These preliminary, unadjusted data from the real-world XALIA study show that treatment allocation may have been influenced by patient characteristics such as age and co-morbidities
- Patients in the rivaroxaban group, whether or not receiving parenteral anticoagulation for ≤2 days, were less-frequently hospitalized and had shorter median lengths of hospital stay compared with the standard therapy group
- Outcomes from XALIA will provide important information on the treatment of DVT in a heterogeneous, unselected patient population in a real-world setting

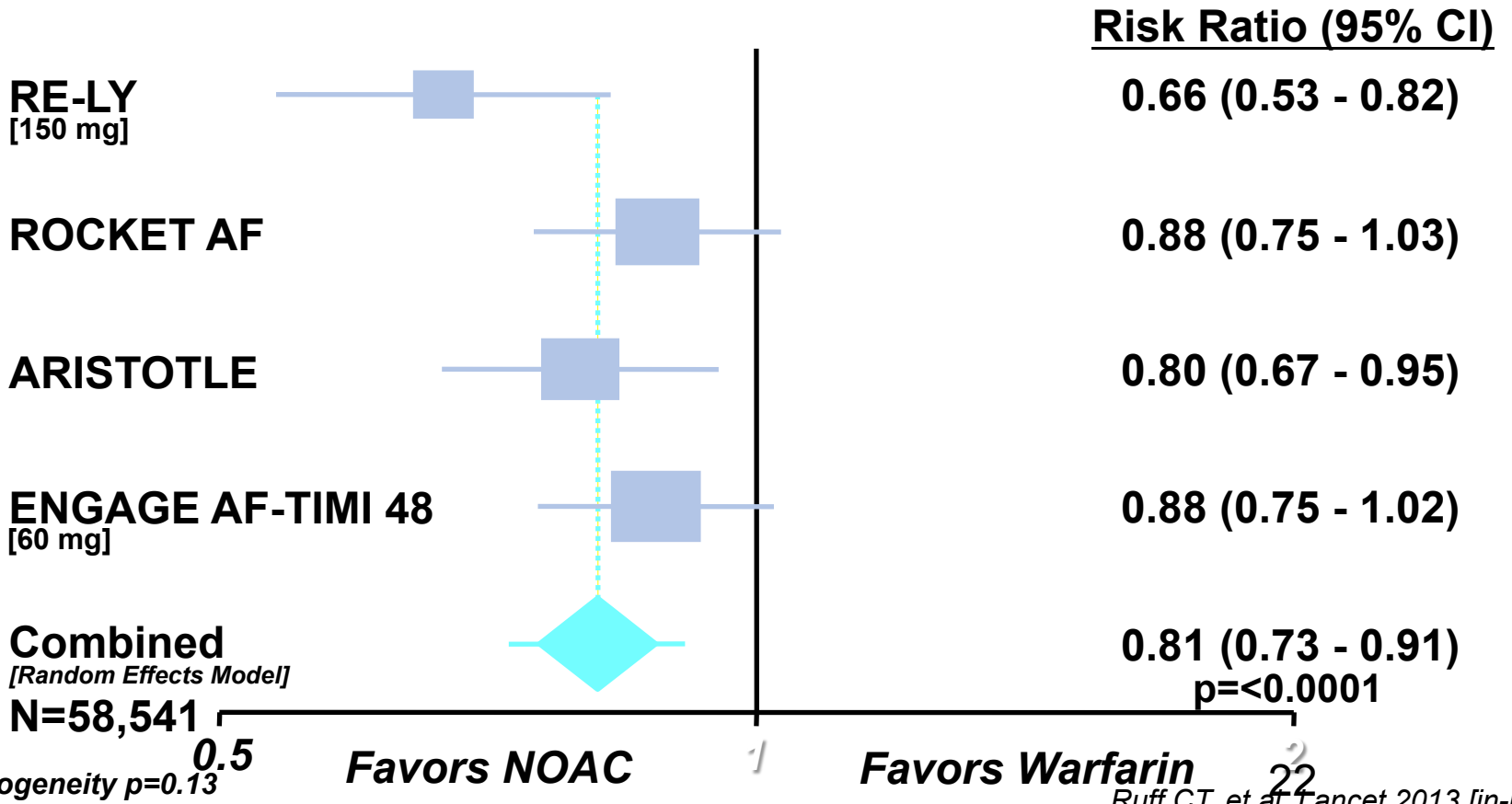
Turpie A *et al*. ISTH 2015 (Poster PO607-TUE)

XALIA

Stroke Prevention in AF

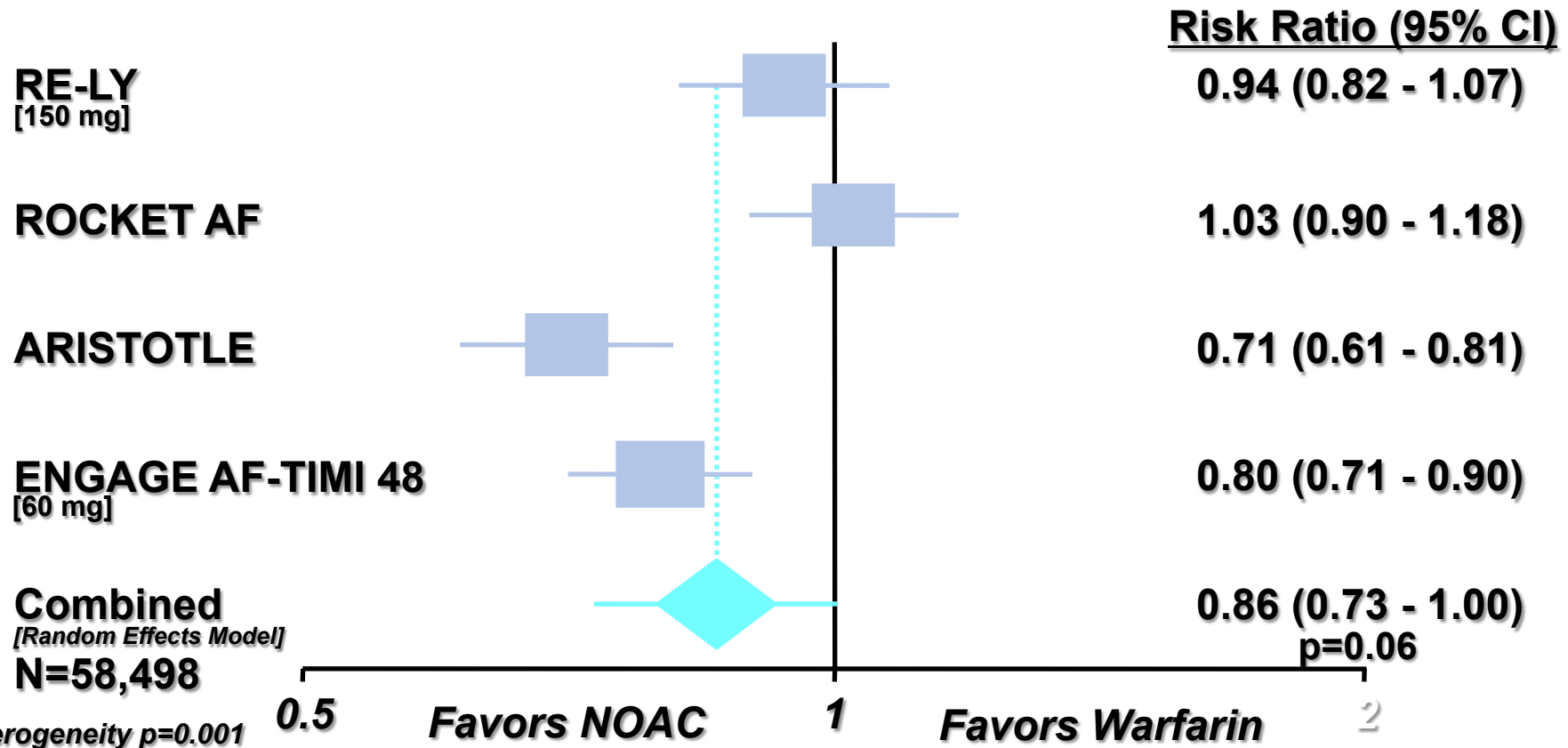


All NOACS: Stroke or SEE



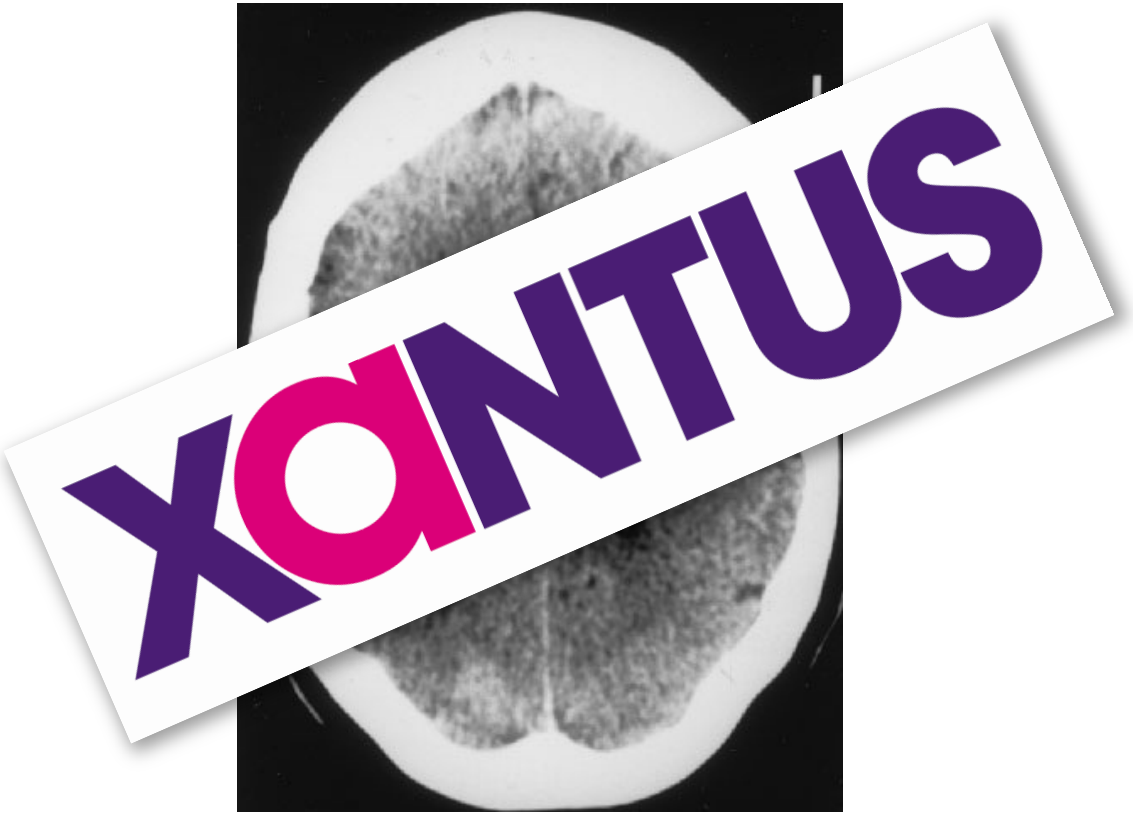
Ruff CT. et al. Lancet 2013 [in-press]

All NOACS: Major Bleeding



Ruff CT, et al. Lancet 2013 [in-press]

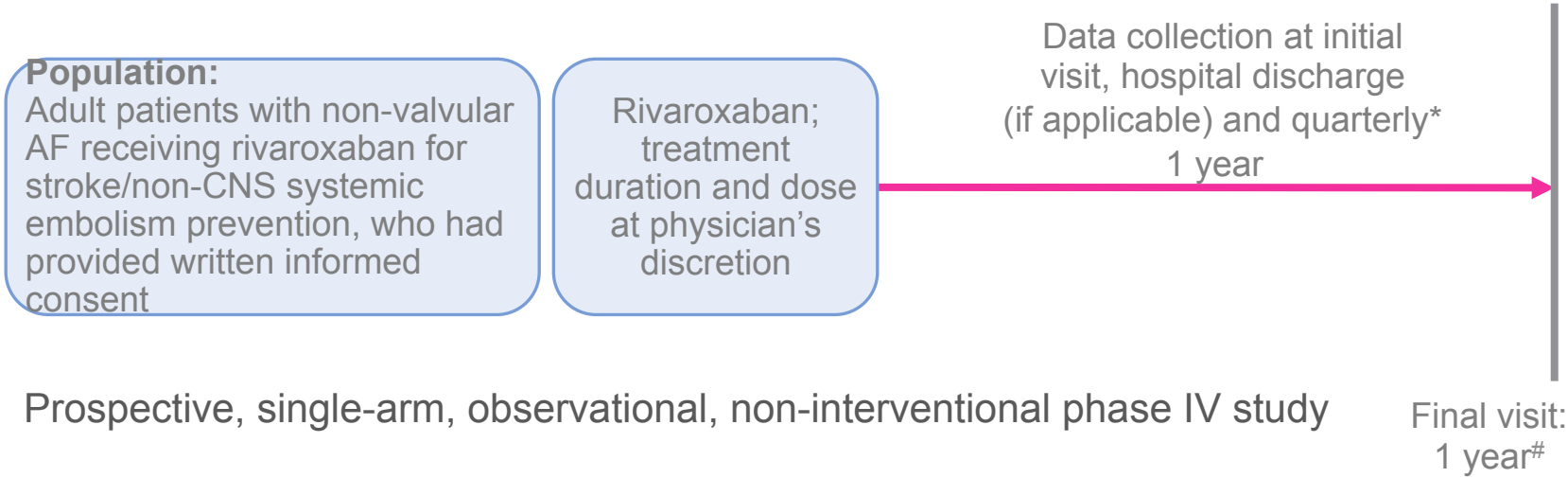
Stroke Prevention in Patients with Atrial Fibrillation



XANTUS: Observational Study of Patients Treated with Rivaroxaban for Stroke Prevention in Atrial Fibrillation

XANTUS: Study Objective and Design

- To collect real-life data on adverse events in patients with non-valvular AF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice



*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

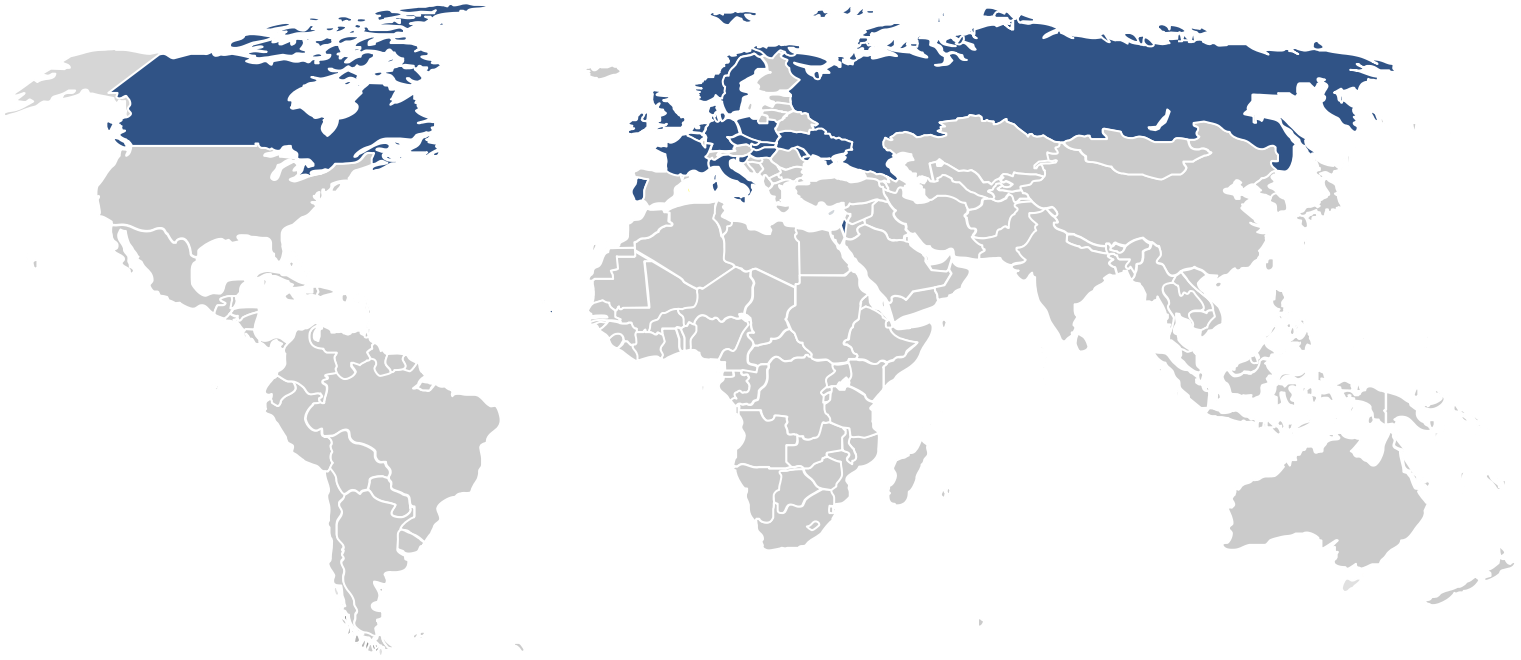
Camm *et al*, *Vasc Health Risk Manag* 2014;10:425–434; www.clinicaltrials.gov/ct2/show/NCT01606995

Primary and Secondary Outcomes

- Primary outcome
  - Major bleeding (ISTH definition)
  - All-cause mortality
  - Any other AEs
  - Any other serious AEs
- Secondary outcomes
  - Symptomatic thromboembolic events
  - Non-major bleeding events
    - Any bleeding event that does not meet the criteria for a major haemorrhage
  - AEs and serious AEs across risk scores
  - AEs and serious AEs in important subgroups
  - Other outcomes collected included:
    - Patient treatment satisfaction using standardized questionnaires
    - Treatment persistence
    - Health care-resource use
    - Details of interventions and how they were managed
    - Concomitant medication use
    - Reasons for switching/interrupting rivaroxaban therapy

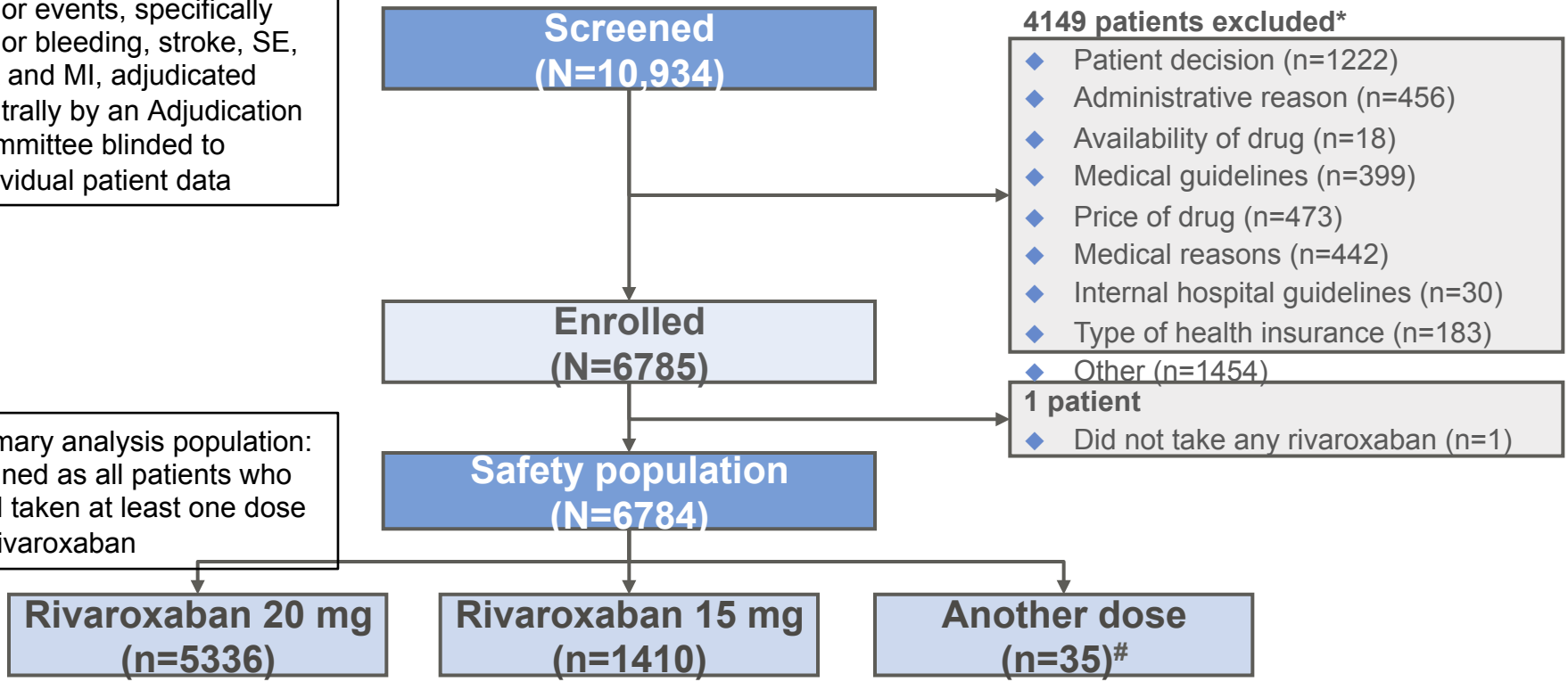
Camm *et al*, *Vasc Health Risk Manag* 2014;10:425–434

XANTUS: Participating Countries



XANTUS: Patient Disposition

Major events, specifically major bleeding, stroke, SE, TIA and MI, adjudicated centrally by an Adjudication Committee blinded to individual patient data



Primary analysis population: defined as all patients who had taken at least one dose of rivaroxaban

*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)

Baseline Demographics and 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
$CHADS_2$ score, mean±SD	2.0±1.3
CHA_2DS_2-VASc score, mean±SD	3.4±1.7
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)
VKA experienced	3089 (45.5)
VKA naïve	3695 (54.5)
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)
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)
Hospitalization at baseline, n (%)	1226 (18.1)

Baseline Demographics

	Rivaroxaban (N=6784)
Prior use of antithrombotics, n (%)	
VKA	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)

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)

Treatment-Emergent Bleeding Events

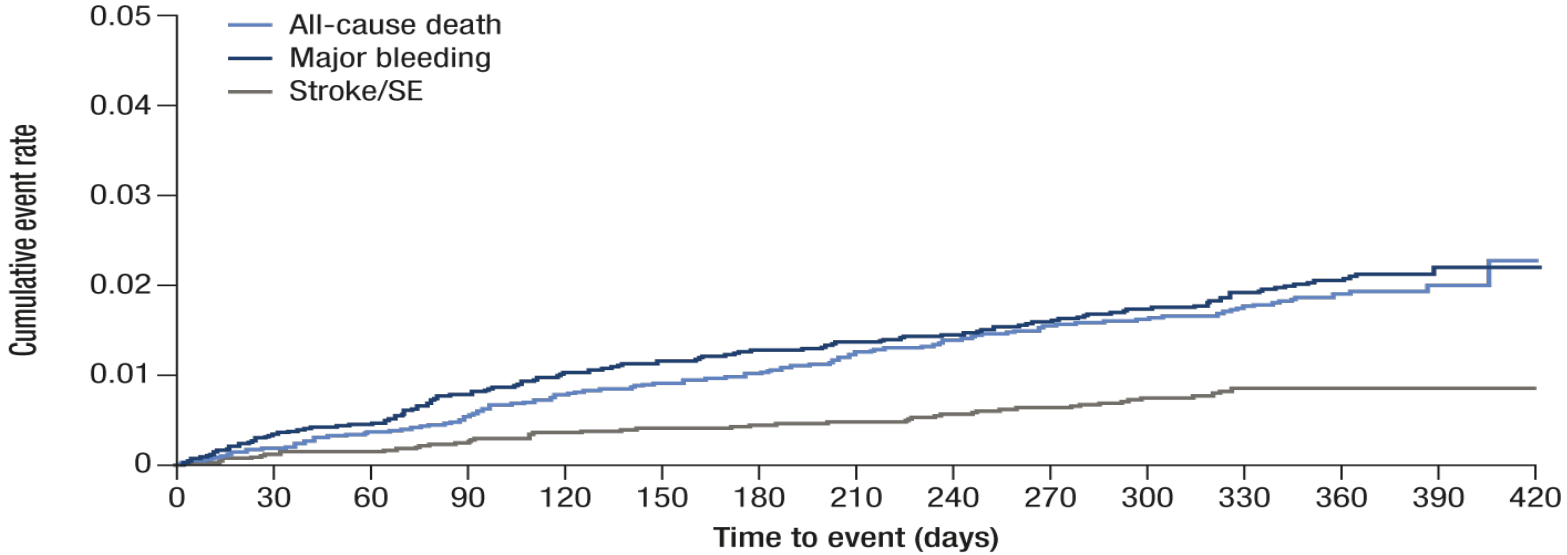
	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)
Major bleeding	128 (1.9)	2.1 (1.8–2.5)
Fatal	12 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	43 (0.6)	0.7 (0.5–0.9)
Intracranial haemorrhage	26 (0.4)	0.4 (0.3–0.6)
Mucosal bleeding*	60 (0.9)	1.0 (0.7–1.3)
Gastrointestinal	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	881 (13.0)	15.5 (14.5–16.5)

Adjudicated Causes of Death

	Number of patients (N=118*), 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

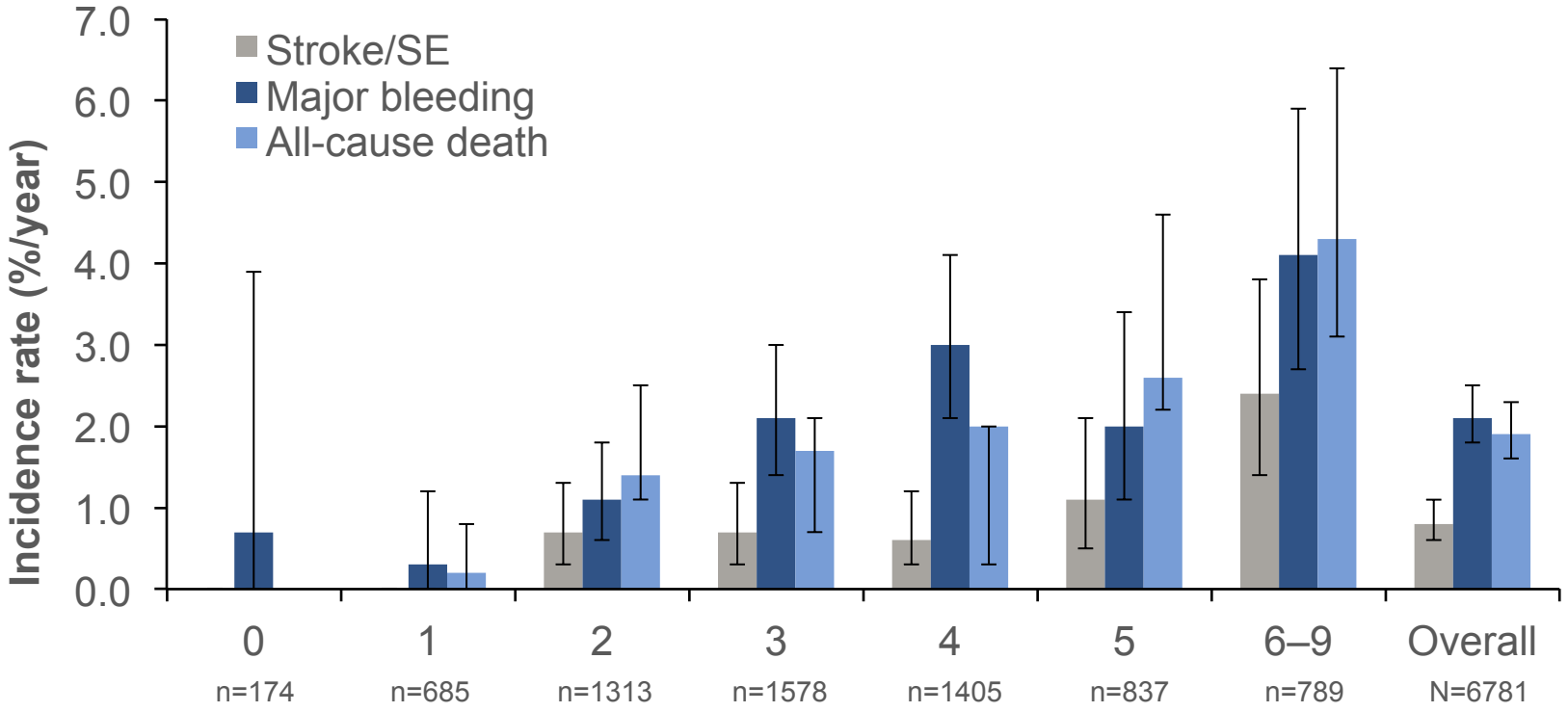
Cumulative Rates (Kaplan–Meier) for Treatment-Emergent Primary Outcomes



Patients at risk:

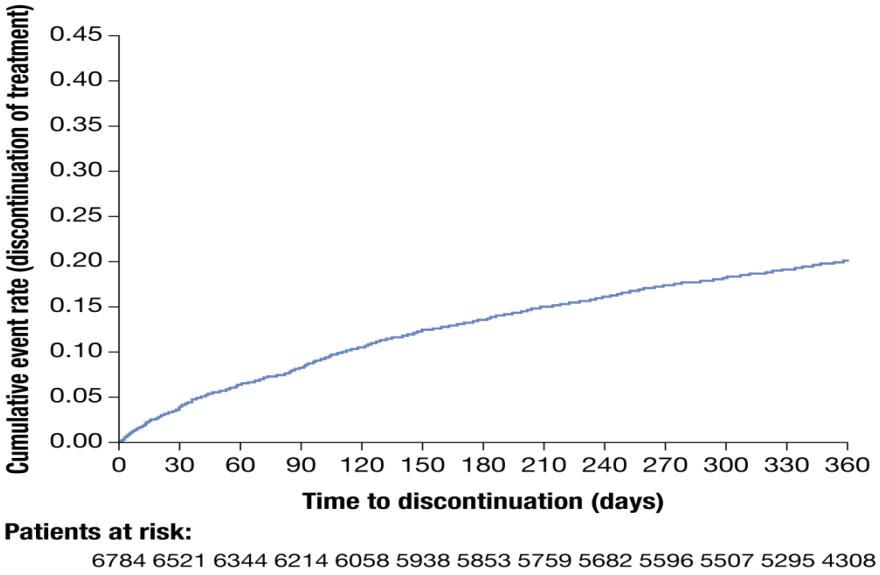
All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/SE	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513

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



Treatment Persistence and Patient Satisfaction

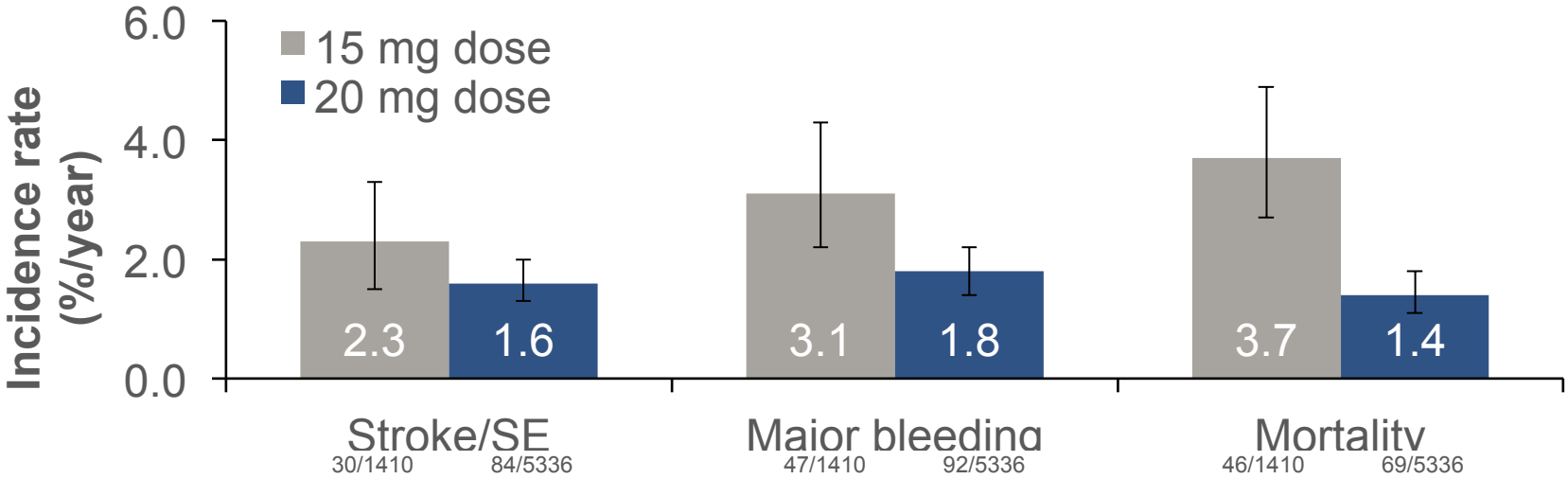
- Persistence with rivaroxaban in XANTUS was 80% at 1 year
- Over 75% of patients were ‘very satisfied/satisfied’ with their treatment



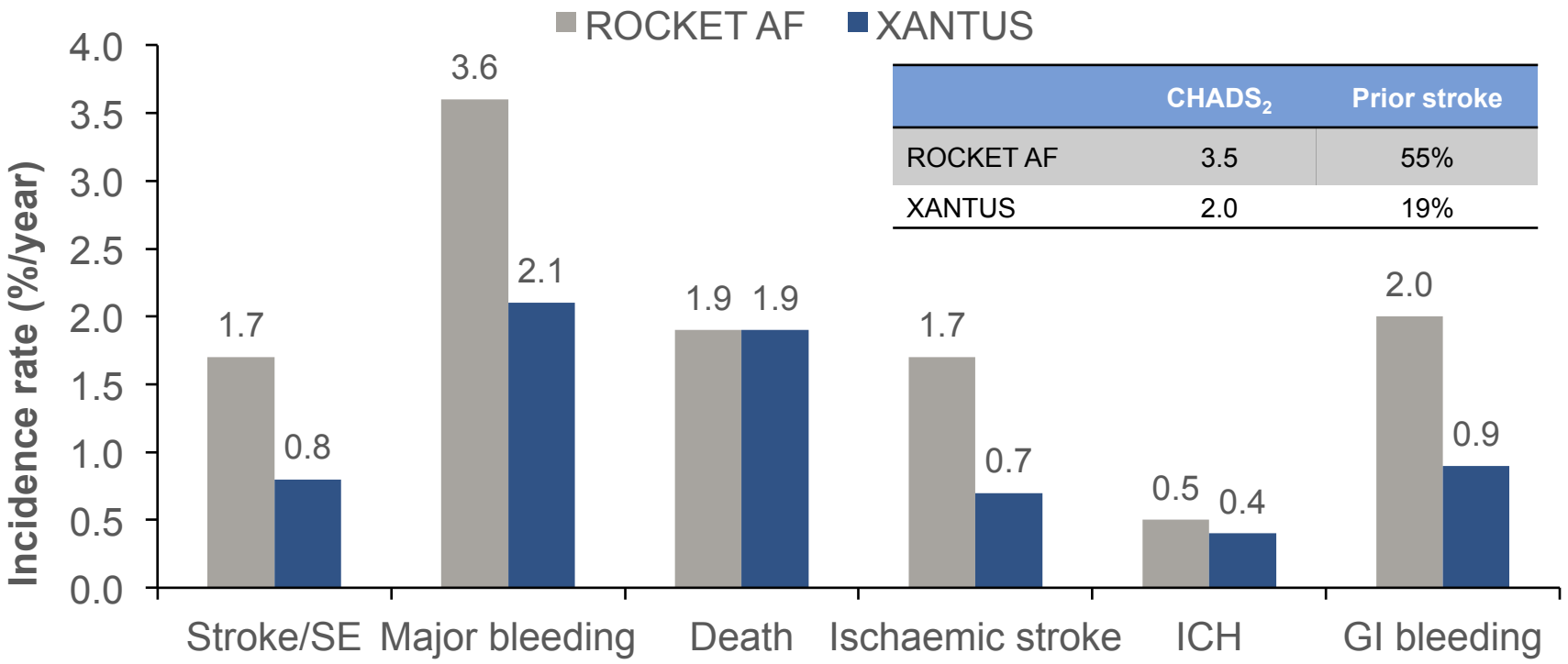
	Rivaroxaban N=6784 n (%)
Very satisfied	2247 (33.1)
Satisfied	2849 (42.0)
Neutral	877 (12.9)
Unsatisfied	340 (5.0)
Very unsatisfied	116 (1.7)
Missing	355 (5.2)

Outcomes According to Dosing (20/15 mg od)

- Major bleeding, all-cause death, and thromboembolic events occurred at higher incidence rates for the 15 mg od versus the 20 mg od dose



Comparison of Main Outcomes: XANTUS versus ROCKET AF



	$CHADS_2$	Prior stroke
ROCKET AF	3.5	55%
XANTUS	2.0	19%

Strengths and limitations of XANTUS

- Strengths
  - Large sample size
  - Prospective design
  - Independent endpoint adjudication
- Limitations
  - Single-arm, open-label study
  - Limited influence on data completeness in observational setting
  - Outcomes not adjusted for baseline risk factors

Summary

- XANTUS is the first large prospective study that describes the use of rivaroxaban in a broad patient population with non-valvular AF
  - Patients in XANTUS were at lower overall risk than those in the rivaroxaban phase III ROCKET AF clinical trial
- The rates of major bleeding and stroke with rivaroxaban were low in routine clinical practice

Management of Interruption of Treatment

Drug	Patient	Procedure
Drug half-life	Renal function	Bleeding risk
Route of clearance	Concomitant drugs (e.g., aspirin)	Thrombosis risk

Last intake of drug before elective surgical intervention

Creatinine clearance (CrCl)	Dabigatran		Apixaban		Rivaroxaban	
No important bleeding risk and/or adequate local haemostasis possible: Perform at trough level (i.e. 12 h or 24 h after last intake)						
	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50-80 ml/min	≥36 h	≥72 h	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 30-50 ml/min*	≥48 h	≥96 h	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 15-30 ml/min*	Not indicated	Not indicated	≥36 h	≥48 h	≥36 h	≥48 h
CrCl <15ml/min	No official indication for use					

*Many of these patients may be on lower dose of NOAC
Low risk = surgery with low risk of bleeding, high risk = surgery with high risk of bleeding

Resumption of NOAC

Procedure	Action
Procedures with immediate and complete haemostasis: Atraumatic spinal/ epidural anaethesia Clean lumbar puncture	Resume 6–8 h after surgery
Procedures associated with immobilization	Initiate reduced venous or intermediate dose of LMWH 6–8 h after surgery if haemostasis achieved
Procedures with post-operative risk of bleeding	Restart NOACs 48–72h after surgery upon complete haemostasis Thromboprophylaxis (e.g. with LMWH) can be initiated 6-8 h after surgery

Heidbuchel *et al,* 2013

Treatment of bleeding

- Measurement of Anticoagulant effect
- General measures
- Reversal of anticoagulation

Monitoring vs Measuring

- Monitoring implies dose adjustment according to test result

- Measuring the drug or drug effect may be useful in:
  - Overdosage
  - Questions of compliance
  - Urgent surgery, interventions, thrombolysis
  - Extreme body weights
  - Children
  - Renal insufficiency

Measurement of anticoagulant effects of NOACs

Test		Dabigatran	Rivaroxaban	Apixaban
Specific Assay	Drug specific	Hemoclot	Anti-Xa	Anti-Xa
	aPTT	↑↑↑	↑	↑
Non-specific assays	PT	↑	↑↑	↑
	TT	↑↑↑↑	No effect	No effect

HAMILTON REGIONAL LABORATORY MEDICINE PROGRAM

SUBJECT:	**RIVAROXABAN ANTI XA LEVELS**
DATE:	JANUARY 23, 2015

Our Special Coagulation laboratory is pleased to inform you that we have added Rivaroxaban anti Xa levels to our test menu

The Future

- Point of care testing

Management of VKA Bleeding

- Hold drug(s)
- Vitamin K
- Resuscitation (i.v. access, fluid administration, blood product transfusion)
- Maintain diuresis to clear drug
- Mechanical compression and surgical methods to stop bleeding

Replace clotting factors

Characteristic	Frozen plasma	PCC
Constituents	All clotting factors	II, (VII), IX, X (C, S)
Dose	10-15 ml/kg	25-50 IU factor IX/kg
Onset	Duration of infusion	15-30 min
Adverse effects	Fluid overload, febrile & allergic reactions, infection, TRALI	Possible excess thromboembolic complications
Other	Vitamin K to sustain reversal*	Vitamin K to sustain reversal*

*Half life of factor VII is 6 hours

Management of NOAC Bleeding

- Hold drug(s)
- *No Vit K*
- Resuscitation (i.v. access, fluid administration, blood product transfusion)
- Maintain diuresis to clear drug
- Mechanical compression and surgical methods to stop bleeding

Reversal of NOACs

- Activate coagulation to overcome the effect of the drug
- Remove drug
- Neutralize drug

Activate coagulation

- Prothrombin complex concentrates (PCC)
  - II, VII, IX, X, C, S,
  - 25-50 units per kg
- Activated prothrombin complex concentrates (aPCC)
- (Antifibrinolytic agents (e.g., tranexamic acid)
- Recombinant factor VIIa (rVIIa)

Effect of NOACs on Prothrombin Time and Endogenous Thrombin Potential with PCC

Circulation
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Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

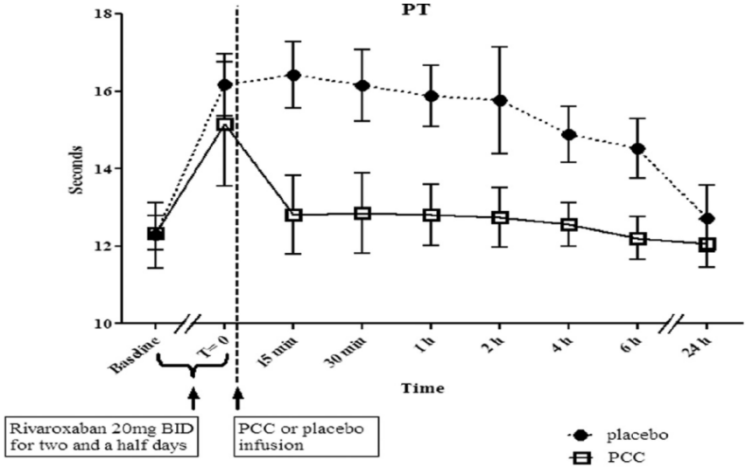
Background—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thromboembolism show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

Methods and Results—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.8±1.3 versus 12.3±0.7 seconds at baseline; $P<0.001$) that was immediately and completely reversed by PCC (12.8±1.0; $P<0.001$). The endogenous thrombin potential was inhibited by rivaroxaban (51±22%; baseline, 92±22%; $P=0.002$) and normalized with PCC (114±26%; $P<0.001$), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests.

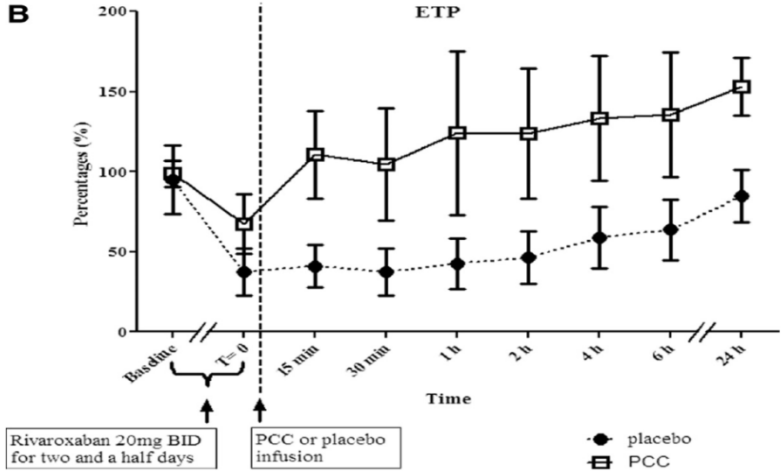
Conclusion—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

Rivaroxaban : Effect on Prothrombin Time and Endogenous Thrombin Potential with PCC

Prothrombin time (PT)



Endogenous thrombin potential (ETP)



- PCC demonstrated the potential to reverse rivaroxaban effects on PT and ETP in humans

Antidotes to Anticoagulants

- Bleeding
- Emergency Intervention
- Elective Intervention
- Overdose

Specific antidotes to NOACs

	Idarucizumab	PER977	Andexanet alpha
Structure	Humanized Fab fragment	Synthetic small molecule	Human rXa variant
Target	Dabigatran	Universal	FXa inhibitors
Binding	Non-competit. High affinity	?	Competitive
Clinical studies	Rapid complete reversal	?	Rapid, near complete reversal

Andexanet Alpha

- FDA-designated breakthrough therapy.
- Universal antidote for patients receiving a Factor Xa inhibitor anticoagulant who suffer a major bleeding episode or who may require emergency surgery
- Under development

Andexanet Alpha

- Phase III Clinical Trials
  - ANNEXA-A : apixaban
  - ANNEXA-R : rivaroxaban
  - ANNEXA-E : edoxaban

Conclusions

- NOACs provide opportunity to minimize growing burden of potentially preventable thromboembolism (especially AF)
- Reductions in both stroke and bleeding translate into important benefits for patients
- Most bleeding can be managed without specific antidotes
- Specific antidotes in development will provide reassurance to physicians
- Education to overcome the fear of bleeding as a barrier to appropriate anticoagulant use important