Prevention of Stroke and non-CNS Embolism with Rivaroxaban Compared with Warfarin in Patients with Non-valvular Atrial Fibrillation and Moderate Renal Impairment

Keith A. A. Fox
on behalf of the ROCKET AF Investigators

Disclosures

- Supported by grants from Johnson & Johnson Pharmaceutical Research & Development L.L.C. (Raritan, NJ) and Bayer HealthCare Pharmaceuticals (Berlin, Germany).
- An international executive committee designed the trial and was responsible for oversight of study conduct, retained independent ability to analyse and present the data, and take responsibility for the accuracy and completeness of data analyses.

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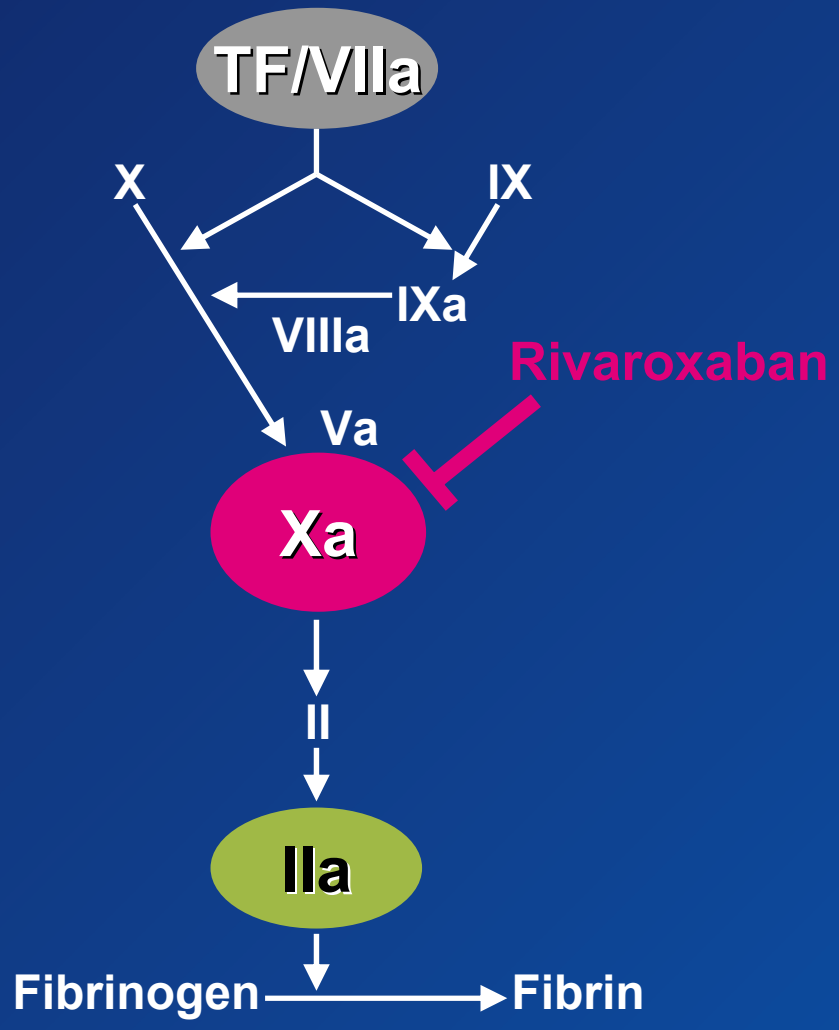
Background
Rivaroxaban

- Direct, specific, competitive factor Xa inhibitor
- Half-life 5-13 hours
- Clearance :
  - 1/3 direct renal excretion
  - 2/3 metabolism via CYP 450 enzymes
- Oral, once daily dosing without need for coagulation monitoring
- Studied in >25,000 patients in post-op, DVT, PE and ACS patients



Adapted from Weitz *et al*, 2005; 2008

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Study Design

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Atrial Fibrillation

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind /
Double Dummy
(n ~ 14,000)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

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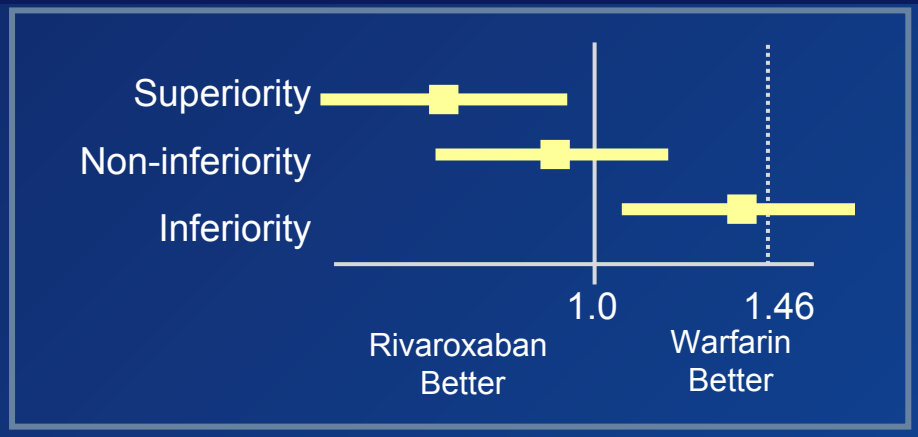
Statistical Methods



- Sample Size
  - Warfarin event rate ~2.3
  - Type 1 error 0.05 (2-sided)
  - 405 events; >95% power
  - ~14,000 patients
- Primary Efficacy Evaluation:
  - Stroke or non-CNS Embolism on treatment
- Primary Safety Evaluation:
  - Major or non-Major Clinically Relevant Bleeding

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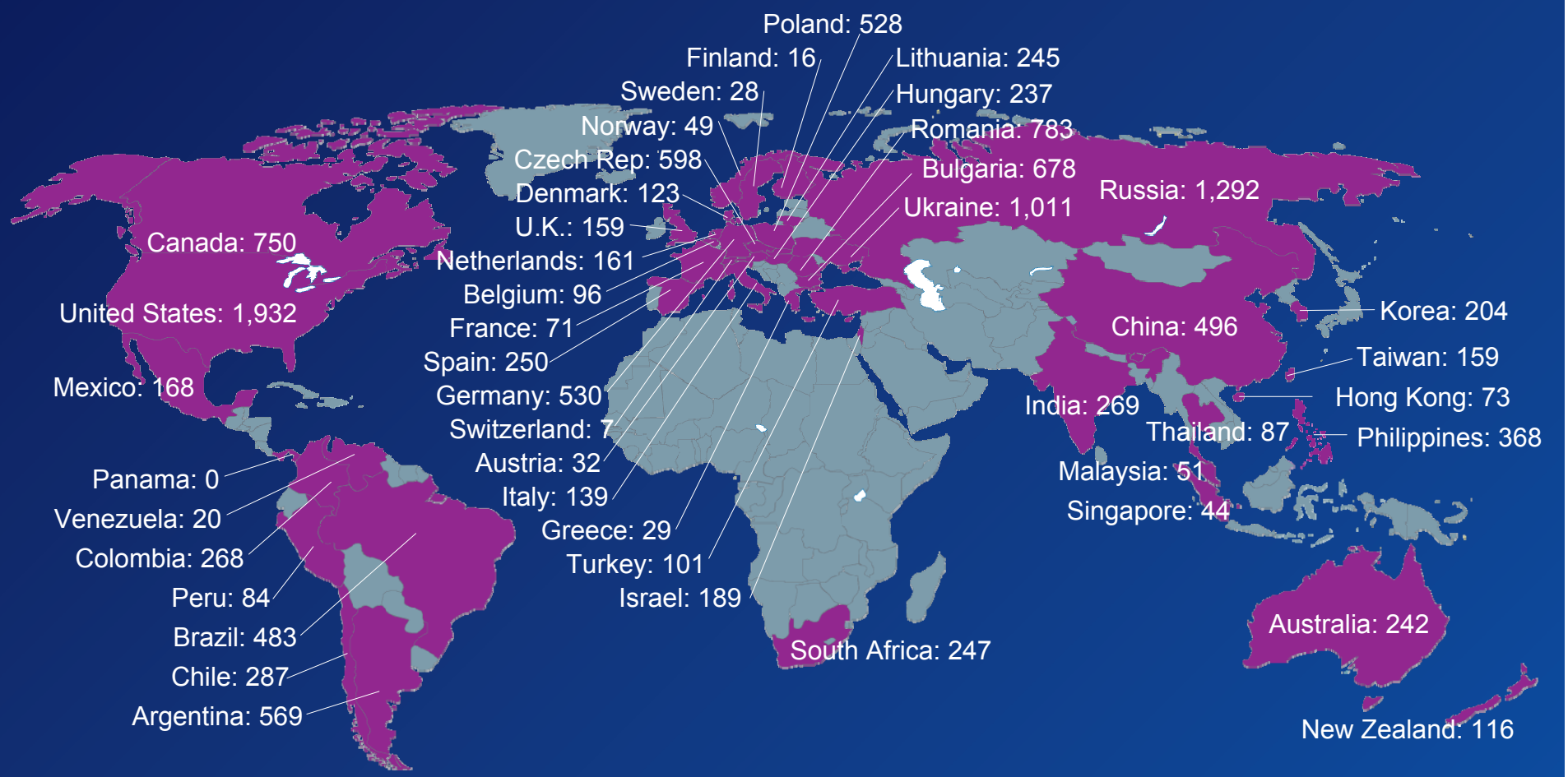
Enrollment

45 countries, 1178 sites, 14,264 patients



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Study Conduct

	Rivaroxaban	Warfarin
Randomized, n	7131	7133
Lost to Follow-up, n	18	18
Premature Discontinuation, n (%)	1691 (23.7)	1584 (22.2)
Withdrew Consent, n	223	224
Median (25th, 75th) Exposure (days)	589 (396, 805)	593 (404, 810)
Median (25th, 75th) Follow-up (days)	706 (522, 884)	708 (518, 886)

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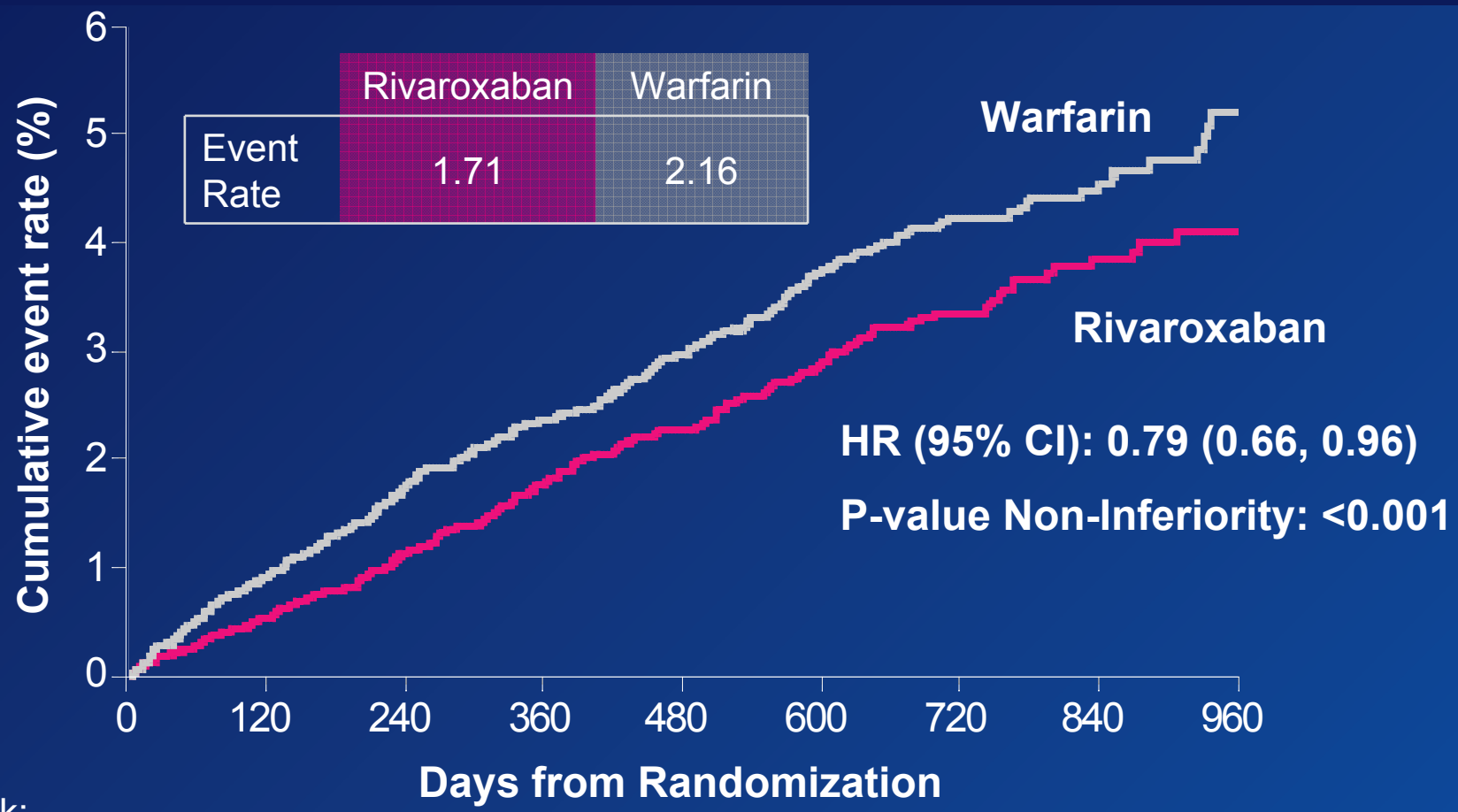
Primary Efficacy Outcome
Stroke and non-CNS Embolism



No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

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Baseline Demographics

Characteristic	CrCl 30 – 49 ml/min		CrCl ≥50 ml/min	
	Riva 15mg (N=1474)	Warfarin (N=1476)	Riva 20mg (N=5637)	Warfarin (N=5640)
Age, median (25th, 75th) yrs	79 (75, 82)	79 (75, 83)	71 (63, 76)	71 (63, 76)
Female, no. (%)	811 (55.0)	825 (55.9)	2008 (35.6)	1999 (35.4)
SBP median (25th, 75th) mmHg	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)
Paroxysmal AF, no. (%)	245 (16.6)	215 (14.6)	997 (17.7)	1052 (18.7)
Prior aspirin use, (%)	529 (35.9)	552 (37.4)	2049 (36.4)	2060 (36.5)
Prior vitamin K antagonist use, no. (%)	924 (62.7)	904 (61.3)	3507 (62.2)	3548 (62.9)

Values are median (IQR)

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Baseline Demographics (con't)

Characteristic	CrCl 30 – 49 ml/min		CrCl ≥50 ml/min	
	Riva 15mg (N=1474)	Warfarin (N=1476)	Riva 20mg (N=5637)	Warfarin (N=5640)
$CHADS_2$ score, mean ± SD	3.68 (1.00)	3.67 (1.01)	3.42 (0.91)	3.41 (0.92)
Prior TIA/stroke or systemic embolism, no. (%)	738 (50.1)	725 (49.1)	3167 (56.2)	3160 (56.0)
Congestive heart failure, no. (%)	973 (66.0)	964 (65.3)	3484 (61.8)	3468 (61.5)
Hypertension, no. (%)	1352 (91.7)	1360 (92.1)	5067 (89.9)	5100 (90.4)
Diabetes mellitus, no. (%)	468 (31.8)	492 (33.3)	2401 (42.6)	2319 (41.1)
Prior myocardial infarction, no. (%)	276 (18.7)	302 (20.5)	902 (16.0)	977 (17.3)

SD, standard deviation; TIA, transient ischaemic attack.

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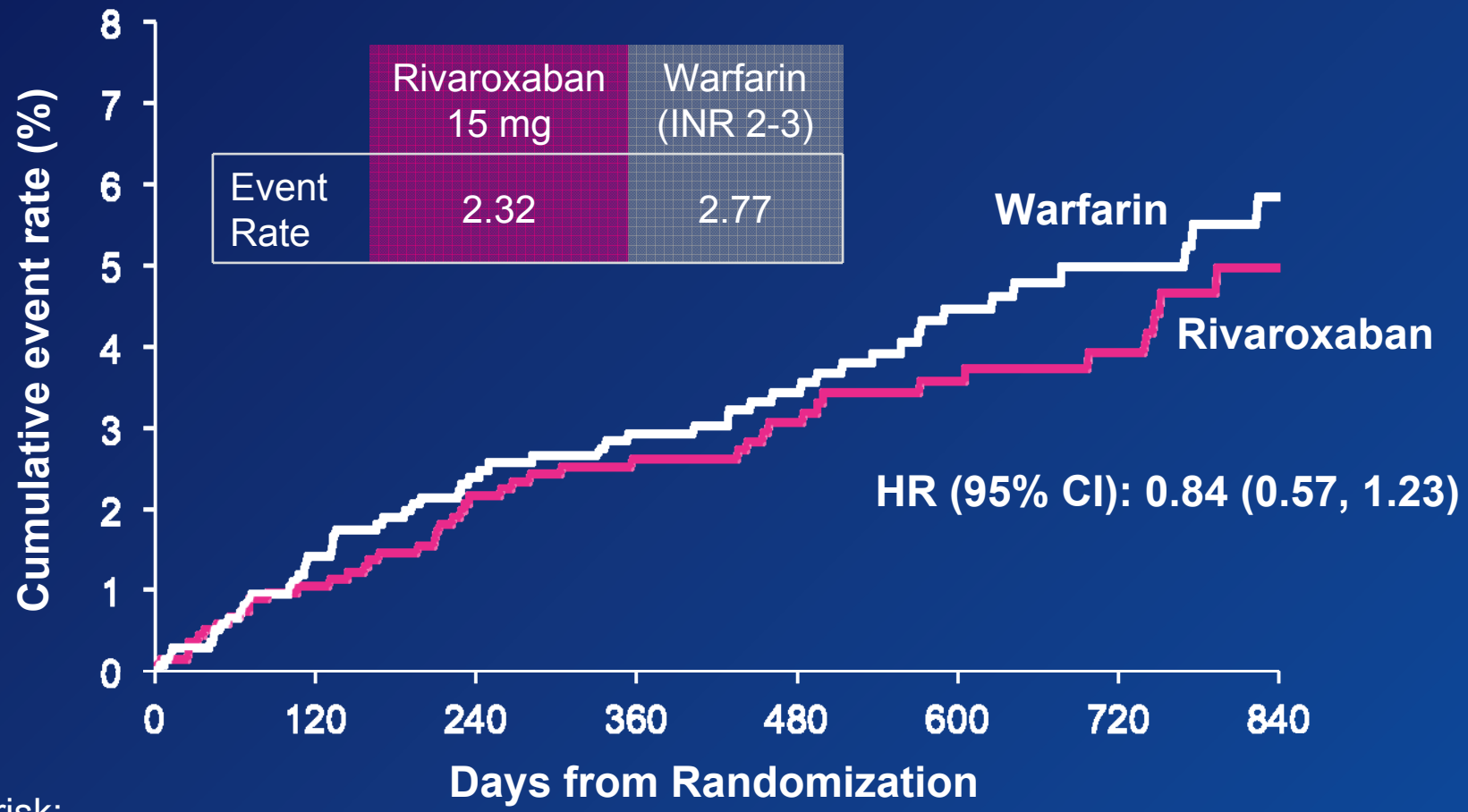
Stroke or non-CNS embolism among those with CrCl 30–49 mL/min



No. at risk:								
Rivaroxaban	1434	1226	1103	1027	806	621	442	275
Warfarin	1439	1261	1140	1052	832	656	455	272

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

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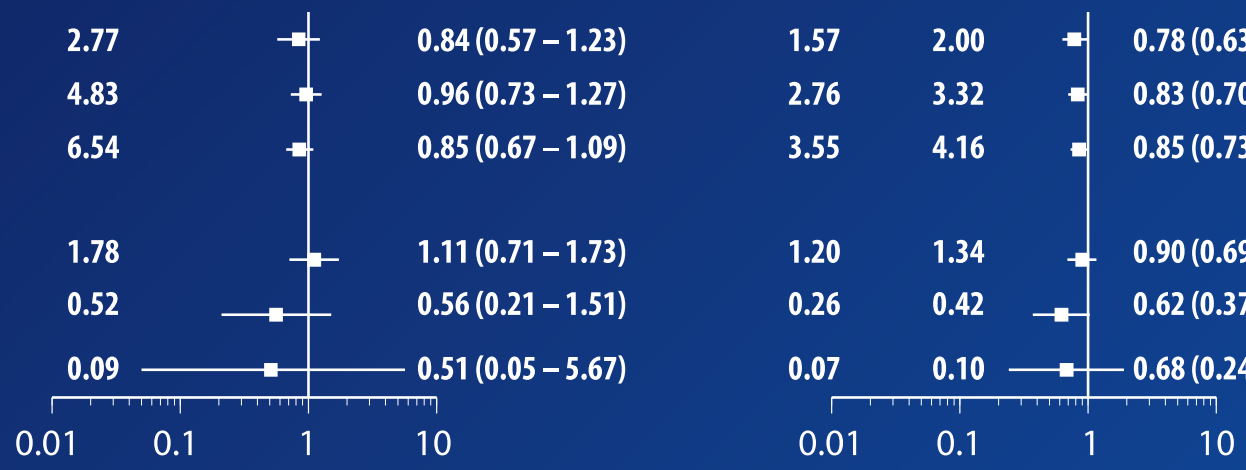
Efficacy Outcomes on Treatment

Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value
	Riva 15 mg (N=1434)†	Warfarin N=1462	HR (95% CI) Riva vs Warfarin	Riva 20 mg (N=5524)†	Warfarin N=5556	HR (95% CI) Riva vs Warfarin	Interaction
Principal Efficacy Endpoint	2.32	2.77	0.84 (0.57 – 1.23)	1.57	2.00	0.78 (0.63 – 0.98)	0.76
PE + Vascular Death	4.64	4.83	0.96 (0.73 – 1.27)	2.76	3.32	0.83 (0.70 – 0.98)	0.38
PE + MI, Vascular Death	5.58	6.54	0.85 (0.67 – 1.09)	3.55	4.16	0.85 (0.73 – 0.99)	0.98
Stroke							
Ischemic	1.98	1.78	1.11 (0.71 – 1.73)	1.20	1.34	0.90 (0.69 – 1.16)	0.41
Hemorrhagic	0.29	0.52	0.56 (0.21 – 1.51)	0.26	0.42	0.62 (0.37 – 1.03)	0.88
Undetermined	0.05	0.09	0.51 (0.05 – 5.67)	0.07	0.10	0.68 (0.24 – 1.90)	0.84



* *The primary analysis was pre-specified to be performed in the per-protocol population on treatment, which included all patients who received at least 1 dose of study drug, did not have major protocol violations, and were followed for events while on study drug or within 2 days of last dose.*

† *Event rates per 100 pt/yrs of follow-up*

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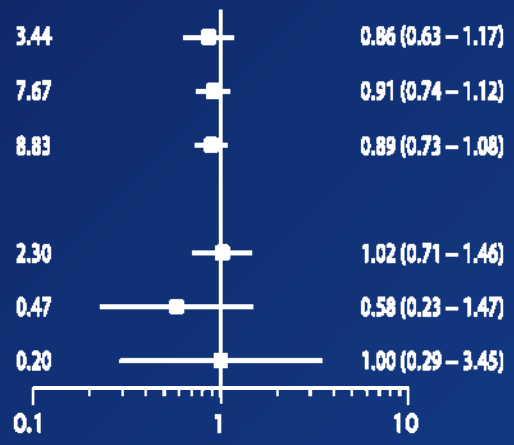
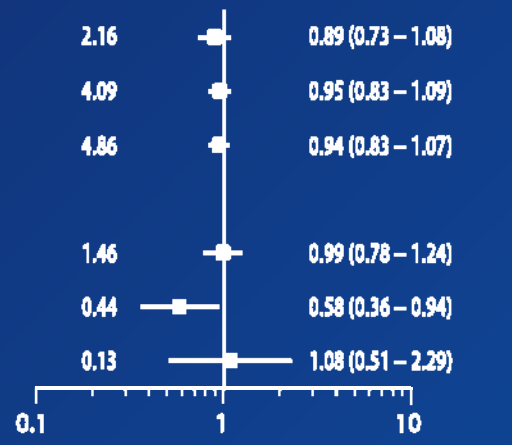
Efficacy Outcomes by Intention to Treat

Clinical Endpoint	CrCl 30 – 49 ml/min: Rivaroxaban 15 mg (N=1462)*	Warfarin N=1459	HR (95% CI) Rivaroxaban vs Warfarin	CrCl ≥50 ml/min: Rivaroxaban 20 mg (N=5619)*	Warfarin N=5622	HR (95% CI) Rivaroxaban vs Warfarin	P Value Interaction
Principal Efficacy Endpoint (Stroke and Systemic Embolism)	2.95	3.44	0.86 (0.63 – 1.17)	1.92	2.16	0.89 (0.73 – 1.08)	0.85
PE + Vascular Death	7.00	7.67	0.91 (0.74 – 1.12)	3.89	4.09	0.95 (0.83 – 1.09)	0.74
PE + MI, Vascular Death	7.86	8.83	0.89 (0.73 – 1.08)	4.59	4.86	0.94 (0.83 – 1.07)	0.61
Stroke							
Ischemic	2.34	2.30	1.02 (0.71 – 1.46)	1.44	1.46	0.99 (0.78 – 1.24)	0.89
Hemorrhagic	0.27	0.47	0.58 (0.23 – 1.47)	0.25	0.44	0.58 (0.36 – 0.94)	0.99
Undetermined	0.20	0.20	1.00 (0.29 – 3.45)	0.14	0.13	1.08 (0.51 – 2.29)	0.92





* Event rates per 100 pt/yrs of follow-up

Event Rates are per 100 patient-years
Based on Intention-to-Treat Population

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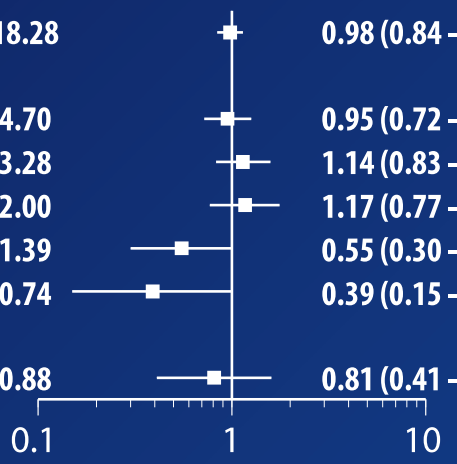
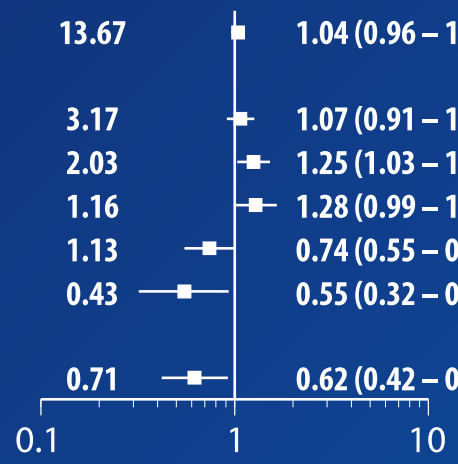
Primary Safety Outcomes

Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value
	Riva 15 mg (N=1474)†	Warfarin N=1476	HR (95% CI) Riva vs Warfarin	Riva 20 mg (N=5637)†	Warfarin N=5640	HR (95% CI) Riva vs Warfarin	Interaction
Primary Safety Endpoint	17.82	18.28	0.98 (0.84 – 1.14)	14.24	13.67	1.04 (0.96 – 1.13)	0.45
Major Bleeding	4.49	4.70	0.95 (0.72 – 1.26)	3.39	3.17	1.07 (0.91 – 1.26)	0.48
Hct or Hgb Drop	3.76	3.28	1.14 (0.83 – 1.58)	2.54	2.03	1.25 (1.03 – 1.52)	0.65
Transfusion	2.34	2.00	1.17 (0.77 – 1.76)	1.49	1.16	1.28 (0.99 – 1.65)	0.71
Clinical Organ	0.76	1.39	0.55 (0.30 – 1.00)	0.83	1.13	0.74 (0.55 – 0.99)	0.39
Fatal Bleeding	0.28	0.74	0.39 (0.15 – 0.99)	0.23	0.43	0.55 (0.32 – 0.93)	0.53
Intracranial Hemorrhage	0.71	0.88	0.81 (0.41 – 1.60)	0.44	0.71	0.62 (0.42 – 0.92)	0.51





Event Rates are per 100 patient-years
Based on Safety on Treatment Population

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Bleeding Sites

	CrCl 30–49 ml/min			CrCl ≥50 ml/min		
	Riva 15 mg (N = 1474)	Warfarin (N=1476)	P-value	Riva 20 mg (N=5637)	Warfarin (N=5640)	P-value
GI (upper, lower, and rectal)	2.88	1.77	0.02	1.79	1.12	0.0002
Intracranial	0.71	0.88	0.54	0.44	0.71	0.02
Macroscopic haematuria	0.05	0.18	0.22	0.28	0.19	0.21
Bleeding associated with non-cardiac surgery	0.24	0.42	0.31	0.15	0.19	0.61
Intra-articular	0.00	0.23	0.99	0.18	0.17	0.98
Epistaxis	0.19	0.09	0.40	0.10	0.13	0.53

**Major bleeding per 100 pt-yrs of follow-up*

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Adverse Events According to Renal Function & Randomised Treatment

	CrCl 0–49 ml/min		CrCl ≥50 ml/min	
Adverse Event, no. (%)	Riva 15 mg (N=1474)	Warfarin (N=1476)	Riva 20 mg (N=5637)	Warfarin (N=5640)
Total patients	1248 (84.7)	1281 (86.8)	4543 (80.6)	4520 (80.1)
Epistaxis	150 (10.2)	121 (8.2)	571 (10.1)	488 (8.7)
Peripheral oedema	115 (7.8)	120 (8.1)	320 (5.7)	324 (5.7)
Dizziness	110 (7.5)	118 (8.0)	323 (5.7)	330 (5.9)
Cardiac failure	104 (7.1)	120 (8.1)	293 (5.2)	299 (5.3)
Bronchitis	94 (6.4)	90 (6.1)	302 (5.4)	326 (5.8)
Dyspnea	83 (5.6)	102 (6.9)	297 (5.3)	292 (5.2)
Diarrhoea	84 (5.7)	96 (6.5)	295 (5.2)	300 (5.3)
Upper respiratory infection	62 (4.2)	70 (4.7)	274 (4.9)	255 (4.5)
Headache	68 (4.6)	70 (4.7)	256 (4.5)	291 (5.2)
Arthralgia	73 (5.0)	69 (4.7)	228 (4.0)	262 (4.6)
Haematuria	47 (3.2)	58 (3.9)	249 (4.4)	183 (3.2)
UTI	72 (4.9)	105 (7.1)	221 (3.9)	216 (3.8)

*15 most frequent treatment-emergent adverse events based on rivaroxaban group.
† Based on safety population, including events that started on/after the first dose of study medication and up to 2 days after the last dose of study medication.

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Conclusions

- Those with renal dysfunction are at higher risk for stroke and higher risk of bleeding events compared with those without renal dysfunction.
- The outcomes among patients with moderate renal dysfunction were similar for rivaroxaban and warfarin and consistent with the findings in those with preserved renal function.
- In summary, the reduced dose of rivaroxaban preserved the benefits of warfarin without an increase in adverse events compared with warfarin and there was less fatal bleeding

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Study Organization

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