EFFETTO DEL RIVAROXABAN SULLA RIDUZIONE DI ICTUS ED EVENTI ISCHEMICI TRANSITORI IN PAZIENTI CON SCOMPENSO CARDIACO, CORONAROPATIA E IN RITMO SINUSALE: DATI DAL TRIAL COMMANDER HF

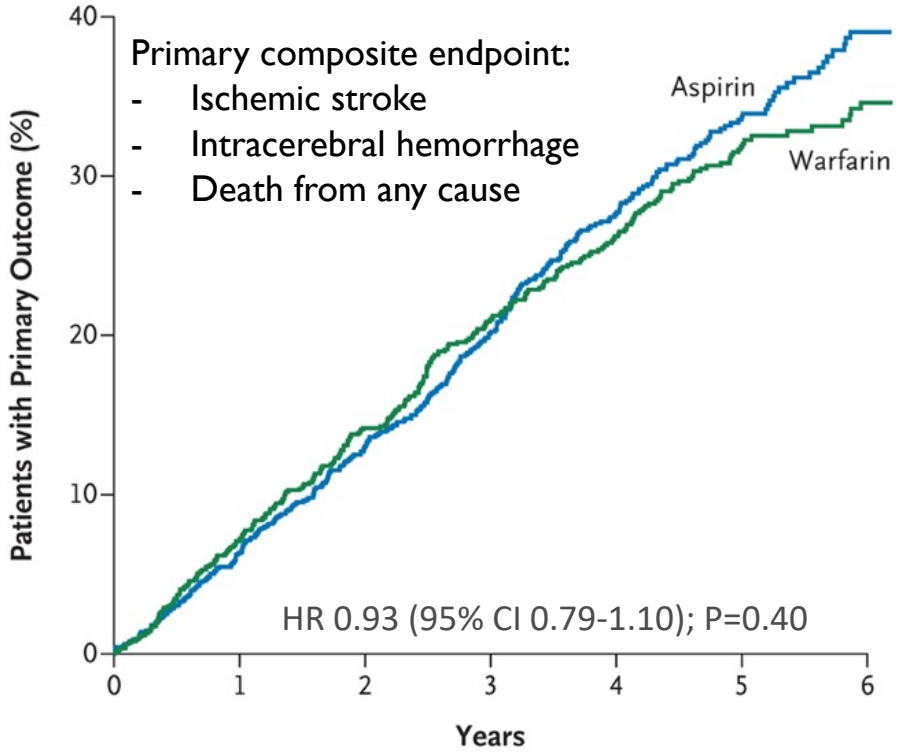
BACKGROUND

- Stroke is a devastating occurrence in patients with heart failure with reduced ejection (HFrEF).
- Although atrial fibrillation (AF) has been the traditional target population for stroke risk reduction, patients with HF and sinus rhythm face elevated risk of stroke compared with the general population.

WARCEF TRIAL

Aspirin vs. Warfarin in pts with HF and sinus rhythm

Primary composite endpoint:
- Ischemic stroke
- Intracerebral hemorrhage
- Death from any cause



No. at Risk							
Aspirin	1163	1073	860	658	508	329	94
Warfarin	1142	1049	852	653	525	363	115

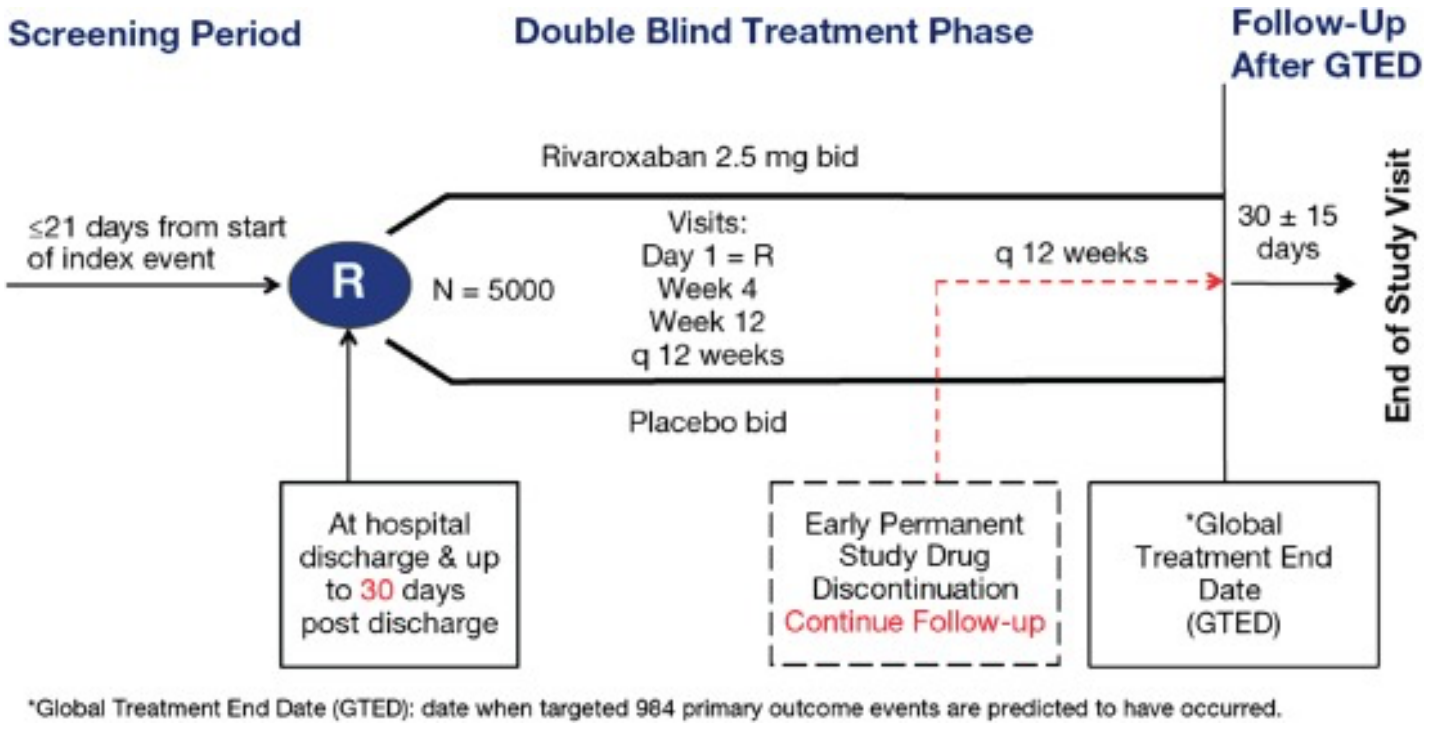
	Warfarin (N=1142)		Aspirin (N=1163)		Hazard Ratio (95% CI)†	P Value
	no. of patients (%)	*unadjusted rate of events/100 patient-yr*	*no. of patients (%)*	*unadjusted rate of events/100 patient-yr*		
Ischemic stroke	29 (2.5)	0.72	55 (4.7)	1.36	0.52 (0.33–0.82)	0.005

N Engl J Med 2012; 366:1859-1869

COMMANDER HF- TRIAL DESIGN

Study population

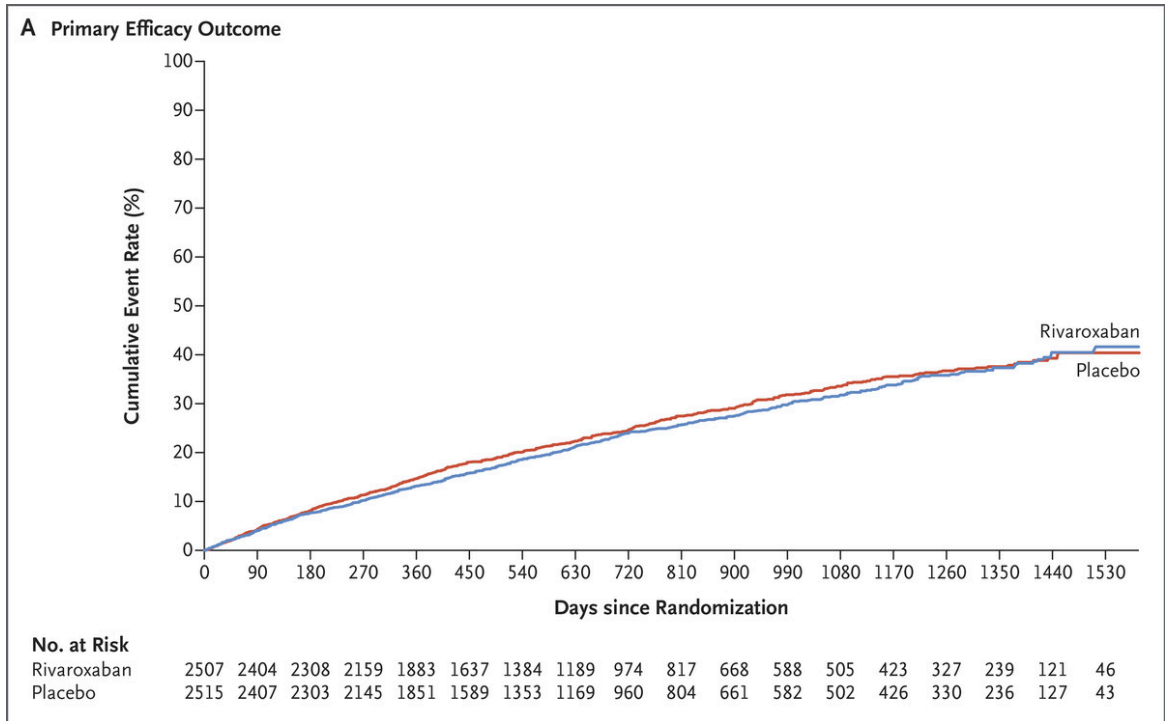
- Chronic heart failure (at least 3 months)
- LVEF ≤ 40%
- Coronary artery disease
- Episode of worsening HF within the previous 21 day

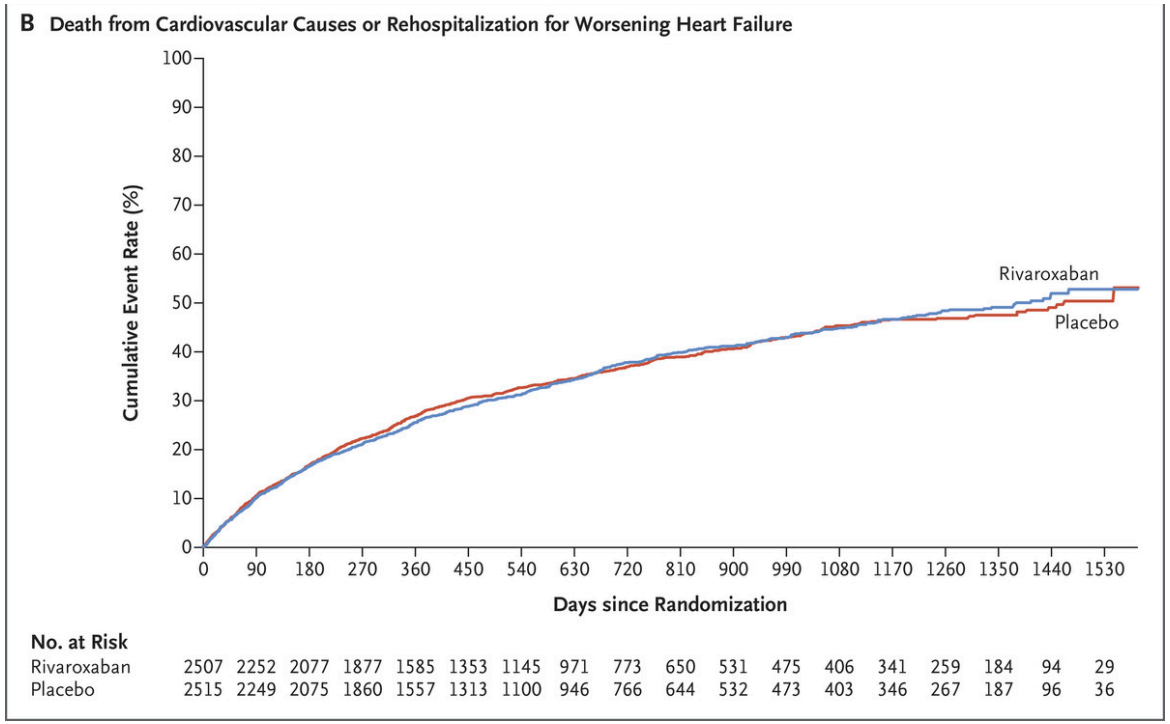


Eur J Heart Fail. 2015 Jul; 17(7): 735–742.

COMMANDER HF

Death from any cause, myocardial infarction, stroke





N Engl J Med 2018; 379:1332-1342

COMMANDER HF - EFFICACY OUTCOMES

Outcome	Rivaroxaban (N=2507)		Placebo (N=2515)		Rivaroxaban vs. Placebo†	
	No. (%)	Events/ 100 Patient-Yr	No. (%)	Events/ 100 Patient-Yr	Hazard Ratio (95% CI)	P Value
Efficacy outcomes‡						
Composite primary efficacy outcome	626 (25.0)	13.44	658 (26.2)	14.27	0.94 (0.84–1.05)	0.27
Death from any cause	546 (21.8)	11.41	556 (22.1)	11.63	0.98 (0.87–1.10)	—
Myocardial infarction	98 (3.9)	2.08	118 (4.7)	2.52	0.83 (0.63–1.08)	—
Stroke	51 (2.0)	1.08	76 (3.0)	1.62	0.66 (0.47–0.95)	—
Secondary and exploratory efficacy outcomes						
Death from a cardiovascular cause or rehospitalization for worsening of heart failure	932 (37.2)	23.32	929 (36.9)	23.46	0.99 (0.91–1.09)	—
Death from a cardiovascular cause	453 (18.1)	9.46	476 (18.9)	9.96	0.95 (0.84–1.08)	—
Rehospitalization for worsening of heart failure	689 (27.5)	17.24	691 (27.5)	17.45	0.98 (0.89–1.09)	—
Rehospitalization for cardiovascular event other than worsening of heart failure	543 (21.7)	13.30	572 (22.7)	14.04	0.95 (0.84–1.07)	—
Death from any cause or rehospitalization for worsening of heart failure	993 (39.6)	24.84	973 (38.7)	24.57	1.01 (0.92–1.10)	—
Symptomatic deep-vein thrombosis	5 (0.2)	0.10	7 (0.3)	0.15	0.71 (0.23–2.24)	—
Symptomatic pulmonary embolism	11 (0.4)	0.23	9 (0.4)	0.19	1.23 (0.51–2.96)	—

N Engl J Med 2018; 379:1332-1342

COMMANDER HF - SAFETY OUTCOMES

	Rivaroxaban (N = 2499)		Placebo (N = 2509)		Rivaroxaban vs. Placebo†	
	No. (%)	Events/ 100 Patient-Yr	No. (%)	Events/ 100 Patient-Yr	Hazard Ratio (95% CI)	P Value
Safety outcomes§						
Composite principal safety outcome	18 (0.7)	0.44	23 (0.9)	0.55	0.80 (0.43–1.49)	0.48
Fatal bleeding	9 (0.4)	0.22	9 (0.4)	0.22	1.03 (0.41–2.59)	0.95
Bleeding into a critical space with potential for causing permanent disability	13 (0.5)	0.32	20 (0.8)	0.48	0.67 (0.33–1.34)	0.25
ISTH-defined major bleeding¶	82 (3.3)	2.04	50 (2.0)	1.21	1.68 (1.18–2.39)	0.003
Hemoglobin decrease of ≥2 g/dl	55 (2.2)	1.37	30 (1.2)	0.73	1.87 (1.20–2.91)	0.005
Transfusion of ≥2 units of packed red cells or whole blood	31 (1.2)	0.77	18 (0.7)	0.43	1.74 (0.98–3.12)	0.06
Bleeding at a critical site	25 (1.0)	0.62	23 (0.9)	0.56	1.12 (0.63–1.97)	0.70
Fatal bleeding	3 (0.1)	0.07	7 (0.3)	0.17	0.45 (0.12–1.72)	0.23
Bleeding requiring hospitalization	61 (2.4)	1.52	48 (1.9)	1.16	1.30 (0.89–1.90)	0.17

N Engl J Med 2018; 379:1332-1342

A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial

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European Heart Journal, ehz427

AIM OF THE STUDY

To explore:

- Incidence, timing, type, and severity of stroke or a transient ischaemic attack (TIA)
- Clinical predictors of the occurrence of stroke or TIA
- Net clinical benefit of treatment with low-dose rivaroxaban compared with placebo on prevention of stroke or TIA

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OUTCOMES

- **Primary neurological outcome**
  - Time to first all-cause stroke or TIA, defined as new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause without another identifiable cause after the study randomization.
  - Categorized based on available imaging as ischaemic, haemorrhagic, subarachnoid, or uncertain.
  - Modified Rankin Scale (mRS) to determine stroke-related disability with higher scores denoting more disability (mRS 0–5) and ultimately death (mRS 6)

- **Principal safety outcome**
  - Fatal bleeding or bleeding into a critical space with a potential for causing permanent disability

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BASELINE CHARACTERISTICS

5022 patients from 628 sites across 32 countries

	Stroke/TIA			No stroke/TIA		
	Rivaroxaban (*n* = 61)	Placebo (*n* = 89)	Total (*N* = 150)	Rivaroxaban (*n* = 2446)	Placebo (*n* = 2426)	Total (*N* = 4872)
Age, mean (SD) (years)	66.5 (9.6)	68.3 (10.2)	67.5 (10.0)	66.0 (10.1)	66.2 (10.3)	66.4 (10.2)
Women, *n* (%)	13 (21.3)	24 (27.0)	37 (24.7)	538 (22.0)	575 (23.7)	1113 (22.8)
White race, *n* (%)	45 (73.8)	73 (82.0)	118 (78.7)	2018 (82.5)	1992 (82.1)	4010 (82.3)
Region, *n* (%)						0.149
Eastern Europe	37 (60.7)	46 (51.7)	83 (55.3)	1573 (64.3)	1568 (64.6)	3141 (64.5)
North America	1 (1.6)	4 (4.5)	5 (3.3)	73 (3.0)	71 (2.9)	144 (3.0)
Asia Pacific	13 (21.3)	12 (13.5)	25 (16.7)	354 (14.5)	354 (14.6)	708 (14.5)
Latin America	7 (11.5)	11 (12.4)	18 (12.0)	222 (9.1)	218 (9.0)	440 (9.0)
Western Europe And South Africa	3 (4.9)	16 (18.0)	19 (12.7)	224 (9.2)	215 (8.9)	439 (9.0)
Medical history, *n* (%)						
Myocardial infarction	45 (73.8)	61 (68.5)	106 (70.7)	1866 (76.3)	1831 (75.5)	3697 (75.9)
Stroke	8 (13.1)	18 (20.2)	26 (17.3)	200 (8.2)	227 (9.4)	427 (8.8)
Hypertension	47 (77.0)	74 (83.1)	121 (80.7)	1850 (75.6)	1812 (74.7)	3662 (75.2)
Diabetes	29 (47.5)	41 (46.1)	70 (46.7)	995 (40.7)	987 (40.7)	1982 (40.7)
Vital sign, median (IQR)						
Systolic blood pressure (mmHg)	123.0 (113.0, 131.0)	128.0 (115.0, 137.0)	125.0 (113.0, 132.0)	122.0 (110.0, 133.0)	122.0 (110.0, 131.0)	122.0 (110.0, 132.0)
Diastolic blood pressure (mmHg)	74.0 (70.0, 80.0)	72.0 (67.0, 80.0)	73.0 (67.0, 80.0)	74.0 (69.0, 80.0)	72.0 (68.0, 80.0)	73.0 (68.0, 80.0)

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BASELINE CHARACTERISTICS

	Stroke/TIA			No stroke/TIA		
	Rivaroxaban (*n* = 61)	**Placebo (*n* = 89)**	**Total (*N* = 150)**	**Rivaroxaban (*n* = 2446)**	**Placebo (*n* = 2426)**	**Total (*N* = 4872)**
Biomarkers, median (IQR)						
BNP (pg/mL)	607.3 (517.4, 1877.5)	780.0 (399.4, 1380.0)	679.0 (461.0, 1380.0)	702.0 (389.5, 1230.0)	686.5 (368.4, 1266.3)	696.0 (382.3, 230.7)
NT-proBNP (pg/mL)	3136.0 (1915.0, 6303.5)	2160.5 (1237.5, 4232.5)	2435.0 (1417.5, 5306.5)	2806.0 (1932.0, 6360.0)	2890.0 (1502.0, 6267.0)	2851.5 (1511.5, 6303.5)
D-dimer (µg/L)	335.0 (270.0, 685.0)	455.0 (265.0, 950.0)	390.00 (267.5, 710.0)	360.0 (215.0, 680.0)	360.0 (215.0, 640.0)	360.00 (215.0, 665.0)
New York Heart Association classification, *n* (%)						0.974
I	4 (6.6)	0	4 (2.7)	76 (3.1)	69 (2.8)	145 (3.0)
II	20 (32.8)	44 (49.4)	64 (42.7)	1102 (45.1)	1052 (43.4)	2154 (44.2)
III	33 (54.1)	43 (48.3)	76 (50.7)	1175 (48.1)	1211 (49.9)	2386 (49.0)
IV	4 (6.6)	2 (2.2)	6 (4.0)	92 (3.8)	94 (3.9)	186 (3.8)
CHA_2DS_2-VASC Score, median (IQR)	4 (3, 6)	5 (4, 6)	5 (4, 6)	4 (3, 5)	4 (3, 5)	4 (3, 5)
Baseline therapies, *n* (%)						
Aspirin	53 (86.9)	85 (95.5)	138 (92.0)	2276 (93.0)	2261 (93.2)	4537 (93.1)
Thienopyridine	30 (49.2)	29 (32.6)	59 (39.3)	1013 (41.4)	943 (38.9)	1956 (40.1)
Dual antiplatelet therapy	24 (39.3)	26 (29.2)	50 (33.3)	1696 (34.8)	883 (36.1)	813 (33.5)
ACEi or ARB	55 (90.2)	83 (93.3)	138 (92.0)	2291 (93.7)	2231 (92.0)	4522 (92.8)
ARNI	0	0	0	18 (0.7)	23 (0.9)	41 (0.8)
β-Blocker	54 (88.5)	81 (91.0)	135 (90.0)	2246 (91.8)	2261 (93.2)	4507 (92.5)
MRA	49 (80.3)	66 (74.2)	115 (76.7)	1869 (76.4)	1856 (76.5)	3725 (76.5)

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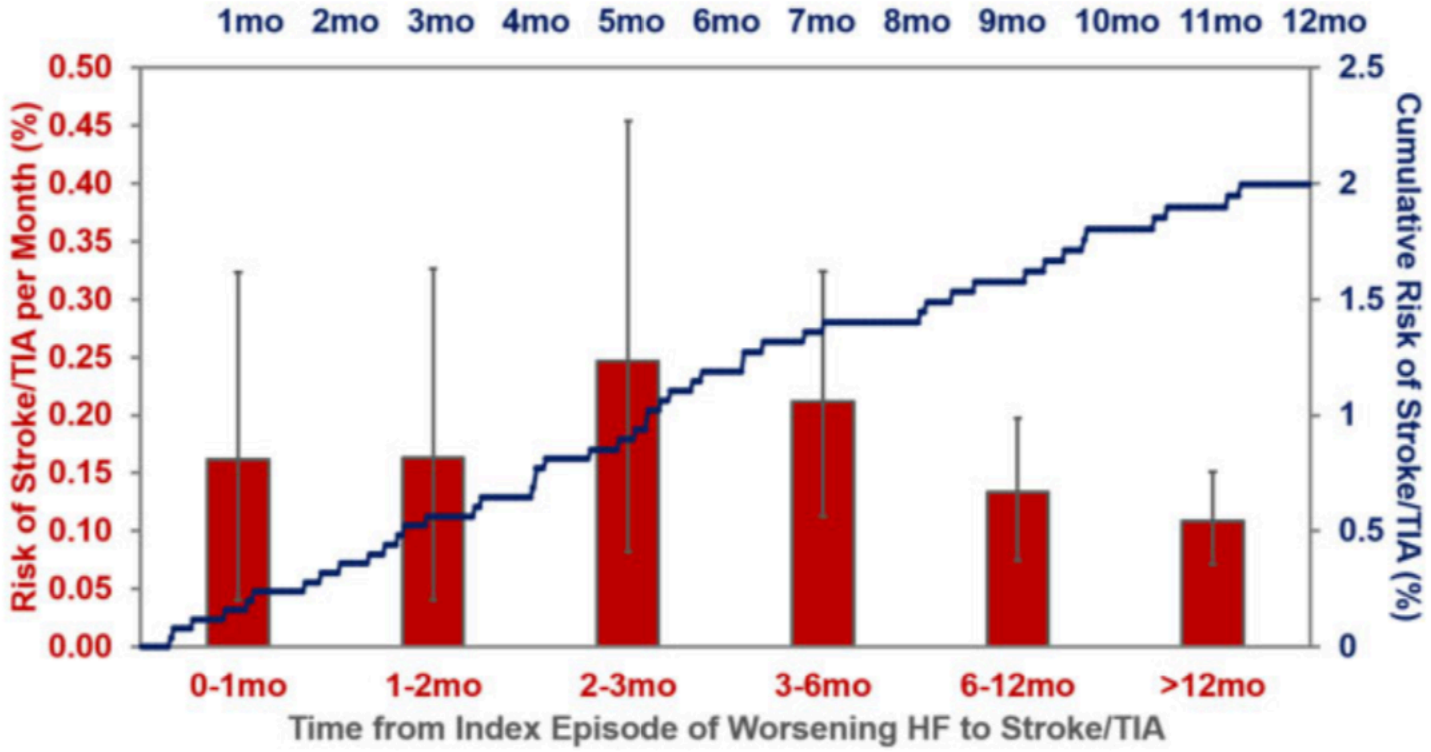
TEMPORAL PATTERN OF RISK OF STROKE/TIA AFTER AN EPISODE OF WORSENING CHF



No. at Risk	2,515	2,499	2,473	2,438	2,338	1,910
# of Stroke/TIA	4	4	6	15	18	42

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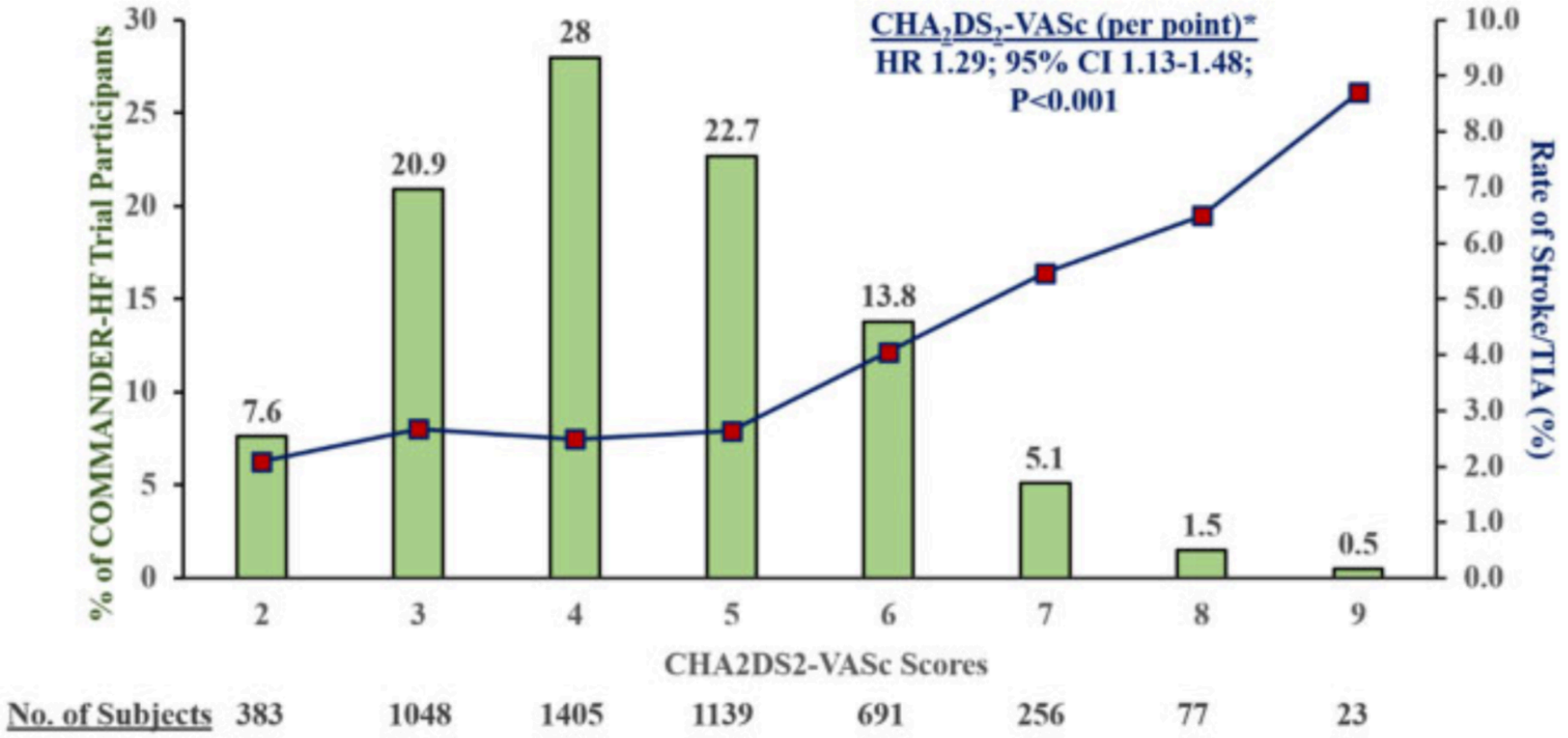
STROKE SEVERITY AND SUBSEQUENT ADVERSE EVENTS

- Stroke severity
  - mRS 6 (fatal): 31%
  - mRS 3–5 (moderate-to-severe disability): 16.5%
  - mRS 0–2 (non-disabling events): 51.1%

- Patients surviving after a stroke or TIA event:
  - mortality of 26% (33 out of 126)
  - recurrent stroke or TIA of 7% (9 out of 126)
  - rehospitalization for HF of 21% (26 out of 126)

European Heart Journal, ehz427

DISTRIBUTION OF PARTICIPANTS AND OBSERVED STROKE OR TIA RATES BY CHA_2DS_2-VASC SCORE



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RISK PREDICTORS OF STROKE OR TIA

	Wald statistics χ^2	Hazard ratio (HR)	*P*-value
Region	14.49		0.006
Asia Pacific vs. Eastern Europe		1.45 (0.41–5.15)	
Western Europe & South Africa vs. Eastern Europe		2.97 (1.59–5.57)	
North America vs. Eastern Europe		1.74 (0.56–5.37)	
Latin America vs. Eastern Europe		2.54 (1.23–5.23)	
History of prior stroke	10.09	2.35 (1.39–3.98)	0.002
Body mass index (kg/m^2)	3.87	0.95 (0.91–1.00)	0.049
History of hypertension	3.01	1.67 (0.94–2.99)	0.083
Age (per year)	1.39	1.01 (0.99–1.04)	0.239
Time from index episode of worsening heart failure to randomization (per day)	0.58	1.01 (0.99–1.03)	0.448
Left ventricular ejection fraction (per %)	0.51	0.99 (0.96–1.02)	0.473
New York Heart Association class	0.34		0.952
Class I vs. Class IV			
Class II vs. Class IV		1.38 (0.33–5.85)	
Class III vs. Class IV		1.49 (0.35–6.37)	
History of diabetes mellitus	0.23	1.11 (0.71–1.74)	0.633
White race	0.10	1.19 (0.40–3.49)	0.754
Optimism-corrected C-statistic (percentile-correct interval)		0.70 (0.65–0.74)	

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EFFECTS OF RIVAROXABAN VS. PLACEBO ON STROKE OR TIA

	Rivaroxaban		Placebo			
	n/*N* (%)	Incidence rate per 100 patient-years	*n*/*N* (%)	Incidence rate per 100 patient-years	HR (95% CI)	*P*-value
Primary neurological endpoint: all-cause stroke or TIA	61/2507 (2.43)	1.29	89/2515 (3.54)	1.9	0.68 (0.49, 0.94)	0.02
All-cause stroke	51/2507 (2.03)	1.08	76/2515 (3.02)	1.62	0.67 (0.47, 0.95)	0.025
Ischaemic stroke	41/2507 (1.64)	0.86	63/2515 (2.50)	1.34	0.64 (0.43, 0.95)	0.028
Haemorrhagic stroke	6/2507 (0.24)	0.13	8/2515 (0.32)	0.17	0.74 (0.25, 2.13)	0.572
Subarachnoid haemorrhage	1/2507 (0.04)	0.02	3/2515 (0.12)	0.06	0.33 (0.03, 3.16)	0.334
Uncertain type of stroke	4/2507 (0.16)	0.08	2/2515 (0.08)	0.04	2.01 (0.37, 10.99)	0.420
TIA	10/2507 (0.40)	0.21	13/2515 (0.52)	0.27	0.77 (0.34, 1.75)	0.525
Ischaemic stroke or TIA	51/2507 (2.03)	1.08	76/2515 (3.02)	1.62	0.66 (0.46, 0.95)	0.023

Decrease in ischemic stroke, no difference in haemorrhagic stroke/subarachnoid haemorrhage

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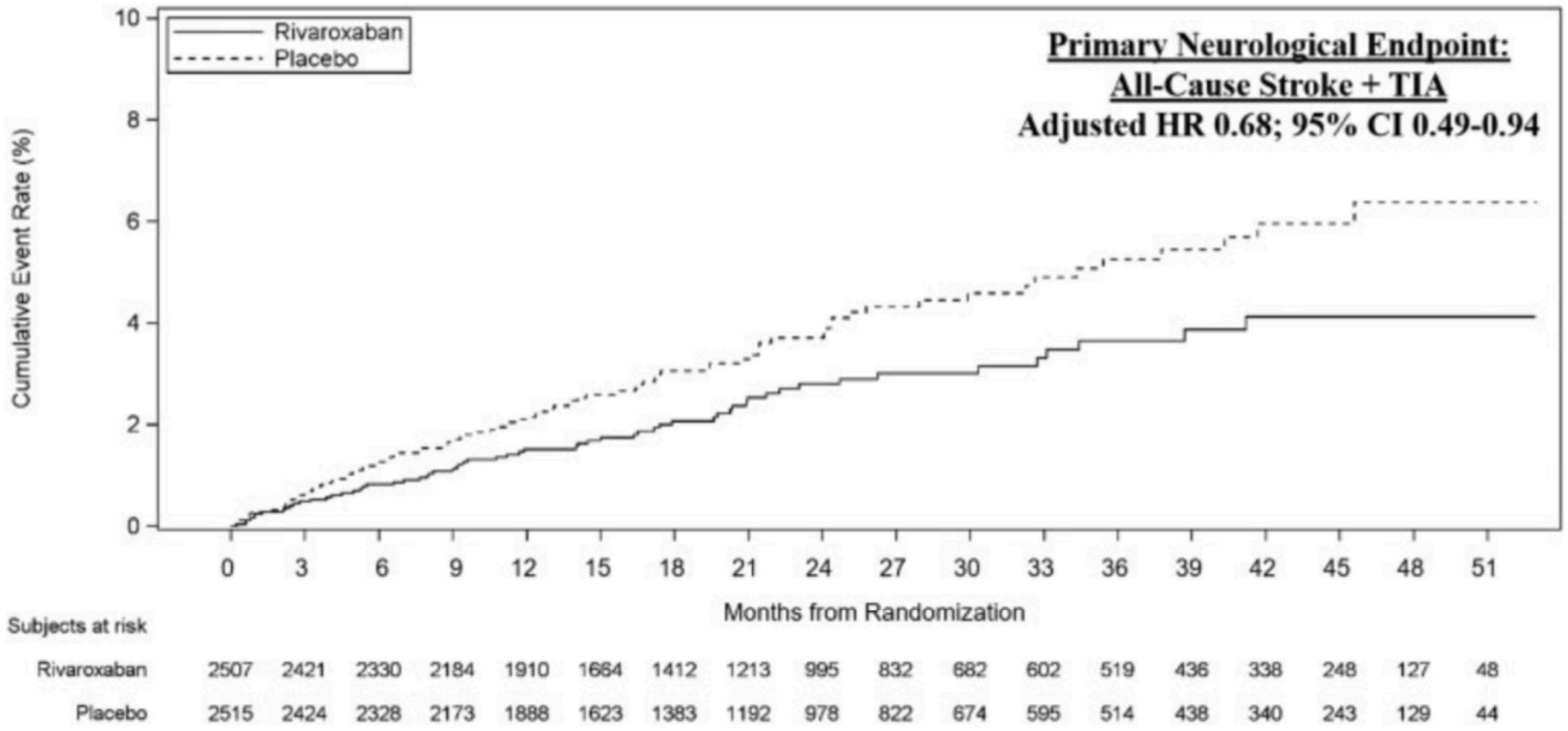
TIME TO FIRST OCCURRENCE OF STROKE OR TIA



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APPLICATION OF THE CHA2DS2-VASC RISK SCORE WITH CUT-OFF AT THE MEDIAN SCORE OF 4 TO THE COMMANDER HF TRIAL

	Rivaroxaban		Placebo				
	n/N (%)	Incidence rate (per 100 patient-years)	*n/N* (%)	Incidence rate (per 100 patient-years)	NNT patient-years	HR (95% CI)	*P*-value
Primary neurological endpoint: all-cause stroke or TIA							
COMMANDER HF cohort	61/2507 (2.4%)	1.29	89/2515 (3.5%)	1.90	164	0.68 (0.49–0.94)	0.02
CHA_2DS_2-VASc ≤ 4	31/1412 (2.2%)	1.13	40/1424 (2.8%)	1.44	316	0.79 (0.49–1.26)	0.382[b]
CHA_2DS_2-VASc > 4	30/1095 (2.7%)	1.52	49/1091 (4.5%)	2.56	96	0.59 (0.37–0.93)	

	Rivaroxaban		Placebo				
	n/N (%)	Incidence rate (per 100 patient-years)	*n/N* (%)	Incidence rate (per 100 patient-years)	NNH patient-years[a]	HR (95% CI)	*P*-value
Principal safety endpoint: fatal bleeding or bleeding into a critical space							
COMMANDER HF cohort	18/2499 (0.7%)	0.44	23/2509 (0.9%)	0.55	–	0.81 (0.44–1.49)	0.491
CHA_2DS_2-VASc ≤ 4	8/1406 (0.6%)	0.33	13/1422 (0.9%)	0.53	–	0.65 (0.27–1.56)	0.495[b]
CHA_2DS_2-VASc > 4	10/1093 (0.9%)	0.60	10/1087 (0.9%)	0.60	–	1.00 (0.42–2.40)	

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MAIN FINDINGS

- Patients recently treated for an episode of worsening HF in sinus rhythm face a **risk of stroke** (1.6 per 100 patient-years) approaching rates observed among patients with chronic HF and AF (2.0 per 100 patient-years)

- **Type**: ischaemic strokes in 82% of patients

- **Timing**: risk increases early immediately following the index episode of worsening HF, peaks by 6-months and persists throughout the period of observation

- **Severity**: nearly half of all first stroke events either fatal or disabling and those individuals that survive these events continue to face risk of major adverse cardiovascular events, including death

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MAIN FINDINGS

- **Predictors of stroke:** prior stroke, low BMI, geographic region

- The addition of **rivaroxaban 2.5 mg b.i.d. to background antiplatelet therapy markedly reduces risk of first stroke or TIA** compared with placebo by 32%, when adjusted for clinically relevant covariates
  - NNT of 164 per year; applying the CHA2DS2-VASc score of >4: NNT of 96 per year.

- **Safe and acceptable bleeding profile**: no differences in fatal or critical space bleeding (the principal safety endpoint), haemorrhagic stroke, or death

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