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Anticoagulation to prevent ischemic stroke and neurocognitive impairment in atrial fibrillation: the BRAIN-AF randomized clinical trial

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Individuals with atrial fibrillation (AF) are at increased risk of stroke, cognitive impairment and dementia. Observational studies suggest that anticoagulation may reduce the risk of cognitive decline in patients with AF and elevated thromboembolic risk, implicating subclinical cerebral emboli as a potential mechanistic link. Whether anticoagulation prevents cognitive deterioration in patients with AF at low risk of stroke remains uncertain. Here we conducted a multicenter, double-blind, placebo-controlled trial in which participants with AF and low thromboembolic risk (CHA_2DS_2-VASc scores of 0 or 1, excluding female sex) were randomized 1:1 to receive rivaroxaban 15 mg daily or placebo. The primary outcome was a composite of cognitive decline (≥2-point drop in Montreal Cognitive Assessment), stroke or transient ischemic attack with a motor deficit or aphasia. The trial was halted after meeting the predetermined futility criterion following a planned interim analysis, with 1,235 of the intended 1,424 participants (919 men; 316 women) enrolled. Over a median follow-up of 3.7 years, the primary outcome occurred in 256 (20.7%) participants, at an annual rate of 7.0% with rivaroxaban versus 6.4% with placebo, yielding a hazard ratio of 1.10 (95% confidence interval (0.86–1.40); $P = 0.46$). Conditional power analysis indicated a 1.2% probability of achieving a statistically significant treatment effect if the trial had been continued to its planned total of 410 events. Major bleeding occurred in two patients treated with rivaroxaban (0.09% per year) and five patients treated with placebo (0.21% per year). In conclusion, despite the high incidence of cognitive decline observed among patients with AF and low stroke risk, the BRAIN-AF trial, which tested a low dose of rivaroxaban to prevent stroke, transient ischemic attack and cognitive decline in patients with prior AF, was stopped early due to futility. ClinicalTrials.gov registration: NCT02387229.

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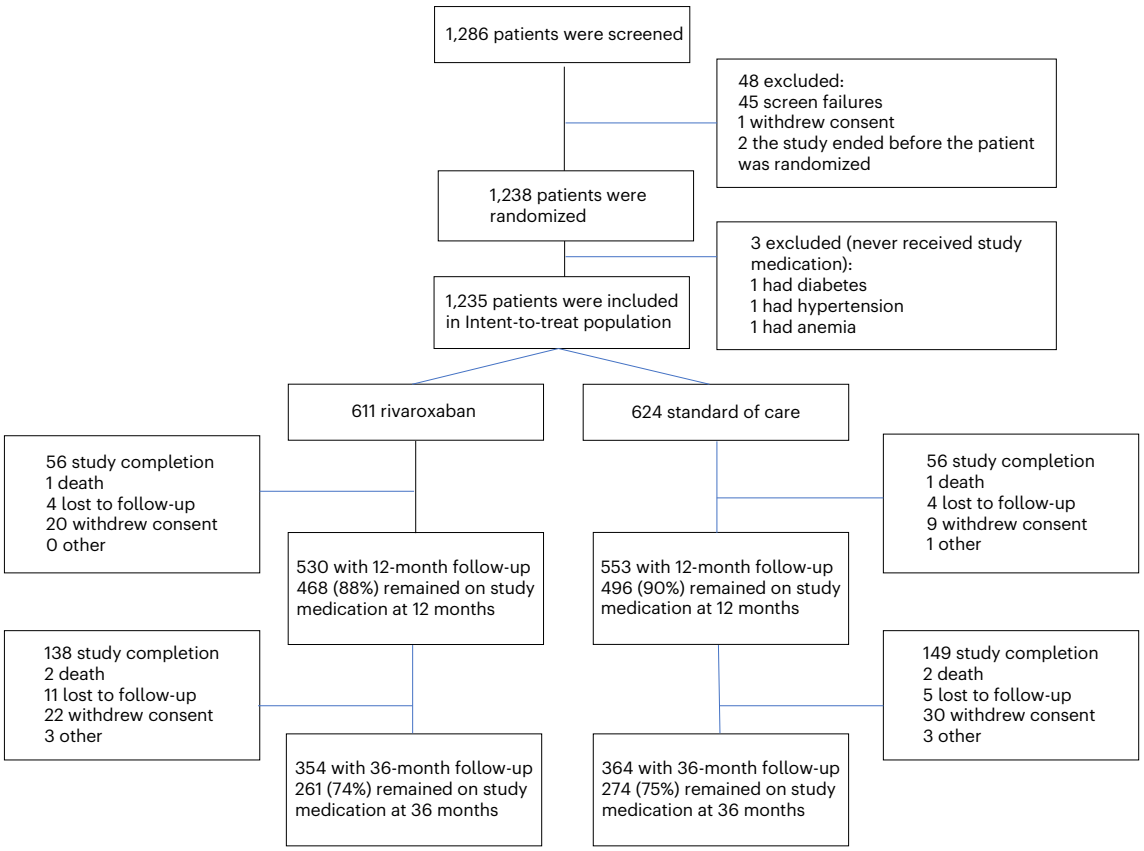

Fig. 1 | Flowchart of participant distribution throughout the study. 'Study completion' refers to patients who either attended the final visit scheduled at trial cessation or had a final visit upon turning 65 years of age before the trial ended.

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, affecting more than 50 million individuals worldwide[1,2]. AF is a major contributor to morbidity and mortality, significantly elevating the risk of thromboembolic complications. Approximately one in four strokes is attributable to AF[3]. More recently, observational studies have also established a link between AF and cognitive decline and dementia[4–11]. The prevalence of both AF and dementia is on the rise, reflecting, in part, the aging population[12–16]. Subclinical cerebral emboli, along with hypoperfusion and neuroinflammation, have been proposed as putative mechanisms linking AF to cognitive decline[17–19]. Oral anticoagulation effectively mitigates stroke risk and improves survival in patients with AF and elevated thromboembolic risk, as determined by clinical stratification tools[1,20,21]. Observational studies and real-world healthcare data further suggest that anticoagulation may reduce cognitive decline and dementia risk in AF patients at high stroke risk[22–26]. Some evidence suggests that in younger individuals with fewer concomitant stroke risk factors, AF may confer an even higher attributable risk for cognitive dysfunction[6,7]. However, potential neurocognitive benefits of anticoagulation must be weighed against bleeding risks, including cerebral microbleeds, which may also contribute to cognitive impairment[27]. We, therefore, conducted the BRAIN-AF trial to determine whether a low dose of rivaroxaban (15 mg once daily) reduces a composite endpoint of cognitive decline, stroke or transient ischemic attack (TIA) compared to placebo in participants with AF who have no established indication for thromboprophylaxis[21].

Results

Participants and follow-up

A total of 1,238 participants were enrolled in the BRAIN-AF trial across 53 sites in Canada between April 2015 and November 2023 (Supplementary Table 1) and followed for a median of 3.7 (interquartile range (IQR) 1.9–6.0) years. Eligible subjects were aged 30–60 years, had documented paroxysmal or non-paroxysmal AF, and were at low stroke risk (full inclusion and exclusion criteria provided in Methods). Three patients were subsequently excluded before receiving the study medication due to hypertension ($n = 1$), diabetes ($n = 1$) or anemia ($n = 1$). The remaining 1,235 participants were randomized in a 1:1 ratio to receive rivaroxaban 15 mg daily ($n = 611$) or placebo ($n = 624$) (Fig. 1). The mean age was 53.4 ± 7.3 years, and 25.6% of participants were female. Per study criteria, men had CHA_2DS_2-VASc scores of 0 or 1, and women had scores of 1 or 2. Baseline demographic and clinical characteristics, including age, education and depressive symptom measures, were well-balanced between groups (Table 1).

Following an interim analysis triggered after 205 adjudicated primary outcome events, which consisted of cognitive decline (defined by a ≥2-point drop in the Montreal Cognitive Assessment (MoCA) score compared to baseline), stroke or TIA, the Data and Safety Monitoring Board (DSMB) recommended early termination of the trial, having met the predefined futility criterion. Recruitment ceased on 27 November 2023, and final participant visits were scheduled, with completion of follow-up in May 2024. Of the 410 primary outcome events prespecified in the trial's sample size and power calculations, 256 (62.4%) had occurred at the time of study termination. The conditional power analysis based on the alternative hypothesis underlying the sample size calculation indicated a 1.2% probability of achieving a statistically significant treatment effect had the trial been continued to its planned completion.

Among 611 participants randomized to rivaroxaban, 551 (90.2%) either completed the trial ($n = 194$; 31.8%), had follow-up ≥3 years ($n = 354$; 57.9%) or died within the first 3 years ($n = 3$; 0.5%). Before reaching 3-year follow-up, 42 (6.9%) participants withdrew consent, 15 (2.5%) were lost to follow-up, and 3 (0.5%) discontinued participation

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Table 1 | Characteristics of patients at baseline

Characteristics	Overall (*n*=1235)	Rivaroxaban (*n*=611)	Placebo (*n*=624)
Age—years	53.4±7.3	53.4±7.5	53.5±7.0
Female sex—no. (%)	316 (25.6)	163 (26.7)	153 (24.5)
Race or ethnic group—no. (%)[a]			
Caucasian	1,181 (95.6)	588 (96.2)	593 (95.0)
Black or African American	6 (0.5)	4 (0.7)	2 (0.3)
Native American	1 (0.1)	1 (0.2)	0 (0.0)
Asian	30 (2.4)	12 (2.0)	18 (2.9)
Hispanic or Latino	9 (0.7)	4 (0.7)	5 (0.8)
Other	8 (0.6)	2 (0.3)	6 (1.0)
CHA_2DS_2-VA score—no. (%)[b]			
Men, 0	874 (70.8)	422 (69.1)	452 (72.4)
Men, 1	45 (3.6)	26 (4.3)	19 (3.0)
Mean	0.05±0.22	0.06±0.22	0.04±0.19
Women, 0	310 (25.1)	161 (26.4)	149 (23.9)
Women, 1	6 (0.5)	2 (0.3)	4 (0.6)
Mean	0.02±0.13	0.01±0.11	0.03±0.16
Predominant pattern of AF—no. (%)			
Paroxysmal (<7 days)	969 (78.5)	481 (78.7)	488 (78.2)
Persistent (7 days to 1 year)	138 (11.2)	72 (11.8)	66 (10.6)
Long-standing persistent (>1 year duration)	128 (10.4)	58 (9.5)	70 (11.2)
Time since initial diagnosis of AF, years	3.9±5.9	3.6±5.5	4.3±6.2
Oral anticoagulation at screening—no. (%)	78 (6.3)	41 (6.7)	37 (5.9)
History of vascular disease—no. (%)	51 (4.1)	28 (4.6)	23 (3.7)
Coronary artery disease	38 (3.1)	17 (2.8)	21 (3.4)
Other	13 (1.1)	11 (1.8)	2 (0.3)
Tobacco use—no. (%)	137 (11.1)	71 (11.6)	66 (10.6)
Sleep apnea—no. (%)	229 (18.6)	116 (19.0)	113 (18.1)
Left ventricular ejection fraction—%	59.8±5.6	59.9±5.4	59.7±5.7
Left atrial volume—ml m^{-2}	36.5±19.0	36.2±17.6	36.8±20.3
Creatinine clearance—ml min^{-1}	118.5±34.9	119.3±34.8	117.8±35.0
Body mass index—m kg^{-2}	29.3±5.4	29.3±5.4	29.3±5.5
Level of education—years of schooling	15.2±3.3	15.1±3.4	15.3±3.2
Regular physical activity—no. (%)	832 (67.4)	407 (66.6)	425 (68.1)
Depression status—no. (%)			
Normal to mild	1,154 (93.4)	574 (93.9)	580 (92.9)
Moderate to severe	79 (6.4)	37 (6.1)	42 (6.7)
Unknown	2 (0.2)	0 (0.0)	2 (0.3)
Alcohol consumption—no. (%)			
≤1 drink per day	832 (67.4)	414 (67.8)	418 (67.0)
>1 drink per day	403 (32.6)	197 (32.2)	206 (33.0)
MoCA score—mean	27.5±2.0	27.6±1.9	27.5±2.0
<26—no. (%)	174 (14.1)	86 (14.1)	88 (14.1)
MMSE—mean	29.3±1.0	29.3±1.0	29.4±1.0

Plus-minus values are means±s.d. Percentages may not total 100 because of rounding. [a]Race or ethnic group was reported by the patient. [b]CHA_2DS_2-VA score (an assessment of the risk of stroke among patients with atrial fibrillation) ranges from 0 to 8, with higher scores indicating a higher risk of stroke.

in the trial for other reasons. Among 624 participants randomized to placebo, 572 (91.7%) either completed the trial (*n* = 205; 32.9%), had follow-up ≥3 years (*n* = 364; 58.3%) or died within the first 3 years (*n* = 3; 0.5%). Before completing a 3-year follow-up period, 39 (6.3%) withdrew consent, 9 (1.4%) were lost to follow-up, and 4 (0.6%) discontinued the trial for other reasons. A total of 10 (0.8%) patients died, 4 (0.7%) of whom were randomized to rivaroxaban and 6 (1.0%) to placebo.

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Throughout the trial, 75 of 611 (12.3%) participants randomized to rivaroxaban and 78 of 624 (12.5%) to placebo developed a clinical indication for anticoagulation after a median follow-up of 3.3 (IQR 1.6–4.7) years, due to reaching the age of 65 years ($n = 38$) or a new diagnosis of congestive heart failure ($n = 20$), hypertension ($n = 69$) or diabetes ($n = 26$). In adherence with the study protocol, among the safety population, 57 of 602 (9.5%) participants randomized to rivaroxaban and 69 of 621 (11.1%) to placebo discontinued the study drug permanently following AF ablation with no subsequent recurrence, after a median time on study medication of 1.4 (IQR 0.8–2.6) years. Among 354 participants randomized to rivaroxaban with 3 years of follow-up, 261 (73.7%) remained on study medication. Similarly, 274 of 364 (75.3%) participants randomized to placebo remained on their study medication at 3 years of follow-up.

Efficacy outcomes

At the time of early termination, the primary efficacy outcome had occurred in 256 of 1,235 participants (20.7%), with cognitive decline accounting for 234 events (91.4%), stroke for 13 (5.1%) and TIA for 9 (3.5%). Among those randomized to rivaroxaban, the primary outcome occurred in 130 of 610 participants (21.3%), compared with 126 of 623 participants (20.2%) in the placebo group, yielding a hazard ratio of 1.10 (95% confidence interval (CI) 0.86–1.40; $P = 0.46$ by generalized log-rank test; Fig. 2a). The corresponding annualized rates were 7.0% in the rivaroxaban group and 6.4% in the placebo group. The incidence of stroke, systemic embolism or TIA was similar between groups, occurring in 15 of 611 participants (2.5%) in the rivaroxaban arm and 17 of 624 participants (2.7%) in the placebo arm, with corresponding annualized rates of 0.66% and 0.72%, respectively. Rates of hospitalization for cardiovascular or bleeding events, as well as changes in cognitive function assessed by either a ≥3-point reduction in MoCA score or a change in Mini-Mental State Examination (MMSE) score, were comparable between groups (Table 2). Longitudinal MoCA score is depicted in Supplementary Fig. 1.

Safety outcomes

In the safety population (patients who took at least one dose of the medication), major bleeding was reported in two participants assigned to rivaroxaban and five assigned to placebo, corresponding to annualized major bleeding rates of 0.09% and 0.21%, respectively ($P = 0.27$). No fatal bleeding events occurred. The classification of bleeding events is detailed in Table 2. A full list of serious adverse events is provided in Supplementary Table 2.

Subgroup and sensitivity analyses

Results were consistent across prespecified subgroups (Fig. 3). In the censored population analysis, in which follow-up was truncated at the time of a new clinical indication for anticoagulation, the primary efficacy outcome occurred in 122 of 610 participants (20.0%) in the rivaroxaban group and 118 of 623 (18.9%) in the placebo group. The corresponding annualized event rates were 7.0% and 6.3%, respectively ($P = 0.44$ by generalized log-rank test; Fig. 2b). In the on-treatment analysis, the primary efficacy outcome was observed in 106 of 601 participants (17.6%) receiving rivaroxaban and 102 of 620 (16.5%) receiving placebo, with annualized event rates of 6.9% and 6.2%, respectively ($P = 0.41$ by generalized log-rank test; Fig. 2c). Comparisons of additional clinical outcomes in the censored population and on-treatment analyses are provided in Extended Data Tables 1 and 2.

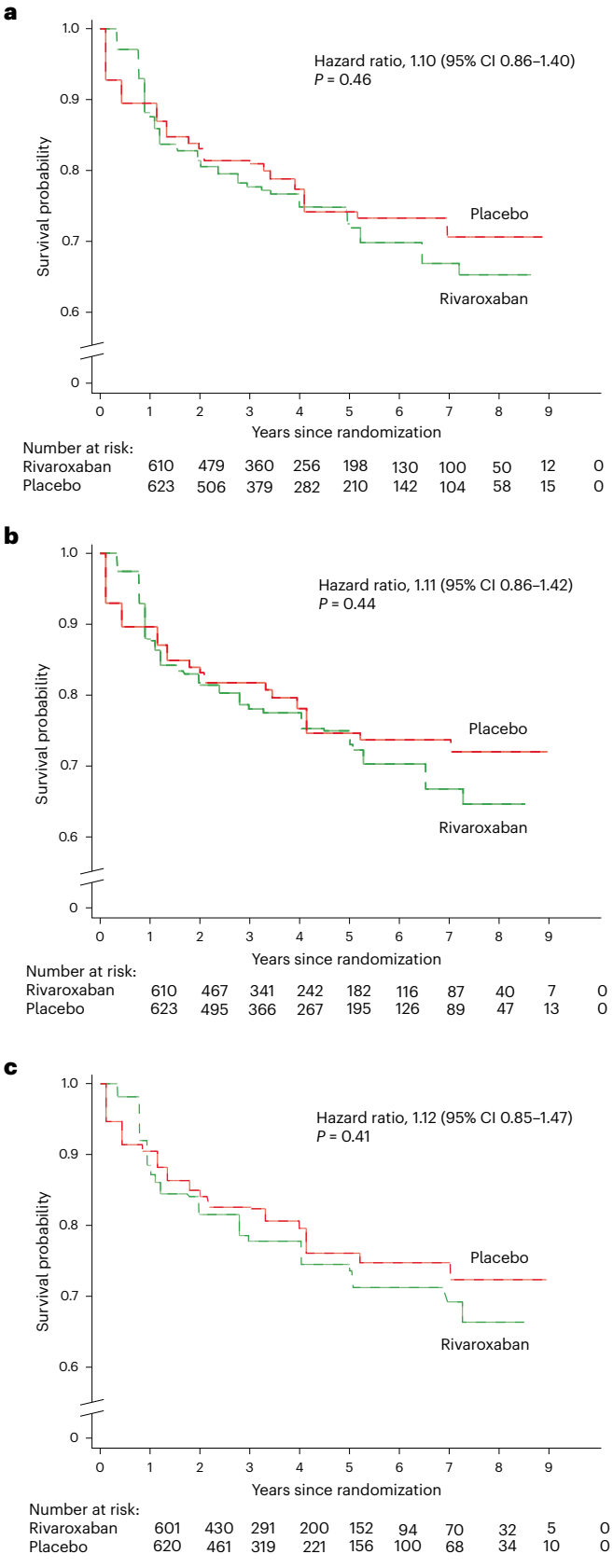

Fig. 2 | Primary efficacy outcome. a–c, The primary efficacy outcome (cognitive decline, stroke or TIA) according to randomization to rivaroxaban versus placebo is shown for the main analysis (**a**), censored analysis (**b**) and on-treatment analysis (**c**). The outcome is interval-censored and graphically displayed using non-parametric maximum likelihood estimates of survival curves for interval-censored data, resulting in stepwise curves. Numbers at risk are approximated by assuming that events occurred at the upper bound of the interval. Hazard ratios, 95% CIs and *P* values were obtained from proportional hazards regression models fitted to handle interval-censored data and stratified for study phase. The trial was terminated early for futility. By the time of study closure, 256 of 410 planned primary events had occurred.

Table 2 | Clinical outcomes

Outcome	Rivaroxaban (*n*=611)	Placebo (*n*=624)	Hazard ratio (95% CI)	*P* value
Cognitive decline, stroke or TIA—no. (%)[a]	130 (21.3)	126 (20.2)	1.10 (0.86, 1.40)	0.46
Cognitive decline	122 (20.0)	118 (18.9)	1.10 (0.85,1.41)	
Stroke	9 (1.5)	7 (1.1)	1.34 (0.50, 3.59)	
TIA	4 (0.7)	5 (0.8)	0.84 (0.23, 3.14)	
Stroke, TIA or systemic embolism—no. (%)	15 (2.5)	17 (2.7)	0.92 (0.50, 1.84)	
Stroke	9	7		
TIA	4	5		
Systemic embolism	2	5		
Decrease in MMSE from baseline to end of follow-up—no. (%)[b]			1.11 (0.88, 1.40)	
≥ 2 points	39 (7.4)	34 (6.1)		
1 point	83 (15.7)	74 (13.2)		
Decrease in MoCA score ≥3 points	57 (9.3)	57 (9.1)	1.04 (0.72, 1.50)	
Major bleeding—no. (%)[c]	2 (0.3)	5 (0.8)	0.41 (0.08, 2.12)	0.27
Fatal bleeding	0 (0.0)	0 (0.0)		
Bleeding in a critical area or organ	2 (0.3)	4 (0.6)		
Bleeding causing a fall in hemoglobin level or leading to transfusion	1 (0.2)	3 (0.5)		
Hospitalization for cardiovascular or bleeding event—no. (%)	40 (6.5)	41 (6.6)	1.00 (0.65, 1.55)	
All-cause death—no. (%)	4 (0.7)	6 (1.0)	0.69 (0.19, 2.43)	
Cardiovascular death—no. (%)	2 (0.3)	5 (0.8)		

[a]The total number of events exceeds the number of participants with events, as some experienced more than one component of the composite outcome. [b]Odds ratio (95% CI) for rivaroxaban versus placebo is presented rather than hazard ratio (95% CI). [c]Assessed in the safety population (patients who took at least one dose of the study medication), which consisted of 602 patients randomized to rivaroxaban and 621 to placebo.

Discussion

BRAIN-AF is the largest randomized controlled trial designed to determine whether oral anticoagulation could prevent cognitive decline in patients with AF. Following randomization of 1,235 participants, the trial was terminated for futility after a median follow-up of 3.7 years. A conditional power analysis indicated a 1.2% probability of detecting a meaningful treatment effect under the current assumptions, demonstrating that continued follow-up was unlikely to yield conclusive evidence of efficacy and leading to early trial termination before reaching the planned enrollment of 1,428 participants. No benefit of anticoagulation was observed across sensitivity analyses (censored and on-treatment analyses) or in any predefined subgroup.

The BRAIN-AF trial specifically targeted the subgroup of patients with AF who do not meet current guideline-based indications for anticoagulation due to the absence of conventional risk factors for stroke. This allowed for a randomized placebo-controlled design. As anticipated, some participants developed new indications for anticoagulation, including upon turning 65 years of age. Such events were incorporated into trial design and power calculations. All participants were enrolled with at least 3 years of eligibility before reaching 65 years. Notably, despite the relatively low-risk profile and mean age of 53 years, a high prevalence of cognitive decline was observed in this population. At baseline, 14% of patients met the MoCA criterion for mild cognitive impairment (score < 26 (ref. 28); Table 1), and 19% experienced a ≥2-point decline in MoCA score during follow-up.

The importance of cognitive decline in patients with AF was made evident by a recent large population-based study using electronic healthcare records that examined over 5 million UK primary care patients, of whom 5.6% had AF and were aged 40–75 years with a low perceived stroke risk[11]. Over a 5-year follow-up, AF was significantly associated with a higher risk of all-cause dementia (adjusted hazard ratio 1.17, $P = 0.010$). Both AF and cognitive impairment impose substantial health and economic burdens[5]. Although a causal relationship between AF and cognitive dysfunction has not been definitively established, the association appears to be independent of clinically overt stroke and shared risk factors[8,9,23,29]. Underlying mechanisms remain to be elucidated and potentially involve microemboli, microbleeds, hypoperfusion, inflammation and blood–brain barrier dysfunction. Mounting evidence supports the hypothesis that subclinical cerebral emboli contribute to AF-related cognitive dysfunction, as indicated by the high prevalence of silent brain infarcts, detection of microembolic signals and observational studies suggesting that anticoagulation may mitigate this risk[17–19,30].

In the BRAIN-AF trial, the primary outcome occurred in more than 20% of participants, with an annual incidence of 6.4% in the placebo group, aligning with the trial's sample size and power calculations. The lack of rivaroxaban's superiority was, therefore, not attributable to an insufficient event rate. Whether anticoagulation could help preserve cognitive function in a different AF population remains uncertain. Subgroup analyses did not indicate a potential for benefit in older patients within the tested age range. Nevertheless, it could be hypothesized that mechanisms underlying cognitive dysfunction in AF vary according to patient-specific factors such as age and vascular disease[31]. For instance, cerebral emboli may be the predominant contributor in patients with an elevated stroke risk, whereas alternative mechanisms may play a greater role in younger, lower-risk individuals, such as those in the BRAIN-AF population. In the latter group, cerebral hypoperfusion and brain–blood barrier dysfunction could potentially play a more important role in precipitating cognitive decline[32]. The irregular cardiac contractions characteristic of AF induces beat-to-beat variability in blood flow, potentially exacerbating hypoperfusion. The loss of atrioventricular synchrony can lead to further reductions in stroke

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Subgroup	Rivaroxaban Events/*N* (%)		Standard of care Events/*N* (%)		Hazard ratio (95% CI)	*P* value
Sex						0.84
Male	102/447	(22.8)	101/470	(21.5)	1.08 (0.82, 1.43)	
Female	28/163	(17.2)	25/153	(16.3)	1.16 (0.67, 1.98)	
Age, years						0.75
Below 40	8/49	(16.3)	5/32	(15.6)	1.03 (0.34, 3.15)	
Between 40 and 55	55/240	(22.9)	62/268	(23.1)	1.00 (0.70, 1.44)	
55 and above	67/321	(20.9)	59/323	(18.3)	1.22 (0.86, 1. 73)	
Pattern of AF						0.56
Paroxysmal	94/481	(19.5)	94/487	(19.3)	1.05 (0.79, 1.40)	
Persistent/long-standing persistent	36/129	(27.9)	32/136	(23.5)	1.24 (0.77, 2.00)	
Sleep apnea						0.20
No apnea	109/493	(22.1)	101/511	(19.8)	1.18 (0.90, 1.54)	
Apnea	20/116	(17.2)	25/112	(22.3)	0.77 (0.43, 1.39)	
Baseline MoCA score						0.22
MoCA < 26	2/86	(2.3)	5/88	(5.7)	0.40 (0.08, 2.09)	
MoCA ≥ 26	128/524	(24.4)	121/535	(22.6)	1.13 (0.88, 1.45)	
Left atrial volume, ml m^{-2}						0.15
Volume < 34	38/202	(18.8)	49/197	(24.9)	0.73 (0.48, 1.12)	
Volume ≥ 34	29/150	(19.3)	29/161	(18.0)	1.20 (0.72, 2.01)	
Vascular disease						0.14
No	124/582	(21.3)	117/600	(19.5)	1.14 (0.89, 1.47)	
Yes	6/28	(21.4)	9/23	(39.1)	0.51 (0.18, 1.44)	
Phase of enrollment in trial						0.54
Phase 1	71/247	(28.7)	65/256	(25.4)	1.18 (0.84, 1.65)	
Phase 2	59/363	(16.3)	61/367	(16.6)	1.01 (0.71, 1.45)	
Body mass index, kg m^{-2}						0.45
Below 25	26/123	(21.1)	24/132	(18.2)	1.15 (0.66, 2.01)	
Between 25 and 30	49/257	(19.1)	55/255	(21.6)	0.92 (0.63, 1.36)	
30 and above	55/228	(24.1)	46/233	(19.7)	1.31 (0.89, 1.94)	
Alcohol consumption						0.10
≤1 drink per day	89/413	(21.5)	74/417	(17.7)	1.28 (0.94, 1.75)	
>1 drink per day	41/197	(20.8)	52/206	(25.2)	0.83 (0.55, 1.25)	

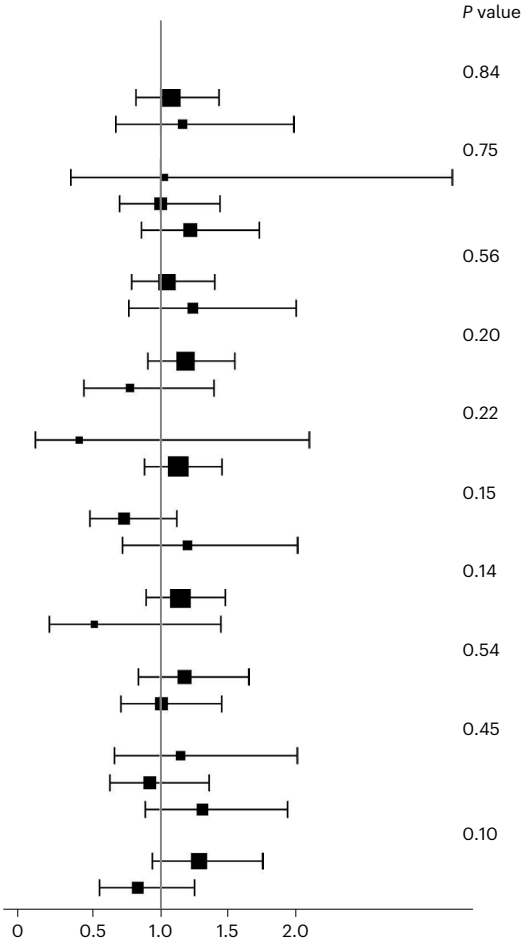

Fig. 3 | Subgroup analyses of the primary outcome. Error bars represent point estimates of hazard ratio ± 95% CI obtained from proportional hazards models fitted to handle interval-censored data. Models included terms for treatment, subgroup and treatment × subgroup interaction and were stratified by study phase (except for the subgroup analysis on study phase). The size of each square (point estimate) is proportional to the number of events. *P* values refer to the test of the treatment × subgroup interaction terms. All tests were two-sided, and no adjustment for multiple comparisons were done.

volume, cardiac output and blood pressure[33]. Studies have demonstrated reduced frontal brain perfusion in AF patients, accompanied by 37% slowing of frontal brain activity during cognitive tasks compared to individuals in sinus rhythm[34,35]. These findings highlight the complex interplay between AF and cognitive dysfunction, warranting further investigation to identify potential therapeutic targets.

Cognitive decline accounted for more than 90% of primary outcome events, limiting the ability of the BRAIN-AF trial to assess the effect of low-dose rivaroxaban on thromboembolism as a subset of the composite outcome. The low rate of stroke or TIA observed (<0.7% per year) is consistent with prior observational studies[11,36]. This low rate, combined with the lack of efficacy of rivaroxaban in improving cognitive outcomes, provides the strongest evidence to date in support of current guidelines that do not recommend anticoagulation in patients without conventional risk factors for stroke.

A few methodological aspects merit consideration. First, by design, the primary outcome was heavily driven by cognitive decline, which accounted for 91.4% of qualifying events. Results are, therefore, dependent on the method of ascertaining cognitive decline. The MoCA test, which assesses multiple cognitive domains, was developed to detect mild cognitive impairment and is a more sensitive tool than the MMSE for this purpose. Although analysis of the reliable change index for serial MoCA testing in a community-based sample revealed that a 2-point decline over an average follow-up of 3.5 years represents a meaningful intrapatient difference, our study might have failed to detect a more subtle effect on cognition, which could potentially be identified by more detailed individualized neuropsychological assessments[37]. Although MoCA is validated and widely used to detect early cognitive impairment, it may have reduced sensitivity to subtle longitudinal changes in high-functioning individuals[28].

Another consideration is the choice of a 15-mg dose of rivaroxaban. The dose was deliberately selected to minimize bleeding risks in a population in whom anticoagulation is not currently recommended. Indeed, major bleeding was rare in the BRAIN-AF trial, occurring in only seven (0.6%) participants, with no significant difference between groups: two (0.3%) in the rivaroxaban arm and five (0.8%) in the placebo arm, three of whom were concomitantly taking aspirin 81 mg daily. At the time of trial design, observational studies and selected clinical trials suggested that 15 mg daily could offer substantial stroke prevention while reducing bleeding risk in certain populations[36,38]. More recent trials, such as the Optimal Anti-Coagulation for Enhanced Risk Patients Post-Catheter Ablation for Atrial Fibrillation study, likewise adopted a 15-mg once-daily regimen[39,40]. Supporting this approach, the approved product monograph and pharmacokinetic data indicate that the 15 mg dose achieves approximately 80–90% of the systemic exposure of the 20 mg dose in patients with preserved renal function[41]. In the absence of a guideline-endorsed dose for prevention of cognitive decline, and in the context of a younger, lower-risk study population, testing this lower dose was considered a reasonable trade-off. It should be acknowledged that for stroke prevention in AF, the 20-mg dose is standard in most

countries, whereas 15 mg is typically reserved for patients with moderate renal impairment, low body weight or relevant drug interactions. It remains unknown whether testing this standard dose of rivaroxaban or a different anticoagulant would have yielded different results. The DaRe2THINK trial is an open-label, pragmatic randomized study evaluating whether early use of a direct oral anticoagulant (per local prescribing guidance) versus standard care in about 3,000 patients with AF at low to intermediate stroke risk reduces a composite of cardiovascular death, ischemic stroke, thromboembolism, myocardial infarction and vascular dementia. Patient-reported cognitive function is assessed as a secondary outcome via annual remote testing[42].

Third, the trial was conducted in young patients with AF at low risk of stroke as defined by Canadian Cardiovascular Society guidelines[21], such that results should not be extrapolated to the AF population at large. Conducting a placebo-controlled anticoagulation trial to assess cognitive outcomes is not feasible in AF patients with high-risk features given the established benefits of thromboprophylaxis for stroke prevention. Recommended risk scores to guide anticoagulation therapy differ across regions of the world. In most European countries, anticoagulation is considered indicated in patients with AF if a modified CHA_2DS_2-VASc score that excludes the sex category (that is, CHA_2DS_2-VA) is ≥2, whereas anticoagulation may be considered in those with a score of 1[1]. American guidelines recommend anticoagulation when the annual stroke risk is ≥2% and consider it reasonable when the risk is ≥1% and <2% (ref. 20). In the BRAIN-AF trial, 51 (4.1%) patients had vascular disease, 36 of whom were older than 55 years at inclusion. Some of these patients might have been considered candidates for anticoagulation in other countries and, hence, excluded from the trial if conducted elsewhere.

Although enrollment occurred over an extended period, baseline characteristics remained balanced between treatment groups within both the early (phase 1) and later (phase 2) phases of the trial, supporting the internal validity of the findings. The study population was primarily limited to Caucasian patients, and there were fewer women than men. The sex distribution reflects the higher prevalence of AF in young men compared to young women, with AF typically occurring later in life in women[43]. Findings may not generalize to other racial or socioeconomic groups. Finally, recent evidence suggests that comprehensive AF management can favorably influence cognitive and clinical outcomes, as well as overall treatment success[1,44,45]. These interventions were not systematically implemented or measured in the BRAIN-AF trial, which specifically tested anticoagulation in isolation. Future strategies for cognitive protection in AF may consider a multipronged approach.

In conclusion, despite the high incidence of cognitive decline in patients with AF and low stroke risk, the BRAIN-AF trial evaluating rivaroxaban 15 mg daily to prevent cognitive decline, stroke and TIA was stopped early for futility, with a final 1.2% conditional probability of achieving statistical significance at planned completion.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-04101-y.

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Methods

Trial design and ethical approval

The BRAIN-AF trial (NCT02387229) was a multicenter randomized double-blind placebo-controlled trial conducted at 53 clinical sites in Canada (Supplementary Table 1). The detailed protocol and rationale have been published previously (the protocol and statistical analysis plan are available in Supplementary Information)[46]. The study was authorized by Health Canada and the institutional review boards of the Montreal Heart Institute (MP-33-2014-1559) and each participating center and was conducted in accordance with the principles of the Declaration of Helsinki. The executive committee designed and conducted the trial, which was managed by the Montreal Health Innovations Coordinating Center (MHICC; now SERIANT). Funding was provided by the Canadian Institutes of Health Research, with additional support from the Montreal Heart Institute Foundation, Canadian Stroke Prevention and Intervention Network and Bayer Inc., including an in-kind contribution of study drugs. The funders had no role in the design or conduct of the trial, in data analysis, in authorship or in the decision to submit for publication. The authors vouch for the accuracy and completeness of the data and all analyses and for fidelity to the trial protocol. The list of participating centers and investigators is provided in Supplementary Information.

Study participants

All patients provided written informed consent to participate. Patients ≥30 and ≤60 years of age were eligible for inclusion if they had AF, no mechanical heart valve or moderate-to-severe mitral stenosis and no indication for anticoagulation per Canadian Cardiovascular Society (CCS)-AF management guidelines. The CCS-AF 'CHADS-65' algorithm recommends anticoagulation in the presence of congestive heart failure, hypertension, diabetes mellitus, prior stroke or TIA or age ≥65 years[21]. Electrocardiographic (ECG) documentation of sustained AF (>30 s) was required within 1 year of inclusion. Protocol amendments expanded inclusion criteria by raising the maximum age limit to 62 years, which still permitted 3 years of follow-up before requiring anticoagulation according to the CHADS-65 algorithm[21] and extending the window for AF documentation to the preceding 2 years. Key exclusion criteria included a known diagnosis of dementia or a MMSE score <25 at screening, a clinical indication for oral anticoagulation or antithrombotic therapy according to CCS-AF management guidelines[21], a history of gastrointestinal bleeding, a condition associated with an increased risk of bleeding, anemia or thrombocytopenia or a creatinine clearance <30 ml min^{-1}. A complete list of exclusion criteria and definitions is provided in Supplementary Information.

Inclusion criteria

(1) Age at consent ≥30 to ≤62 years;
(2) Non-valvular AF (paroxysmal, persistent or permanent) documented within the past 2 years by any electrical recording or device, including a 12-lead electrocardiogram, Holter monitor (continuous ECG recording), rhythm strip, intracardiac electrogram or interrogation of a pacemaker or implantable cardioverter-defibrillator (minimum duration ≥30 s), transcutaneous monitor or other equivalent method (non-valvular AF is defined according the 2020 Canadian guidelines by the absence of any mechanical heart valve and moderate-to-severe mitral stenosis (rheumatic or non-rheumatic));
(3) Low risk of stroke as defined by the absence of all of the following:
   (i) Prior stroke or TIA;
   (ii) Hypertension (defined according to the 2017 Canadian guidelines by any of the following: a daytime mean ambulatory blood pressure measurement ≥135/85 (or 24 h mean ambulatory blood pressure measurement ≥130/80) or a mean home blood-pressure series ≥135/85 or mean office blood pressure ≥180/110 during one dedicated office visit);
   (iii) Diabetes mellitus (defined by a history of diabetes requiring pharmacological treatment (insulin or oral hypoglycemic agent) or an HbA1c level ≥6.5%. For the purpose of the trial, subjects with prediabetes or diet-controlled diabetes with an HbA1c level <6.5% are not considered to have this exclusion criterion);
   (iv) Congestive heart failure (defined by a New York Heart Association class II or higher at the time of enrollment or a known left ventricular ejection fraction <35%).

Exclusion criteria

(1) Known diagnosis of dementia;
(2) MMSE score <25;
(3) Valvular AF (mechanical heart valve, moderate-to-severe mitral stenosis (rheumatic or non-rheumatic) or hypertrophic cardiomyopathy);
(4) Other indication for antiplatelet therapy or anticoagulation;
(5) History of gastrointestinal bleeding;
(6) Conditions associated with an increased risk of bleeding described as follows:
   (a) Major surgery within the previous month;
   (b) Planned surgery or intervention within the next 3 months;
   (c) History of intracranial, intraocular, spinal, retroperitoneal or a traumatic intra-articular bleeding;
   (d) Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days;
   (e) Hemorrhagic disorder or bleeding diathesis;
   (f) Fibrinolytic agents within 48 h of study entry;
   (g) Recent malignancy or radiation therapy (within 6 months from the time of enrollment) and not expected to survive 3 years.
(7) Reversible cause of AF (for example, cardiac surgery, pulmonary embolism, untreated hyperthyroidism);
(8) Absence of recurrence of AF 3 months after AF ablation;
(9) Severe renal impairment (creatinine clearance 30 ml min^{-1} or less);
(10) Active infective endocarditis;
(11) Active liver disease (for example, acute clinical hepatitis, chronic active hepatitis, cirrhosis) or ALT > 3 times the upper limit of normal;
(12) Women who are pregnant or of childbearing potential not using a medically acceptable form of contraception throughout the study;
(13) Women who are breast feeding;
(14) Anemia or thrombocytopenia (according to the normal range values of the local laboratory);
(15) Participation in another study involving an investigational drug (under development) at the same time or within 30 days of randomization;
(16) Subjects considered unreliable or having a life expectancy of less than 3 years or having any condition which, in the opinion of the investigator, would not allow safe participation in the study (for example, drug addiction, alcohol abuse). (This criterion was incorporated as a precautionary measure to allow investigators to exclude individuals for whom safe participation or reliable data collection might not be feasible. Although not formally tracked, none of the 48 patients excluded before randomization among the 1,286 who provided informed consent were excluded solely on the basis of this criterion);
(17) History of allergic reaction to rivaroxaban;
(18) History of allergic reaction, in the absence of desensitization to acetylsalicylic acid in patient with vascular disease.

Trial procedures

All patients provided written, informed consent before any trial activities. At baseline (prerandomization), each patient underwent cognitive testing (MMSE and MoCA)[47,48]; the medical history was taken, including key data for cognition (years of education, depression status, sleep apnea, alcohol consumption, physical activity); echographic data were recorded; blood was tested for hematology and biochemistry, including renal function; an ECG was performed; depression status was assessed using the Beck Depression Inventory-II[49]; and quality of life was assessed using the SF-36 questionnaire.

The first patient was enrolled in April 2015 and the last patient in November 2023. Baseline characteristics remained balanced between treatment groups within both the early (Phase I) and later (Phase II) phases of the trial (Extended Data Table 3). Follow-up visits were performed every 6 months. Blood tests for hematology and biochemistry, including renal function, were taken yearly and at the 6- and 18-month visits. Cognitive testing was performed yearly (MoCA test with MMSE readministered solely at the final visit[47,48]). An ECG was performed yearly. At the final visit, quality of life (SF-36) and depression status (Beck Depression Inventory-II) were reassessed.

Interventions

Patients with an MMSE score ≥25 were then randomized in a 1:1 ratio to receive either rivaroxaban 15 mg once daily orally or a matching placebo through an interactive web response system (IWRS) using a permuted block randomization method. In addition, patients with vascular disease (coronary artery disease or peripheral arterial disease; Supplementary Information), were subjected to a double-dummy design. They received either rivaroxaban along with an aspirin placebo or a rivaroxaban placebo along with aspirin 100 mg daily, ensuring that one active drug was dispensed in a manner consistent with CCS-AF management guidelines[21]. Participants who developed vascular disease during the trial converted from a single-dummy to a double-dummy strategy via the IWRS without breaking the blind. The IWRS was configured for site stratification by automatically assigning the first available block to a site that became active and as randomization progressed. Within each site, the allowable imbalance between treatment arms was limited to a maximum of three. Patients and investigators remained blinded to treatment assignments until data analysis. If patients developed an indication for long-term oral anticoagulation, the study drug was discontinued, and they were transitioned to open-label oral anticoagulation therapy. However, follow-up continued until the end of the trial, and they were analyzed according to their original randomization group. Per protocol, participants completed their final visit either at trial cessation (or withdrawal) or upon reaching the age of 65 years, whichever came first. Management of study drugs in the event of AF ablation, cardioversion or other interventions was defined in the protocol (Supplementary Information). Concomitant use of a non-steroidal anti-inflammatory drug, antiplatelet therapy or strong inhibitors of both cytochrome P450 3A4 and P-glycoprotein was prohibited.

Study medication interruptions

Atrial fibrillation ablation. For participants who underwent AF ablation during the study, study medication was interrupted 2 days before the procedure. After ablation, short-term anticoagulation was prescribed at the investigator's discretion (typically for 1–3 months). Study medication was restarted only if AF recurrence was documented after a 3-month blanking period, based on rhythm monitoring (symptomatic or asymptomatic episodes). If no AF recurrence was detected, study medication was permanently discontinued, and participants continued with annual study visits only.

Atrial flutter ablation. For participants in sinus rhythm at the time of ablation, study medication was stopped at least 2 days before the procedure, according to investigator judgment. If participants were in atrial flutter of ≥48 h duration at the start of the procedure, a transesophageal echocardiogram was performed beforehand. Study medication was restarted once bleeding risk had resolved, at the investigator's discretion.

Cardioversion. If AF lasted ≥48 h, management followed guideline recommendations: either a transesophageal echocardiogram was performed or study medication was interrupted and 3 weeks of therapeutic anticoagulation were administered before cardioversion. Unblinding was not performed, as the 15-mg dose of rivaroxaban used in this study differed from the approved 20-mg dose for cardioversion. Following electrical or pharmacological cardioversion, anticoagulation was continued for 4 weeks, during which the study medication remained interrupted. It was restarted thereafter.

Pacemaker implantation. Study medication was interrupted at least 2 days before device insertion and was resumed once the bleeding risk had subsided, according to investigator judgment.

Endpoints

The primary efficacy outcome was a composite of cognitive decline initially defined by a ≥3-point reduction in the MoCA score from baseline, stroke or TIA with aphasia or a motor deficit. A protocol amendment subsequently modified the definition of cognitive decline to a ≥2-point reduction in MoCA score to align the trial with updated evidence[50]. Other secondary outcomes included individual components of the primary outcome; composite of stroke, TIA or systemic embolism; hospitalization for cardiovascular or bleeding event; cardiovascular and all-cause death; change in MMSE score from baseline to final visit; and a reduction in the MoCA score by ≥3 points. The primary safety outcome was major bleeding, as defined by the International Society of Thrombosis and Hemostasis.

With the exception of the change in MMSE score, all components of the primary and secondary outcomes were adjudicated in a blinded fashion by two members of an independent committee, with full committee review in case of disagreement.

Definitions

Stroke. Stroke was defined as a new focal neurological deficit of sudden onset, corresponding to a recognizable vascular territory, that either persisted for ≥24 h, was treated with thrombolysis/thrombectomy or lasted <24 h with confirmatory evidence of acute cerebral infarction by brain imaging.

TIA. TIA was defined as a transient focal neurological deficit of sudden onset corresponding to a recognizable vascular territory and lasting <24 h, with no confirmatory evidence of acute cerebral infarction by brain imaging. To qualify as a TIA, the event must have included a motor deficit or aphasia.

Vascular disease was defined as.

(1) Coronary artery disease:
   (a) History of myocardial infarction;
   (b) Coronary disease (stenosis ≥50% confirmed by invasive coronary angiography or non-invasive imaging or stress studies (for example, exercise or pharmacologic) suggestive of significant ischemia in at least one territory);
   (c) Percutaneous coronary intervention or coronary artery bypass graft surgery.
(2) Peripheral arterial disease:
   (a) Previous aortofemoral bypass surgery, limb bypass surgery or percutaneous transluminal angioplasty revascularization of the iliac or infrainguinal arteries or previous limb or foot amputation for arterial vascular disease;

(b) History of intermittent claudication and one or more of the following: an ankle/arm blood pressure ratio <0.90 or significant peripheral artery stenosis (≥50%);
(c) Previous carotid revascularization or carotid artery stenosis ≥50%.

Statistical analysis

Efficacy outcomes were analyzed based on the original randomization groups for all participants, including those who discontinued the trial early or switched to open-label anticoagulant therapy after developing a new clinical indication for oral anticoagulation post-randomization. An initial internal pilot phase (phase 1) was incorporated to assess feasibility and refine sample size calculations. Rollover of participants into the main trial phase (phase 2) was performed while maintaining the double blind. It was initially assumed that the primary composite outcome would occur in 6% of the combined study population per year. The final sample size calculation accounted for a yearly study medication discontinuation rate of 8.5% and yearly study discontinuation rates of 4% for the first 3 years, 10% for the fourth year and 12% for subsequent years. Based on these assumptions, a sample size of 1,424 patients was required to detect a relative risk reduction of 30% with a power of 85% and a two-sided significance level of 0.05. This sample size corresponded to an expected 410 patients with a primary efficacy outcome event. One interim analysis was planned after 205 patients had a positively adjudicated primary efficacy outcome event. Predetermined stopping rules were based on the Lan–DeMets procedure with the O'Brien–Fleming alpha-spending function for efficacy, and a futility boundary based on conditional power, defined as <20% probability of achieving statistical significance under the original alternative hypothesis. The primary efficacy outcome included an interval-censored component (that is, cognitive decline) such that it was analyzed using a generalized log-rank test for interval-censored data, stratified for the study phase. The primary efficacy outcome was also analyzed using a proportional hazards regression model fitted to handle interval-censored data and stratified for study phase. The primary outcome was graphically displayed using non-parametric maximum likelihood estimates of survival curves for interval-censored data.

Predefined sensitivity analyses on the primary outcome included censoring patients who developed a clinical indication for anticoagulation at the time of the new indication (censored population) and an on-treatment analysis of patients who took at least one dose of the study medication, with censoring 30 days following permanent discontinuation of study medication for any reason (on-treatment population).

Safety parameters were analyzed based on patients who took at least one dose of the study medication (safety population). Right-censored outcomes and the primary safety outcome of major bleeding were analyzed using log-rank tests and proportional hazards regression models, stratified for study phase. Change from baseline to last MMSE was analyzed as a categorical variable using an ordinal logistic regression model. All statistical analyses were conducted using SAS software version 9.4.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

In accordance with Quebec's *Act to modernize legislative provisions as regards the protection of personal information* (Law 25) and the Montreal Heart Institute's institutional policies, individual-level participant data cannot be transferred or released outside the coordinating center. Deidentified data underlying the results reported in this article are stored in a secure research environment at SERIANT (formerly the Montreal Health Innovations Coordinating Centre). Qualified academic investigators may request controlled on-site access to analyze these data after completion of all prespecified primary and secondary analyses and beginning 12 months after publication, for a period of 36 months. Requests, including a brief research proposal and analysis plan, will be reviewed by the BRAIN-AF Steering Committee and the Montreal Heart Institute Research Ethics Board for scientific merit and legal compliance within 3 months. Approved investigators will conduct analyses within the secure environment under a signed data-use agreement consistent with Quebec privacy legislation. Requests should be directed to the corresponding author.

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Author contributions

L.R., P.K. and D.R. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. L.R., P.K., D.R., M.T., J.C.-T., J.-S.H., S.E.B., J.G.A., I.N., L.B., F.M. and S.L. conceived and designed the study. L.R., P.K., D.R., M.T., J.-C.T., S.E.B., J.G.A., N.R., J.-F.R., I.G., P.G.G., H.M., C.C., Y.D., R.K.S., J.M., Y.K., A.V., B.M., K.D., J.C.-T., B.T., A.R.-P., M.A., A. Roussin, G.G., A. Robillard, M.T.-G. and L.-P.D. acquired, analyzed or interpreted data. L.R., P.K. and D.R. drafted the manuscript. J.G.A., T.S.F., S.N., L.M., D.C., C.B., J.B., R.T. and R.P. performed critical reviews of the manuscript for important intellectual content. M.C. and M.-C.G. performed statistical analyses.

Competing interests

L.R. reports research grants from Canadian Stroke Prevention Intervention Network (CSPIN), Canadian Institutes of Health Research (CIHR), Montreal Heart Institute Foundation and salary support from the Fonds de recherche du Québec (FRQS); honoraria and consulting fees from Boston Scientific and honoraria from Biosense.

J.-C.T. reports research grants from Boehringer-Ingelheim, Ceapro, DalCor Pharmaceuticals, Esperion, Merck, Novartis, Novo Nordisk, Pfizer and Verve; honoraria from DalCor Pharmaceuticals and Pfizer; minor equity interest from Dalcor Pharmaceuticals; authorship on a patent 'use of colchicine after myocardial infarction' assigned to the Montreal Heart Institute (J.-C.T. has waived his rights in the colchicine patents and does not stand to gain financially); and authorship on a patent 'pharmacogenomics-guided CETP inhibition'. J.-S.H. reports support, grant, honoraria and consulting fees from Boston Scientific; grant and honoraria from BMS/Pfizer; grant from Medtronic; honoraria from Servier and Novartis; payment for expert testimony from Bayer. S.E.B. reports grants from Genentech, Optina, Roche, Eli Lilly, Eisa/Biogen Idec, Novo Nordisk, Lilly Avid, ICON, Aribio Co, Ontario Brain Institute, CIHR, Leducq Foundation, Heart and Stroke Foundation of Canada, NIH, Alzheimer's Drug Discovery Foundation, Brain Canada, Weston Brain Institute, Canadian Partnership for Stroke Recovery, Canadian Foundation for Innovation, Focused Ultrasound Foundation, Alzheimer's Association US, Queen's University, Compute Canada Resources for Research Groups, CANARIE, Networks of Centres of Excellence of Canada; consulting fees from Roche, Biogen, Novo Nordisk, Eisai, Eli Lilly, DSR; honoraria from Biogen, Roche, Eisai and Cpdnetwork; participation on DSMB for Conference Board of Canada, World Dementia Council, University of Rochester and Ontario Dementia Care Alliance. J.G.A. reports honoraria from Abbott, Biosense-Webster Medtronic, Boston Scientific and Kardium. T.S.F. reports honoraria from Astrazeneca; payment for expert testimony from CMPA; participation on a DSMB for Novartis, Astrazeneca and Bayer; Board member for DESTINE Health and VGH/UBC Hospital Foundation. I.N. reports honoraria from Bayer, Servier, Medtronic and Biosense; support for travel from ERIM meeting 2024. F.M. reports consulting fees from Novo Nordisk and Eisai; honoraria from Pfizer. N.R. reports honoraria and participation on a DSMB from Clinical Event Committee. J.-F.R. reports consulting fees from Servier; honoraria from Bayer, BMS-Pfizer and Servier. R.T. reports grants and consulting fees from Bristol-Myers-Squibb Canada. G.G. reports grants from Novo Nordisk Canada Inc, Dalcor pharmaceutiques Canada Inc, Duke University, Merck Canada Inc, PPD Investigator Services, Novartis Canada, Montreal Heart Institute and Janssen Research & Development, LLC. D.C. received speaker fees from Servier, consulting fees from Trimedics and is supported by a PHRI career award. C.B. reports stock options from Imeka. Y.D. reports honoraria for presentation for Association des neurologues du Québec, Société de radiologie du Québec, Heart and Stroke Foundation of Canada and Centre de pédagogie appliquée aux sciences de la santé (Université de Montréal). R.K.S. reports grant NIH; consulting fees from Bayer. A.V. reports grants and consulting fees from Biosense, Medtronic, Abbott and medlumics; participation on a Data Safety Monitoring Board for Limit trial. J.C.-T. reports consulting fees from Bayer and BMS/Pfizer. J.B. reports consulting fees from Clinical Event Committee. M.A. reports consulting and speaker fees from Biosense-Webster and Abbott. R.P. reports research grants from Medtronic and Abbott; consulting fees from Medtronic and Biosense Webster. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-04101-y.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-04101-y.

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Extended Data Table 1 | Clinical outcomes, censored population

Outcome	Rivaroxaban (*n*=611)	Placebo (*n*=624)	Hazard Ratio (95% CI)	*P* Value
Cognitive decline, stroke, or TIA — no. (%)	122 (20.0)	118 (18.9)	1.11 (0.86, 1.42)	0.44
Cognitive decline	113 (18.5)	107 (17.2)	1.13 (0.87, 1.47)	
Stroke	8 (1.3)	7 (1.1)	1.20 (0.43, 3.31)	
TIA	3 (0.5)	5 (0.8)	0.60 (0.14, 2.51)	
Change from baseline to last MMSE — no. (%)[a]			1.13 (0.88, 1.44)	
≥ 2-point decline	34 (7.0)	28 (5.5)		
1-point decline	74 (15.2)	63 (12.3)		
no change	238 (49.0)	277 (54.1)		
1-point increase	92 (18.9)	105 (20.5)		
≥ 2-point increase	48 (9.9)	39 (7.6)		
Decrease MoCA score ≥ 3	51(8.4)	52 (8.3)	1.03 (0.70, 1.51)	
Stroke, TIA, or systemic embolism — no. (%)	13 (2.1)	16 (2.6)	0.84 (0.40, 1.74)	
Hospitalization for cardiovascular or bleeding event — no. (%)	34 (5.6)	39 (6.3)	0.90 (0.57, 1.43)	
All-cause death — no. (%)	3 (0.5)	6 (1.0)	0.52 (0.13, 2.07)	
Cardiovascular death — no. (%)	1 (0.2)	5 (0.8)		

[a]Odds ratio (95% CI) for rivaroxaban vs placebo is presented rather than a hazard ratio (95% CI).

https://doi.org/10.1038/s41591-025-04101-y

Extended Data Table 2 | Clinical outcomes, on-treatment population

Outcome	Rivaroxaban (*n*=602)	Placebo (*n*=621)	Hazard Ratio (95% CI)	*P* Value
Cognitive decline, stroke, or TIA — no. (%)	106 (17.6)	102 (16.5)	1.12 (0.85, 1.47)	0.41
Cognitive decline	101 (16.8)	93 (15.0)	1.17 (0.88, 1.55)	
Stroke	5 (0.8)	6 (1.0)	0.88 (0.27, 2.87)	
TIA	2 (0.3)	4 (0.6)	0.53 (0.10, 2.90)	
Change from baseline to last MMSE — no. (%)[a]			1.05 (0.80, 1.37)	
≥ 2-point decline	29 (7.1)	25 (5.8)		
1-point decline	60 (14.8)	52 (12.1)		
no change	202 (49.8)	230 (53.4)		
1-point increase	75 (18.5)	90 (20.9)		
≥ 2-point increase	40 (9.9)	34 (7.9)		
Decrease MoCA score ≥ 3	44 (7.3)	40 (6.5)	1.17 (0.76, 1.79)	
Stroke, TIA, or systemic embolism — no. (%)	8 (1.3)	15 (2.4)	0.56 (0.24, 1.32)	
Hospitalization for cardiovascular or bleeding event — no. (%)	27 (4.5)	34 (5.5)	0.83 (0.50, 1.38)	
All-cause death — no. (%)	3 (0.5)	6 (1.0)	0.52 (0.13, 2.07)	
Cardiovascular death — no. (%)	2 (0.3)	5 (0.8)		

[a]Odds ratio (95% CI) for rivaroxaban vs placebo is presented rather than a hazard ratio (95% CI).

https://doi.org/10.1038/s41591-025-04101-y

Extended Data Table 3 | Characteristics of patients at baseline according to study phase and treatment assignment

Characteristics	PHASE 1			PHASE 2			p-value for comparison between study phases
	Overall (*n*=503)	Rivaroxaban (*n*=247)	Placebo (*n*=256)	Overall (*n*=732)	Rivaroxaban (*n*=364)	Placebo (*n*=368)	
Age — yr	53.1±7.0	52.7±7.2	53.4±6.8	53.7±7.5	53.8±7.7	53.5±7.2	0.1503
Female sex — no. (%)	116 (23.1)	56 (22.7)	60 (23.4)	200 (27.3)	107 (29.4)	93 (25.3)	0.0918
Race or ethnic group — no. (%)[a]							0.2527
Caucasian	488 (97.0)	241 (97.6)	247 (96.5)	693 (94.7)	347 (95.3)	346 (94.0)	
Black or African American	1 (0.2)	1 (0.4)	0 (0.0)	5 (0.7)	3 (0.8)	2 (0.5)	
Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	
Asian	11 (2.2)	5 (2.0)	6 (2.3)	19 (2.6)	7 (1.9)	12 (3.3)	
Hispanic or Latino	1 (0.2)	0 (0.0)	1 (0.4)	8 (1.1)	4 (1.1)	4 (1.1)	
Other	2 (0.4)	0 (0.0)	2 (0.8)	6 (0.8)	2 (0.6)	4 (1.1)	
CHA_2DS_2-VA score — no. (%)[b]							
Men no vascular disease, 0	372 (74.0)	183 (74.1)	189 (73.8)	502 (68.6)	239 (65.7)	263 (72.3)	0.2214
Men vascular disease, 1	15 (3.0)	8 (3.2)	7 (2.7)	30 (4.1)	18 (4.9)	12 (3.3)	
Men, CHA_2DS_2-VA score (continuous)	0.04±0.19	0.04±0.20	0.04±0.19	0.06±0.23	0.07±0.26	0.04±0.20	
Women no vascular disease, 0	113 (22.5)	56 (22.7)	57 (22.3)	197 (26.9)	105 (28.8)	92 (25.3)	0.4953
Women vascular disease, 1	3 (0.6)	0 (0.0)	3 (1.2)	3 (0.4)	2 (0.5)	1 (0.3)	
Women, CHA_2DS_2-VA score (continuous)	0.03±0.16	0.0±0.0	0.05±0.22	0.02±0.12	0.02±0.14	0.01±0.10	
Predominant pattern of AF — no. (%)							0.0002
Paroxysmal (<7 days)	368 (73.2)	183 (74.1)	185 (72.3)	601 (82.1)	298 (81.9)	303 (82.3)	
Persistent (7 days to 1 year)	63 (12.5)	32 (13.0)	31 (12.1)	75 (10.3)	40 (11.0)	35 (9.5)	
Long-standing persistent (>1 year duration)	72 (14.3)	32 (13.0)	40 (15.6)	56 (7.7)	26 (7.1)	30 (8.2)	
Time since initial diagnosis of AF, years	4.3±5.9	4.0±5.6	4.6±6.3	3.7±5.8	3.3±5.5	4.0±6.1	0.0292
Oral anticoagulation at screening — no. (%)	38 (7.6)	23 (9.3)	15 (5.6)	40 (5.5)	18 (4.9)	22 (6.0)	0.1379
History of vascular disease — no. (%)	18 (3.6)	8 (3.2)	10 (3.9)	33 (4.5)	20 (5.5)	13 (3.5)	0.4198
Coronary artery disease	14 (2.8)	5 (2.0)	9 (3.5)	24 (3.3)	12 (3.3)	12 (3.3)	
Other	4 (0.8)	3 (1.2)	1 (0.4)	9 (1.2)	8 (2.2)	1 (0.3)	
Tobacco use — no. (%)	58 (11.5)	31 (12.6)	27 (10.6)	79 (10.8)	40 (11.0)	39 (10.6)	0.1654
Sleep apnea — no. (%)	85 (16.9)	41 (16.6)	44 (17.2)	144 (19.7)	75 (20.6)	69 (18.8)	0.2239
Left ventricular ejection fraction — %	60.1±6.1	60.5±5.9	59.7±6.3	59.6±5.2	59.6±5.1	59.7±5.3	0.1209
Left atrial volume — mL/m^2	35.9±19.1	35.8±19.5	36.0±19.0	36.8±18.9	36.4±16.7	37.2±21.0	0.3126
Creatinine clearance — mL/min	120.1±37.0	121.0±35.5	119.3±38.4	117.4±33.3	118.2±34.3	116.7±32.3	0.1941
Body mass index — m/kg^2	29.7±5.4	29.4±5.2	30.0±5.7	29.0±5.4	29.2±5.6	28.8±5.3	0.0246
Level of education — yrs of schooling	14.9±3.2	14.8±3.4	15.0±3.1	15.3±3.3	15.3±3.4	15.4±3.3	0.0123
Regular physical activity — no. (%)	323 (64.2)	157 (63.6)	166 (64.8)	509 (69.5)	250 (68.7)	259 (70.4)	0.0501
Depression status — no. (%)							0.6286
Normal to mild	473 (94.0)	232 (93.9)	241 (94.1)	681 (93.0)	342 (94.0)	339 (92.1)	
Moderate to severe	29 (5.8)	15 (6.1)	14 (5.5)	50 (6.8)	22 (6.0)	28 (7.6)	
Unknown	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	1 (0.3)	
Alcohol consumption — no. (%)							0.1428
≤1 drink per day	327 (65.0)	166 (67.2)	161 (62.9)	505 (69.0)	248 (68.1)	257 (69.8)	
>1 drink per day	176 (35.0)	81 (32.8)	95 (37.1)	227 (31.0)	116 (31.9)	111 (30.2)	
MoCA score — mean	27.6±2.0	27.7±2.0	27.5±2.0	27.5±1.9	27.5±1.9	27.6±2.0	0.4020
<26 — no. (%)	70 (13.9)	34 (13.8)	36 (14.1)	104 (14.2)	52 (14.3)	52 (14.1)	0.4958
MMSE — mean	29.3±1.0	29.3±1.0	29.4±0.9	29.3±1.0	29.3±1.0	29.4±1.0	0.5327

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	eCRF bulit in Inform 6.0 from Oracle
Data analysis	All statistical analyses were conducted using SAS software version 9.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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In accordance with Quebec's Act to modernize legislative provisions as regards the protection of personal information (Law 25) and the Montreal Heart Institute's institutional policies, individual-level participant data cannot be transferred or released outside the coordinating center. De-identified data underlying the results reported in this article are stored in a secure research environment at SERIANT (formerly the Montreal Health Innovations Coordinating Centre). Qualified academic investigators may request controlled on-site access to analyze these data after completion of all prespecified primary and secondary analyses and beginning 12

months after publication, for a period of 36 months. Requests, including a brief research proposal and analysis plan, will be reviewed by the BRAIN-AF Steering Committee and the Montreal Heart Institute Research Ethics Board for scientific merit and legal compliance. Approved investigators will conduct analyses within the secure environment under a signed data-use agreement consistent with Quebec privacy legislation. Requests should be directed to the corresponding author.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex were collected based on self-report and reported
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were collected based on self report.
Population characteristics	All baseline patient characteristics are provided in Table 1 of the manuscript.
Recruitment	Patients ≥30 and ≤60 years of age were eligible for inclusion if they had non-valvular atrial fibrillation and the absence of an anticoagulation indication according to Canadian Cardiovascular Society (CCS)-AF management guidelines, which recommend anticoagulation in the presence of congestive heart failure, hypertension, diabetes mellitus, prior stroke or transient ischemic attack , or age ≥65 years (so-called "CHADS-65" algorithm). Participants were recruited by participating institutions in the clinical study based on direct conversations between healthcare providers and patients. All participants were required to meet inclusion/exclusion criteria. After signed consent, patients underwent cognitive testing (MMSE and MoCA) anf those with MMSE > or = 25 were eligible for randomization.. Randomization between the treatment and control arms serves as a method of experimental control for human clinical trials to reduce selection bias introduced by the sampling methods. All subjects, research staff and medical team were blinded to their treatment assignment.
Ethics oversight	The study was authorized by Health Canada and the institutional review boards of the Montreal Heart Institute (MP-33-2014-1559) and each participating center, and was conducted in accordance with the principles of the Declaration of Helsinki

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	A sample size of 1424 patients was required to detect a relative risk reduction of 30% with a power of 85% and a two-sided significance level of 0.05.This sample size corresponded to an expected 410 patients with a primary efficacy outcome event. One interim analysis was planned after 205 patients had a positively adjudicated primary efficacy outcome event.
Data exclusions	Three patients were subsequently excluded before receiving the study medication due to hypertension (n=1), diabetes (n=1), or anemia (n=1).
Replication	All study data entered into the clinical study database was 100% source data verified by clinical study monitors. Study data was monitored against source documentation, and queried for accuracy of data collection. An independent statistician reproduced analyses of the primary and several secondary endpoints reported in the manuscript, and all other data points were verified by a peer reviewer. An independent clinical events committee adjudicated all primary event (stroke, transient ischemic attack, cognitive decline), death, cardiovascular hospitalization, hospitalization for bleeding event , major bleeding and systemic embolic event.
Randomization	1,235 participants were randomized in a 1:1 ratio to receive rivaroxaban (n=611) or placebo (n=624) through an interactive web response system (IWRS) using a permuted block randomization method.
Blinding	double-blind

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n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov # NCT02387229
Study protocol	The full trial protocol is available in the Supplementary Material.
Data collection	Data were collected on-site by clinical research associates onto a single digital database (inform) . Patients were recruted between April 2015 and November 2023. Last patient last visit occured in May 2024. Completed list of centers in Supplementary Table 1
Outcomes	According to the SAP available in Supplementary note, predefined endpoint were: The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite endpoint of stroke, TIA and neurocognitive decline (defined by a decrease in the MoCA score ≥ 2 at any follow-up visit from baseline) as adjudicated by the CEC. The secondary efficacy endpoints are the time from randomization to first occurrence of the following events, some of which will be adjudicated by the CEC: • Total death; • Cardiovascular death; • Composite endpoints of stroke/TIA and systemic embolic events; • Neurocognitive decline; • Hospitalization for cardiovascular (myocardial infarction, heart failure, atrial fibrillation, stroke, unstable angina or other cardiovascular event) or bleeding event; • Change from baseline to last MMSE score; • Rate of decline of MoCA score; • Change from baseline to last MoCA score; • MMSE <25; • New onset of MoCA <26; • New onset of MoCA <24; • Decrease in the MoCA score ≥ 3 at any follow-up visit from baseline

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A