SUPPLEMENTAL MATERIAL

Methods

A complete presentation of methods is given in reference 3. This includes a complete list of covariables that were included in the adjustments. These are repeated here:

For the efficacy endpoints: age, sex, body mass index, prior stroke/transient ischaemic attack, vascular disease (myocardial infarction, peripheral artery disease, carotid occlusive disease), chronic heart failure, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, paroxysmal AF, diastolic blood pressure, creatinine clearance (Cockcroft–Gault), heart rate, and abstinence from alcohol use.

For the safety endpoints: age, sex, prior stroke/transient ischaemic attack, anaemia, prior gastrointestinal bleeding, chronic obstructive pulmonary disease, diastolic blood pressure, creatinine clearance (Cockcroft–Gault), platelets, albumin, and prior aspirin, vitamin K antagonist, or thienopyridine use.

Regarding patient selection, the following sections from reference 3 are relevant

Definitions and endpoints (from reference 3)

The case report form asked whether there was ‘significant valvular disease,’ and if so, it asked for ‘valve location and abnormality’ and ‘etiology.’ Thus, for the purpose of this study, any type of valvular lesion that did not meet the above exclusion criteria was included in SVD if it was considered to be significant by the recruiting physician(s) in order to reflect clinical practice (external validity).

Limitations (from reference 3)

The protocol did not include precise quantification of valve disease. However, the term ‘significant’ valvular lesion implied that the physician did not consider it as less than moderate. On the other hand, it could also not be of such haemodynamic significance that cardiac surgery would be necessary in the foreseeable future since this was an exclusion criterion. Thus, the majority of patient can be suspected to have had moderate valve disease.

Supplemental Table 1. Treatment comparisons for efficacy and safety endpoints among SVD subtypes and for no-SVD patients.

1A. Event rates.

Outcomes	AS		MR or AR		No SVD	
	Rivaroxaban events/ 100 pt-yrs (total events)	Warfarin events/ 100 pt-yrs (total events)	Rivaroxaban events/ 100 pt-yrs (total events)	Warfarin events/ 100 pt-yrs (total events)	Rivaroxaban events/ 100 pt-yrs (total events)	Warfarin events/ 100 pt-yrs (total events)
Efficacy outcomes						
Stroke or SE	4.74 [1.11,8.37] (9)	3.73 [0.75,6.71] (8)	1.70 [1.02,2.38] (28)	2.29 [1.53,3.05] (41)	1.96 [1.69,2.23] (231)	2.22 [1.93,2.51] (256)
Stroke, SE, or vascular death	9.77 [4.63,14.91] (18)	11.87 [6.81,16.93] (23)	4.42 [3.34,5.50] (71)	4.64 [3.58,5.70] (81)	4.16 [3.77,4.55] (478)	4.47 [4.06,4.88] (504)
Stroke, SE, vascular death, MI	10.37 [5.07,15.67] (19)	13.75 [8.23,19.27] (26)	5.43 [4.23,6.63] (86)	5.99 [4.77,7.21] (103)	4.81 [4.39,5.23] (549)	5.17 [4.73,5.61] (579)
Stroke	4.74 [1.11,8.37] (9)	2.75 [0.22,5.28] (6)	1.45 [0.82,2.08] (24)	1.95 [1.25,2.65] (35)	1.86 [1.60,2.12] (219)	2.07 [1.79,2.35] (239)
All-cause death	9.06 [4.26,13.86] (17)	13.28 [8.06,18.50] (26)	4.88 [3.76,6.00] (78)	4.92 [3.84,6.00] (86)	4.19 [3.80,4.58] (482)	4.60 [4.19,5.01] (520)
Safety outcomes						
Major or NMCR bleeding	26.22 [16.51,35.93] (28)	22.90 [14.84,30.96] (31)	19.30 [16.75,21.85] (220)	16.17 [13.94,18.40] (202)	14.19 [13.39,14.99] (1222)	14.14 [13.34,14.94] (1209)
Major bleeding	9.90 [4.30,15.50] (12)	5.82 [2.02,9.62] (9)	5.95 [4.61,7.29] (76)	3.88 [2.85,4.91] (55)	3.22 [2.86,3.58] (307)	3.33 [2.96,3.70] (318)
Gastrointestinal bleeding	4.12 [0.51,7.73] (5)	1.94 [-0.26,4.14] (3)	2.89 [1.96,3.82] (37)	3.88 [2.85,4.91] (55)	3.22 [2.86,3.58] (307)	3.33 [2.96,3.70] (318)
Intracranial hemorrhage	1.53 [0,3.65] (2)	1.28 [0,3.06] (2)	0.84 [0.35,1.33] (11)	0.69 [0.26,1.12] (10)	0.43 [0.30,0.56] (42)	0.74 [0.57,0.91] (72)

Event rates are unadjusted. All abbreviations can be found in Supplemental Table 1A.

Abbreviations: AS, aortic stenosis; MR or AR, mitral or aortic regurgitation; ITT, intention-to-treat; MI, myocardial infarction; NMCR, non-major clinically relevant; pt-years, patient-years; SE, systemic embolism; SVD, significant valve disease; CI, confidence interval.

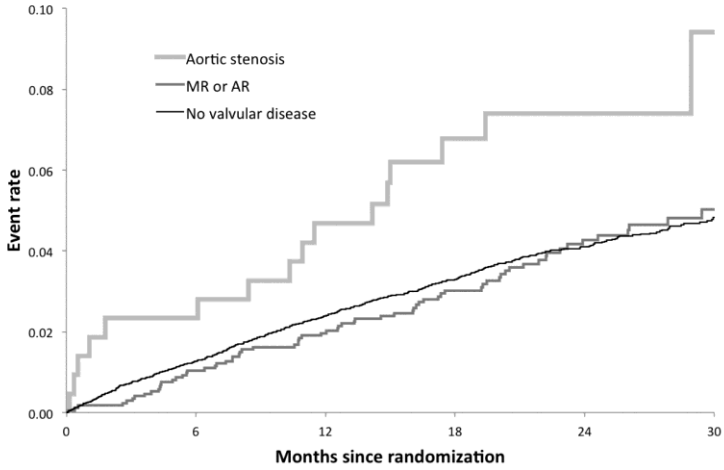
1B. Interaction tests and treatment comparisons within subgroups.[*]

Outcomes	P-value for test of interaction between treatment and SVD subtype	AS rivaroxaban vs. warfarin HR (95% CI)	MR or AR rivaroxaban vs. warfarin HR (95% CI)	No SVD rivaroxaban vs. warfarin HR (95% CI)
Efficacy outcomes				
Stroke or SE	0.71			
Stroke, SE, or vascular death	0.63			
Stroke, SE, vascular death, or MI	0.42			
Stroke	0.49			
All-cause death	0.33			
Safety outcomes				
Major or NMCR bleeding	0.047	1.18 (0.70, 1.97)	1.32 (1.08, 1.60)	1.01 (0.93, 1.10)
Major bleeding	0.016	1.73 (0.73, 4.12)	1.63 (1.15, 2.31)	0.97 (0.83, 1.14)
Gastrointestinal bleeding	0.34			
Intracranial hemorrhage	0.24			

[*]Hazard ratios are shown only where there was a significant interaction. The p-value for the test of interaction between treatment and subgroups was derived from a single overall test performed in each model to determine treatment effect differences among the three groups.

Abbreviations: see Supplemental Table 1.

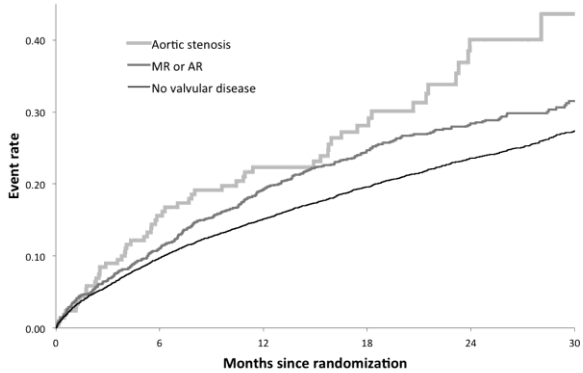
Suppl. Figure 1. Primary efficacy endpoint by subgroup.



Number at risk						
Aortic stenosis	214	209	204	157	91	36
MR or AR	1726	1708	1687	1302	874	427
No valvular disease	12179	12025	11856	8860	5505	2330

Primary efficacy endpoint (stroke or systemic embolism) by subgroup (unadjusted data). For results of detailed statistical analyses, see Table 3.

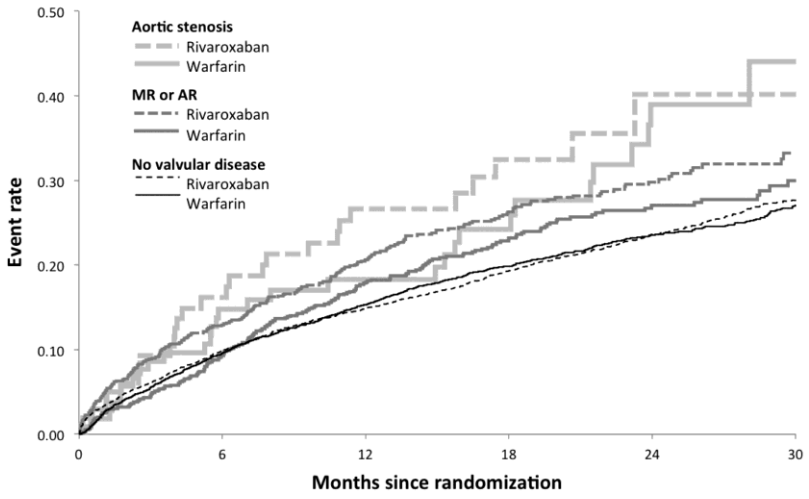
Suppl. Figure 2. Primary safety endpoint by SVD subtype.



Number at risk						
Aortic stenosis	214	148	116	74	36	10
MR or AR	1731	1368	1138	785	464	213
No valvular disease	12237	9784	8486	5817	3274	1282

Primary safety endpoint (major or NMCR bleeding) by SVD subtype. For results of detailed statistical analyses, see Table 3. NMCR, non-major clinically relevant; SVD, significant valve disease

Suppl. Figure 3. Primary safety endpoint by SVD subtype and randomized treatment.



Number at risk						
AS - Rivaroxaban	104	66	54	30	11	3
AS - Warfarin	110	82	62	44	25	7
MR or AR - Rivaroxaban	836	646	546	376	222	96
MR or AR - Warfarin	895	722	592	409	242	117
None - Rivaroxaban	6146	4882	4266	2934	1640	645
None - Warfarin	6091	4902	4220	2883	1634	637

Primary safety endpoint (major or NMCR bleeding) by SVD subtype and randomized treatment. For results of detailed statistical analyses, see Supplemental Table 1. AS, aortic stenosis; NMCR, non-major clinically relevant; SVD, significant valve disease