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

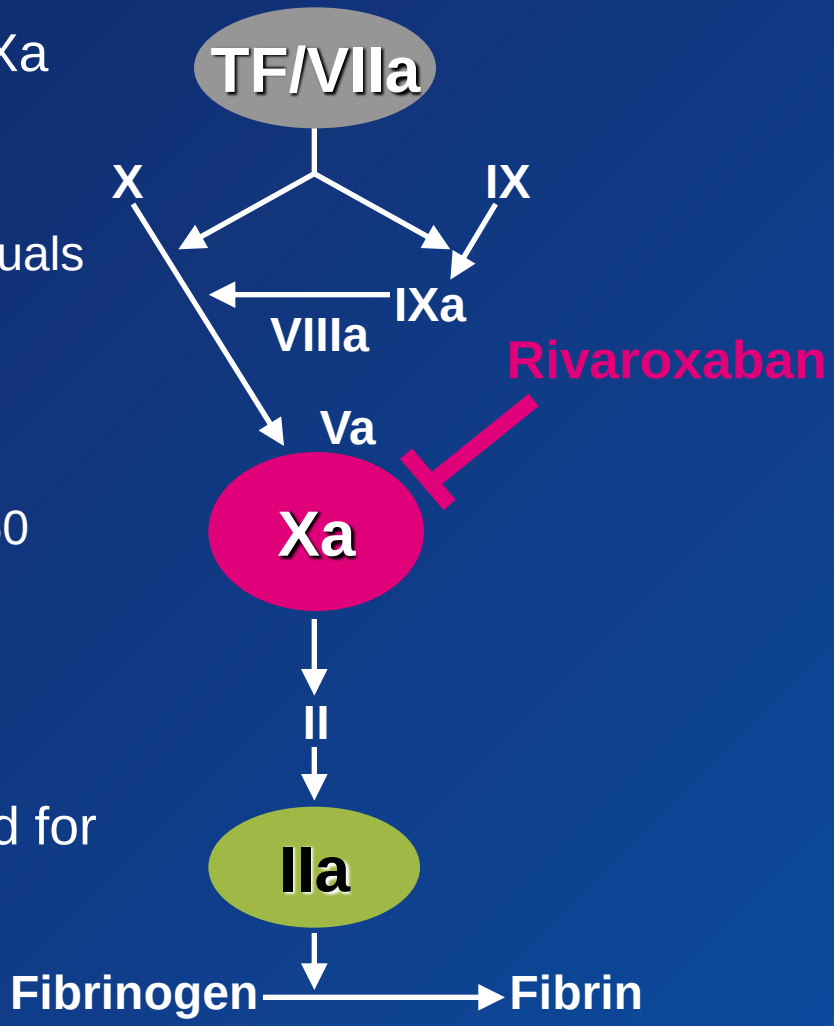
Keith A. A. Fox
on behalf of the ROCKET AF Investigators

Disclosures

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

Background
Rivaroxaban

- Direct, specific, competitive Factor Xa inhibitor
- Half-life:
  - 5–9 hours in young, healthy individuals
  - 11–13 hours in the elderly
- Clearance:
  - 1/3 direct renal excretion
  - 2/3 metabolism, mainly via CYP 450 enzymes, of which
    - half is excreted renally
    - half is excreted via the biliary-faecal route
- Oral, once-daily dosing without need for coagulation monitoring
- Studied in >25,000 patients in post-operative THR or TKR, DVT, PE, medically ill, and ACS patients



Adapted from Weitz *et al*, 2005; 2008

Study Design

Risk Factors
Stroke, TIA or Systemic embolus
OR
- **CHF**
- **Hypertension**
- **Age ≥ 75**
- **Diabetes**

At least 2 or 3 required*

Atrial Fibrillation

Rivaroxaban

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

Randomized 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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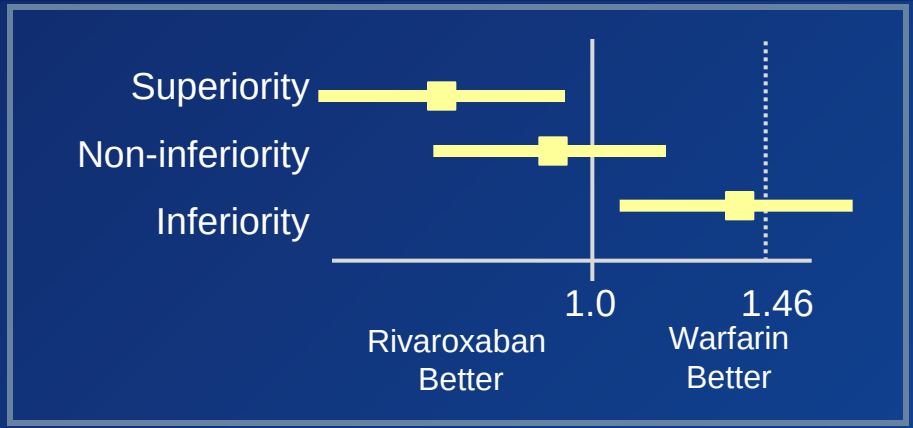
Statistical Methods



- 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 (non-inferiority: per-protocol, on treatment)
- Primary Safety Evaluation:
  - Major or non-Major Clinically Relevant Bleeding

Enrollment

45 countries, 1178 sites, 14,264 patients

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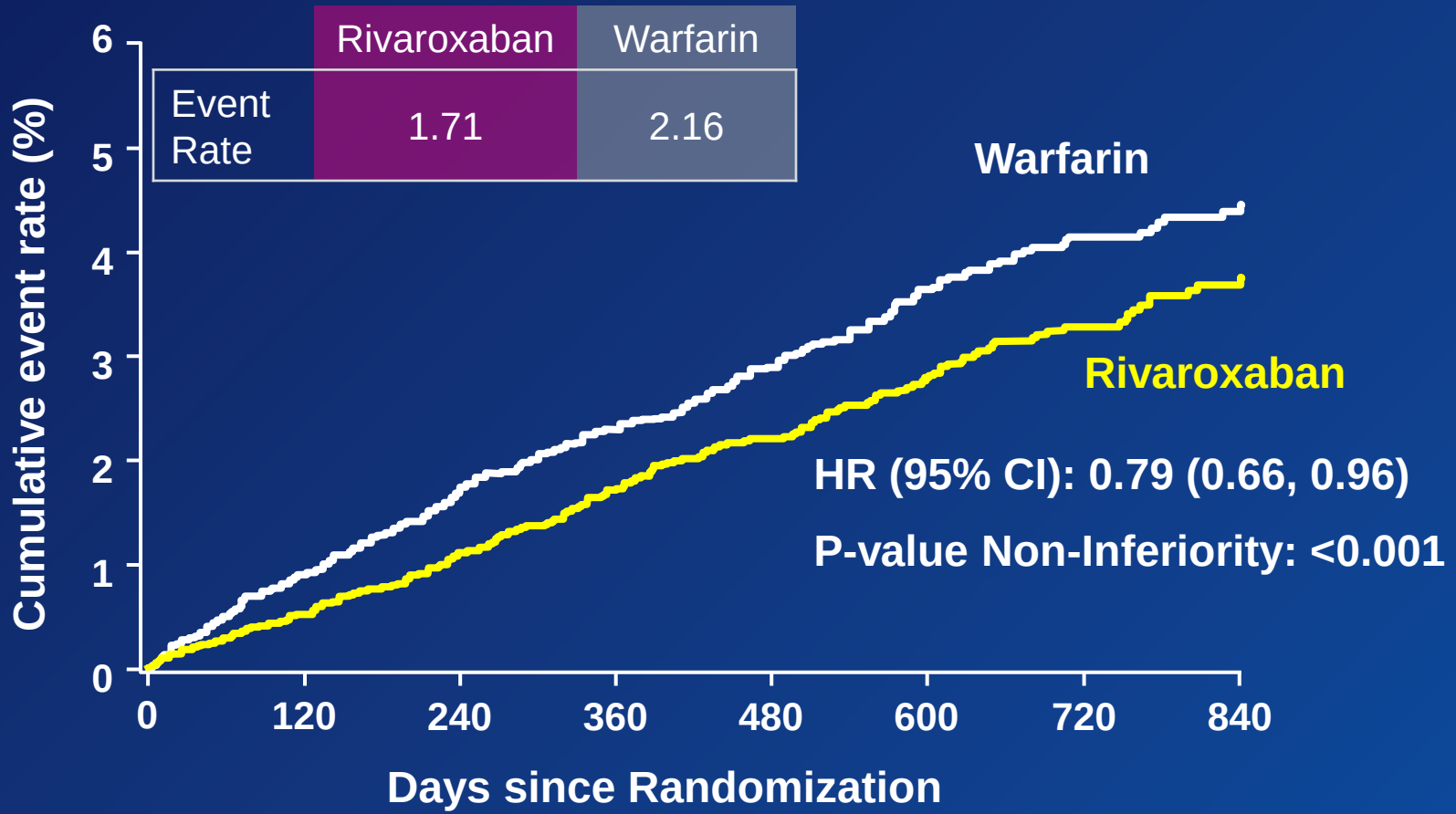
Study Conduct

	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 (25^{th}, 75^{th}) Exposure (days)	589 (396, 805)	593 (404, 810)
Median (25^{th}, 75^{th}) Follow-up (days)	706 (522, 884)	708 (518, 886)

Primary Efficacy Endpoint
Stroke and non-CNS Embolism



No. at risk:								
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538

Event rates are % per year
Based on Protocol Compliant on Treatment Population

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Baseline demographics

Characteristic	CrCl 30–49 ml/min		CrCl ≥50 ml/min	
	Rivaroxaban 15 mg od (N=1474)	Warfarin (N=1476)	Rivaroxaban 20 mg od (N=5637)	Warfarin (N=5640)
Age, median (IQR), yrs	79 (75–82)	79 (75–83)	71 (63–76)	71 (63–76)
Female (%)	55.0	55.9	35.6	35.4
BMI, median (IQR), kg/m^2	25.1 (22.7–28.0)	25.2 (22.8–27.9)	29.2 (26.1–33.0)	28.9 (26.0–32.7)
SBP, median (IQR), mm Hg	130 (120–140)	130 (120–140)	130 (120–140)	130 (120–140)
Paroxysmal AF (%)	16.6	14.6	17.7	18.7
Prior ASA use (%)	35.9	37.4	36.4	36.5
Prior VKA use (%)	62.7	61.3	62.2	62.9

ASA, acetylsalicylic acid; IQR, interquartile range; VKA, vitamin K antagonist
Safety population (minus 9 pts in warfarin arm with no CrCl data)

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Baseline demographics (continued)

Characteristic	CrCl 30–49 ml/min		CrCl ≥50 ml/min	
	Rivaroxaban 15 mg od (N=1474)	Warfarin (N=1476)	Rivaroxaban 20 mg od (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 stroke/TIA or systemic embolism (%)	50.1	49.1	56.2	56.0
Congestive heart failure (%)	66.0	65.3	61.8	61.5
Hypertension (%)	91.7	92.1	89.9	90.4
Diabetes mellitus (%)	31.8	33.3	42.6	41.1
Prior myocardial infarction (%)	18.7	20.5	16.0	17.3

SD, standard deviation; TIA, transient ischaemic attack
Safety population (minus 9 pts in warfarin arm with no CrCl data)

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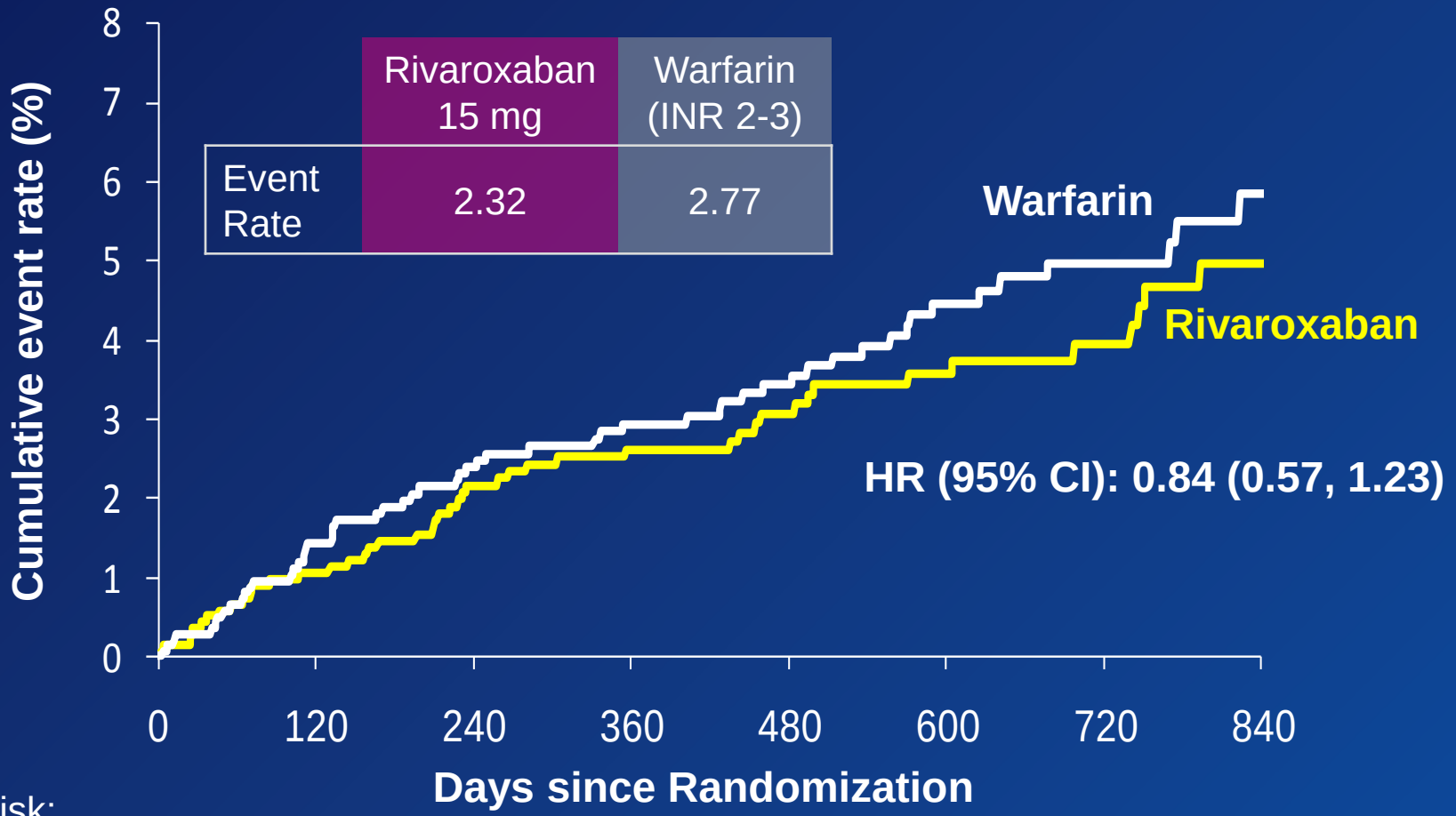
Stroke or non-CNS embolism among those with CrCl 30–49 mL/min



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 year
Based on Protocol Compliant on Treatment Population

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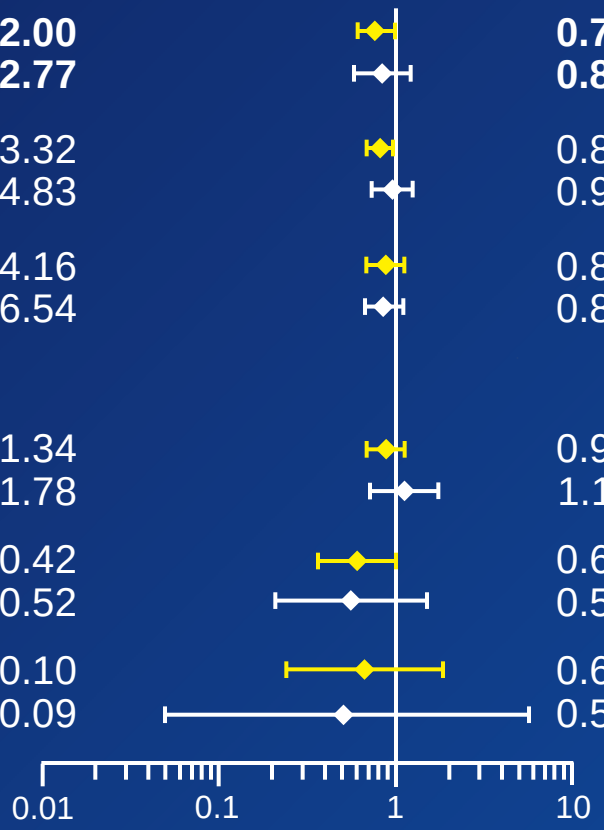
Efficacy endpoints on treatment

Clinical endpoint (% per year)	Rivaroxaban (N=7111)	Warfarin (N=7116)	HR (95% CI) Rivaroxaban vs warfarin	*P* (interaction)
Primary efficacy endpoint*	**1.57** **2.32**	**2.00** **2.77**	**0.78 (0.63–0.98)** **0.84 (0.57–1.23)**	**0.76**
PE + vascular death	2.76 4.64	3.32 4.83	0.83 (0.70–0.98) 0.96 (0.73–1.27)	0.38
PE + MI, vascular death	3.55 5.58	4.16 6.54	0.85 (0.73–0.99) 0.85 (0.67–1.09)	0.98
Stroke				
Ischaemic	1.20 1.98	1.34 1.78	0.90 (0.69–1.16) 1.11 (0.71–1.73)	0.41
Haemorrhagic	0.26 0.29	0.42 0.52	0.62 (0.37–1.03) 0.56 (0.21–1.51)	0.88
Undetermined	0.07 0.05	0.10 0.09	0.68 (0.24–1.90) 0.51 (0.05–5.67)	0.84



Based on per-protocol population on treatment
*Stroke and systemic embolism
†Rivaroxaban 20 mg od. ‡Rivaroxaban 15 mg od

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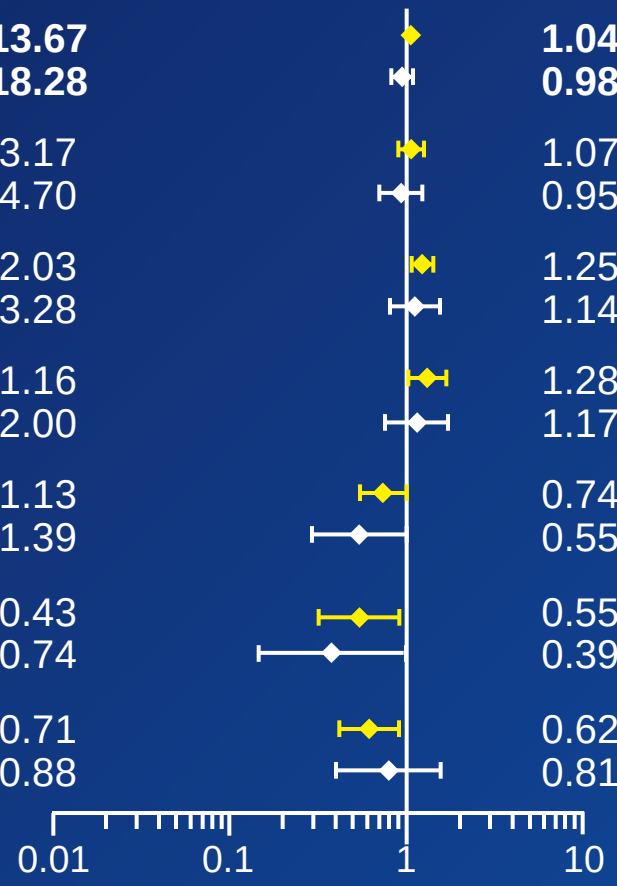
Safety outcomes

Clinical endpoint (% per year)	Rivaroxaban (N=7111)	Warfarin (N=7116)	HR (95% CI) Rivaroxaban vs warfarin	*P* (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
Hct or Hb 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



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

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Bleeding sites

Major bleeding (% per year)	CrCl 30–49 ml/min		CrCl ≥50 ml/min	
	Rivaroxaban 15 mg (N = 1474)	Warfarin (N=1476)	Rivaroxaban 20 mg (N=5637)	Warfarin (N=5640)
GI (upper, lower, and rectal)†	2.88	1.77	1.79	1.12
Intracranial haemorrhage‡	0.71	0.88	0.44	0.71
Macroscopic haematuria	0.05	0.18	0.28	0.19
Bleeding associated with non-cardiac surgery	0.24	0.42	0.15	0.19
Intra-articular	0.00	0.23	0.18	0.17
Epistaxis	0.19	0.09	0.10	0.13

† p=0.02 (riva vs. warf in CrCl 30–49 ml/min); p=0.0002 (riva vs. warf in CrCl ≥50 ml/min)
‡ p=0.02 (riva vs. warf in CrCl ≥50 ml/min)

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Adverse Events* according to Renal Function & Randomised Treatment

Adverse Event (%)	CrCl 30–49 ml/min		CrCl ≥50 ml/min	
	Riva 15 mg (N=1474)	Warfarin (N=1476)	Riva 20 mg (N=5637)	Warfarin (N=5640)
Total patients†	84.7	86.8	80.6	80.1
Epistaxis	10.2	8.2	10.1	8.7
Peripheral oedema	7.8	8.1	5.7	5.7
Dizziness	7.5	8.0	5.7	5.9
Cardiac failure	7.1	8.1	5.2	5.3
Bronchitis	6.4	6.1	5.4	5.8
Diarrhoea	5.7	6.5	5.2	5.3
Dyspnea	5.6	6.9	5.3	5.2
Cough	5.5	5.0	4.6	4.9
Nasopharyngitis	5.2	5.7	6.1	6.5
Arthralgia	5.0	4.7	4.0	4.6
Haematuria	3.2	3.9	4.4	3.2

* Treatment-emergent adverse events with frequency ≥5% based on rivaroxaban group, plus haematuria
† Based on safety population on treatment

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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
- In summary, the reduced dose of rivaroxaban in this patient subgroup yielded efficacy and safety results consistent with the overall trial, with similar rates of bleeding and adverse events and fewer fatal bleeds, compared with warfarin

Study Organization

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Available now online from *European Heart Journal*

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doi:10.1093/eurheartj/ehr342

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Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment

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