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Clinical Research

Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation (BRAIN-AF): Methods and Design

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ABSTRACT

Background: Compelling evidence showing a link between atrial fibrillation (AF) and cognitive decline and dementia is accumulating.

Methods: Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation (BRAIN-AF) is a prospective, multicentric, double-blind, randomized-controlled trial, recruiting patients with nonvalvular AF and a low risk of stroke. Patients with a high risk of bleeding will be excluded from the study. Participants will be randomized to receive either rivaroxaban (15 mg daily) or standard of care (placebo in patients without vascular

RÉSUMÉ

Contexte : Les données probantes montrant l'existence d'un lien entre la fibrillation auriculaire (FA) et le déclin cognitif et la démence sont de plus en plus nombreuses.

Méthodologie : L'étude BRAIN-AF (***Blinded Randomized trial of Anticoagulation to prevent Ischemic stroke and Neurocognitive impairment in Atrial Fibrillation***) est une étude prospective multicentrique à double insu et à répartition aléatoire menée auprès de patients présentant une FA non valvulaire et un faible risque d'accident vasculaire cérébral (AVC). Les patients présentant un risque élevé

Atrial fibrillation (AF) and dementia are prevalent health issues afflicting 0.4% and 1.5% of Canadians, respectively,[1,2] and are associated with substantial morbidity and mortality.[1,3] Numerous prospective and retrospective studies suggest that the rate of cognitive impairment and all forms of dementia is magnified in patients with AF[4-15] regardless of the presence of stroke (Table 1). Furthermore, the association appears to be stronger in patients younger than 75 years.[6,12] Proposed pathophysiological mechanisms linking AF to cognitive dysfunction include silent cerebral ischemia, cerebral hypoperfusion, inflammation, reduction in hippocampal brain volume, and genetic factors.[16]

Patients deemed at low risk of stroke (eg, without congestive heart failure, hypertension, diabetes, or prior stroke or transient ischemic attack [TIA] and younger than 65 years) constitute a large subset (20%-25%) of the AF population.[17] In this

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disease or acetylsalicylic acid 100 mg daily in patients with vascular disease).

Results: The primary outcome is the composite of stroke, transient ischemic attack, and cognitive decline (defined by a decrease in the Montreal Cognitive Assessment score $\geq$ 3 at any follow-up visit after baseline). Approximately 3250 patients will be enrolled in approximately 130 clinical sites until 609 adjudicated primary outcome events have occurred.

Conclusions: BRAIN-AF determines whether oral anticoagulation therapy with rivaroxaban compared with standard of care reduces the risk of stroke, transient ischemic attack, or cognitive decline in patients with nonvalvular AF and a low risk of stroke.

d'hémorragie seront exclus de l'étude. Les participants seront répartis aléatoirement pour recevoir soit du rivaroxaban (à raison de 15 mg par jour), soit un traitement de référence (placebo chez les patients ne présentant pas de maladie vasculaire et acide acétylsalicylique à 100 mg par jour chez les patients présentant une maladie vasculaire).

Résultats : Le paramètre principal regroupe l'AVC, l'ischémie cérébrale transitoire et le déclin cognitif (défini par une baisse $\geq$ 3 du score à l'échelle MoCa [*Montreal Cognitive Assessment*, Évaluation cognitive de Montréal] à n'importe quelle visite de suivi après le début de l'étude). Environ 3 250 patients seront recrutés dans quelque 130 centres, et l'étude se poursuivra jusqu'à ce que 609 événements confirmés correspondant au paramètre principal soient survenus.

Conclusions : L'étude BRAIN-AF vise à comparer l'efficacité du traitement anticoagulant à prise orale par le rivaroxaban et du traitement de référence à l'égard de la réduction du risque d'AVC, d'ischémie cérébrale transitoire et de déclin cognitif chez les patients présentant une FA non valvulaire et un faible risque d'AVC.

population, the risk of stroke has been estimated to be 0.5%-1.4% per year[18-20] and oral anticoagulation (OAC) is generally not currently indicated (with the exception of patients with vascular disease). Non—vitamin K antagonist oral anticoagulants (NOACs) have been shown to be associated with a lower risk of intracranial haemorrhages and major bleedings compared with warfarin.[21] The risk-to-benefit ratio could shift towards anticoagulation therapy in patients with AF at low risk of stroke if the NOACs are demonstrated to be more effective in reducing silent cerebral ischemia and cognitive decline.

The **B**linded **R**andomized Trial of **A**nticoagulation to Prevent **I**schemic Stroke and **N**eurocognitive Impairment in **A**trial **F**ibrillation (BRAIN-AF) is a prospective, randomized, double-blind, controlled trial (ClinicalTrials.gov #NCT02387229). It is currently assessing whether rivaroxaban 15 mg daily can reduce the composite outcome of stroke/TIA or neurocognitive decline in patients with AF considered to be at a low risk for stroke compared with standard therapy (ie, placebo in patients without vascular disease and acetylsalicylic acid [ASA] in patients with vascular disease). During the internal pilot phase of the study, 503 patients (mean age, 53.1 $\pm$ 7.0 years) were randomized in 42 Canadian centres.

Link between AF and cognitive decline

The most convincing pathophysiological mechanism linking AF to cognitive impairment is silent cerebral ischemia due to microembolization. In the Cardiovascular Health Study, silent cerebral ischemia was a risk factor for mild cognitive impairment (MCI).[12] In the Rotterdam Scan Study, the presence of silent cerebral ischemia more than doubled the risk of dementia, including Alzheimer's disease.[22] In line with this hypothesis, Gaita et al.[8] conducted an observational study on the prevalence of silent cerebral ischemia assessed by cerebral magnetic resonance imaging (MRI) in patients with paroxysmal and persistent AF (60.5% with a low risk of stroke). At least 1 area of silent cerebral ischemia was observed in most patients with paroxysmal and persistent AF (89% and 92%, respectively). Patients with AF had a higher prevalence of silent cerebral ischemia and a worse cognitive performance compared with patients with sinus rhythm (odds ratio, 11.2; 95% confidence interval [CI], 6-21; $P < 0.01$).[8] The investigators demonstrated a significant link between the extent of silent cerebral ischemia areas and the degree of cognitive impairment. Furthermore, in the Rotterdam Study, the risk of dementia was strongly associated with the duration of exposure to AF in the younger participants (in the highest stratum: odds ratio, 3.30; 95% CI, 1.16-9.38; $P = 0.003$ for trend).[23]

Clinical data supporting a beneficial role of anticoagulation (Table 2)

Several studies have shown a protective effect of anticoagulation therapy in patients with AF and a current indication for OAC,[24-26] with NOACs having a greater protective effect than warfarin.[24,27] A recent meta-analysis including 97,595 patients showed a significant association between the use of NOACs and the lower risk of cognitive impairment when compared with vitamin K antagonists/ASA (hazard ratio [HR], 0.80; 95% CI, 0.63-0.98 for the fixed-effects model; and HR, 0.77; 95% CI, 0.53-1.01 for the random-effects model).[28] Furthermore, observational data suggest that delaying warfarin therapy in patients with AF increases the risk of dementia.[29] A substudy of the **A**trial Fibrillation **C**lopidogrel **T**rial With **I**rbesartan for Prevention of **V**ascular **E**vents (ACTIVE) W study reported that low modified Mini-Mental State Examination (MMSE) scores (suggesting dementia or cognitive impairment) were correlated with nontherapeutic anticoagulation.[30] Likewise, OAC showed a protective effect against dementia in 2685 dementia-free participants from the Swedish National Study.[31] In the AVERROES-MRI assessment study, brain MRI was performed at baseline and in 931 participants with AF randomized to ASA or apixaban. At baseline, 26.2% of subjects had brain infarcts (>15 mm). After a mean follow-up of 1 year, the rate of new infarcts was 2.5% in the apixaban group compared with 2.2% in the ASA group (HR, 1.09; 95% CI, 0.47-2.52).[32]

Methods and Analysis

Study design (Fig. 1)

The BRAIN-AF is a prospective, randomized, double-blind, controlled trial (ClinicalTrials.gov #NCT02387229).

Table 1. Meta-analysis assessing the association between atrial fibrillation and cognitive impairment/dementia

References	Patients (N)	Endpoint	Point estimate (95% CI)
Kwok et al.[5]	45,637	All-cause dementia	OR, 1.6 (1.0-2.7)
Santangeli et al.[59]	77,668	Incident dementia	HR, 1.42 (1.17-1.72)
Kalantarian et al.[60]	85,770	Incident dementia	RR, 1.40 (1.19-1.94)
Udompanich et al.[61]	7805	Incident dementia	OR, 2.3 (1.4-3.7)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, risk ratio.

Participants

The study population consists of patients aged between 30 and 62 years, with AF (paroxysmal, persistent, or permanent) and a low risk of stroke defined by the absence of the following: prior stroke or TIA, hypertension, diabetes mellitus, and congestive heart failure. At least 1 episode of AF $\geq$ 30 seconds must be documented by an electrical tracing by any device within 24 months of randomization. Detailed inclusion and exclusion criteria are listed in Table 3. Main exclusion criteria consist of known dementia or MMSE score of $<$ 25, valvular AF, conditions associated with an increased risk of bleeding, severe renal impairment, liver disease, women who are pregnant or breast feeding, and known diagnosis of major depression.

Screening and selection

Patients with AF meeting eligibility criteria are offered the opportunity to participate in the trial. Informed consent and baseline clinical data are obtained by the physician investigator.

Randomization

Patients who meet eligibility criteria and provide informed consent are randomized 1:1 to either 15 mg/d of rivaroxaban or standard of care, with therapy dictated according to vascular status (Fig. 2). Randomization is stratified by centres to ensure balance across potential local differences in treatment practice, with variable block sizes to minimize the potential for unblinding. Patients in the internal pilot phase (phase I) were initially randomized 1:1 to either rivaroxaban or ASA. The protocol was modified to align it with Canadian and international AF guidelines such that the comparator arm was changed from ASA to placebo in patients without vascular disease. Subjects who were initially randomized in phase I of the BRAIN-AF trial were transitioned to the current protocol without unblinding through the redistribution system (ie, subjects with vascular disease initially randomized to rivaroxaban or ASA maintained the same study treatment, whereas subjects without vascular disease were changed over from double-dummy to single-dummy therapy with those randomized to rivaroxaban continuing the same treatment and those initially randomized to ASA receiving only the rivaroxaban placebo).

Cognitive testing and psychological assessment

Neurocognitive tests for outcome measures were selected based on recommendations from the National Institute of Neurological Disorders and Stroke, Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards,[33] and the Third Canadian Consensus Conference on the diagnosis and treatment of dementia.[34] Global cognitive function is assessed by the MMSE and the Montreal Cognitive Assessment (MoCA).[35] The MMSE appears to be the most useful in ruling out dementia (high negative predictive

Table 2. Summary of studies assessing anticoagulation for prevention of cognitive dysfunction in patients with atrial fibrillation

Treatment	References	Methods	Findings
ASA vs warfarin	Mavaddat et al.[62]	Open label RCT N = 973 Age $\geq$ 75 y	No difference in MMSE scores after a mean follow-up of 2.7 y
DOAC vs warfarin	Jacobs et al.[24]	Cohort study N = 5254 Mean age: 72.4 y	Dementia (ICD-9) more prevalent in patients on warfarin compared with DOAC (0.7% vs 0.3%; $P = 0.03$) at the mean follow-up of 1.1 y
OAC vs no treatment	Friberg and Rosenqvist[25]	Retrospective study N = 444,106	Increase risk of dementia in patients without OAC (HR, 2.08; 95% CI, 1.73-2.53)
OAC vs no treatment	Ding et al.[31]	Population-based cohort study N = 2685	In patients with AF, use of OAC, but not antiplatelet treatment, was associated with a lower risk of dementia (HR, 0.4; 95% CI, 0.18-0.92)
Warfarin vs dabigatran vs rivaroxaban vs apixaban	Chen et al.[27]	US database N = 468,445	In patients with AF, use of direct OACs was associated with lower risk of dementia compared with warfarin. No difference in rates of dementia between NOACs

AF, atrial fibrillation; ASA, acetylsalicylic acid; CI, confidence interval; DOAC, direct-acting oral anticoagulants; HR, hazard ratio; ICD-9, International Classification of Diseases; MMSE, Mini-Mental State Examination; NOAC, non−vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation; RCT, randomized-controlled trial.

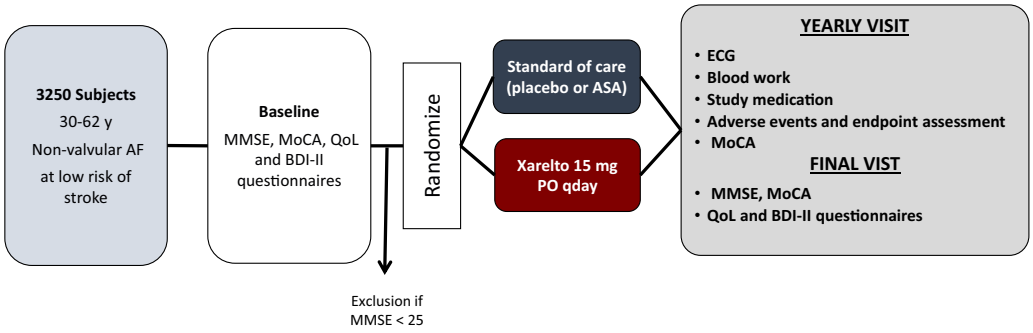

Figure 1. Overview of the trial. AF, atrial fibrillation; ASA, acetylsalicylic acid; BDI-II, Beck Depression Inventory-II; ECG, electrocardiogram; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PO, per os; QoL, quality of life.

value)[36] but has poor sensitivity for detecting complex cognitive deficits. The MoCA exhibits excellent sensitivity in identifying MCI and Alzheimer's disease (90% and 100%, respectively) with good specificity[37,38] associated with a cutoff value of 25/30. The MoCA was retained as the preferred neurocognitive test for MCI, as opposed to the less sensitive MMSE test. In addition to accumulating literature supporting a 3-point decline in the MoCA score as being clinically relevant,[39] our pilot data also suggest that the MoCA is more sensitive than the MMSE as a neurocognitive test in this specific young population. The MMSE will be performed at screening/baseline and at the final visit. The MoCA is performed at baseline and at yearly visits. As per standard recommendations, the MMSE is always performed before the MoCA with a minimum interval of 1 hour between tests and both tests are performed before randomization at baseline. All tests have been validated and are available in primary language of subjects involved. The Beck Depression Inventory-II[40,41] is administrated at baseline and at the final visit. The flow chart is described in Table 4.

Table 3. Main inclusion and exclusion criteria

Inclusion criteria
1. Age at consent $\geq$ 30 to $<$ 62 y
2. Nonvalvular AF documented by any electrocardiographic tracing in the 2 preceding years
3. Low risk of stroke as defined by the absence of the following: prior stroke or TIA, hypertension, diabetes mellitus, and congestive heart failure
4. Signed written informed consent

Exclusion criteria
1. Known diagnosis of dementia or MMSE score $<$ 25
2. Valvular AF (clinically significant [severe or moderate] rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, or mitral valve repair) or hypertrophic cardiomyopathy
3. Other indication for antiplatelet therapy or anticoagulation
4. History of gastrointestinal bleeding
5. Conditions associated with an increased risk of bleeding:
   a. Major surgery within the previous month
   b. Planned surgery or intervention within the next 3 mo
   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 d
   e. Haemorrhagic disorder or bleeding diathesis
   f. Fibrinolytic agent received within 48 h of study entry
   g. Recent malignancy or radiation therapy (within 6 mo from the time of enrolment)
6. Reversible cause of AF (eg, cardiac surgery, pulmonary embolism, hyperthyroidism)
7. Absence of recurrence of AF 3 mo after AF ablation
8. Severe renal impairment (creatinine clearance, $\leq$ 30 mL/min)
9. Active infective endocarditis
10. Active liver disease or ALT $>$ 3 times upper limit of normal
11. Women who are pregnant or breast feeding or of childbearing potential not using a medically acceptable form of contraception throughout the study
12. Anemia or thrombocytopenia
13. Participation in another study involving investigational drug within 30 d of randomization
14. Subjects considered unreliable or having a life expectancy of $<$ 2 y or having any condition that would not allow safe participation in the study
15. History of allergic reaction to rivaroxaban or ASA in patients with vascular disease

AF, atrial fibrillation; ALT, alanine aminotransferase; ASA, acetylsalicylic acid; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack.

Study outcomes

Primary endpoint. The primary efficacy outcome of the study is the first occurrence of any component of the composite endpoint of stroke, TIA, and neurocognitive decline. Stroke is defined as a new focal neurologic deficit of sudden onset, corresponding to a recognizable vascular territory, that either persists for $\geq$ 24 hours, is treated with thrombolysis/thrombectomy, or lasts $<$24 hours with confirmatory evidence of acute cerebral infarction by brain imaging.[42] Severity of the stroke will be assessed by the Rankin scale at least 3 months after the event.[43] TIA is defined as a transient focal neurologic deficit of sudden onset corresponding to a recognizable vascular territory and lasting $<$ 24 hours, with no confirmatory evidence of acute cerebral infarction by brain imaging.[42] Only events that include a motor deficit or aphasia can qualify as a TIA. Cognitive decline is defined by a decrease in the MoCA score of $\geq$ 3 at any follow-up visit. All components of the primary endpoint will be independently adjudicated by a committee blinded to treatment allocation.

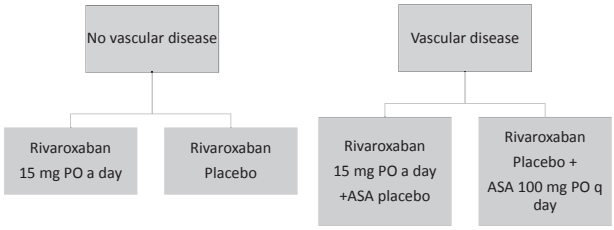

Figure 2. Randomization schema. ASA, acetylsalicylic acid; PO, oral.

Table 4. Flow chart

	Baseline	Follow-up visits										
Visits	Day −30 to day 0	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	6 mo visits until final visit[††]	Annual visits until final visit[††]	Final visit[‡‡]
Total duration (y)		0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5 and next	5.0 and next	
Visit windows (wk)		± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	±2	
Consent	X											
Medical history	X											
Vital signs	X		X		X		X		X		X	X
Height	X											
ECG[*]	X		X		X		X		X		X	X
MMSE (neurocognitive assessment)	X											X
MoCA (neurocognitive assessment)	X		X		X		X		X		X	X
Psychosocial, QoL questionnaires[†]	X											X
Laboratory testing[‡]	X	X	X		X		X		X		X	X
Pregnancy testing[§]	X											
Blood draw for biomarkers (optional)[‖]	(X)											
Blood draw for pharmacogenomic evaluation (optional)[¶]	(X)											
Assess study medication use, collect study medication		X	X	X	X	X	X	X	X	X	X	X
Dispense study medication	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Study endpoints other than neurocognitive assessments[**]		X	X	X	X	X	X	X	X	X	X	X

ALT, alanine transaminase; AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; ECG, electrocardiogram; INR, international normalized ratio; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; QoL, quality of life; TIA, transient ischemic attack; TSH, thyroid-stimulating hormone; (X), optional.

For stroke, assess the Rankin scale $\geq$ 3 months after the event.

[*] Results of any additional ECG recorded as part of routine clinical practice or because medically indicated will also be collected.

[†] Psychosocial, QoL questionnaires include the Beck Depression Inventory-II and Short Form 36.

[‡] Laboratory testing: at baseline (within 3 months of randomization): hemoglobin, hematocrit, platelet, serum electrolytes, renal function, TSH, ALT, AST, bilirubin, aPTT and INR; at 6 months: hemoglobin, hematocrit, platelet; and yearly: hemoglobin, hematocrit, platelet, ALT, AST, bilirubin, and serum renal function. Creatinine clearance will be calculated using the method of Cockcroft and Gault.

[§] Blood or urinary pregnancy test will only be performed for female subjects with childbearing potential.

[‖] Biomarkers collection will only occur at randomization visit (or at any follow-up visit if not done at baseline).

[¶] Blood draw for pharmacogenomic evaluation can be collected at any follow-up or final visit.

[**] Study endpoints other than neurocognitive are death, stroke, TIA, major bleeding, systemic embolism, and hospitalization for cardiovascular/bleeding events.

[††] Subjects enrolled in the study for > 48 months will continue to visit the clinic until the end of study every 6 months and will have the same assessments as previous visits.

[‡‡] Final visit should be scheduled as soon as possible after being notified by Montreal Health Institute Coordinating Center that study is completed.

Table 5. Baseline characteristics from the internal pilot phase

Baseline characteristics	N = 503, n (%)
Age, y	53.1 ± 7.0
> 50	367 (76.9)
> 45	435 (86.5)
Male sex	387 (76.9)
First-degree family history of AF	134 (26.6)
First-degree family history of dementia	106 (21.1)
Mean MoCA	27.6 ± 2.1
< 26	73 (14.5)
< 24	25 (5.0)
Mean MMSE	29.3 ± 0.9
Type of AF	
Paroxysmal	368 (73.3)
Persistent	62 (12.4)
Permanent	72 (14.3)
Years of education	14.7 ± 3.5
Vascular disease	16 (3.2)
Left ventricular ejection fraction, %	60.3 ± 6.2
Left atrial volume, mL	36.7 ± 19.7
Sleep apnoea	85 (16.9)
Dyslipidaemia	82 (16.3)

AF, atrial fibrillation; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

Secondary endpoint. The secondary endpoint will comprise death (total and cardiovascular); individual components of the primary outcome (ie, stroke/TIA and neurocognitive decline) and systemic embolization; hospitalization for cardiovascular (myocardial infarction, heart failure, AF, stroke, unstable angina, or other cardiovascular events) or bleeding event; rate of decline of MMSE score; rate of decline of MoCA score; MMSE score of < 25; and new onset of MoCA < 26 and < 24.

Event adjudication

The clinical events committee (CEC) is composed of a cardiologist as chairperson and 8 CEC reviewers (cardiologists, neurologists, internists, and psychiatrists) with expertise in clinical event adjudication. Additional members may be added if necessary. Two reviewers will be assigned to review each end point and serious adverse events with disagreement resolved by the chairperson or entire CEC. All components of the primary endpoint and the endpoints of death, systemic embolism, and hospitalization for myocardial infarction, heart failure, AF, stroke, unstable angina, or other cardiovascular or bleeding events are defined below and will be adjudicated by the CEC.

Data management

A unique subject number not derived from personal identifiers is used for subject identification. Study information using this unique subject number is collected using case report forms, which are entered into a secure online platform (InForm V.6.0). All electronic data are encrypted, password protected, and stored on a secure network within the Montreal Health Innovations Coordinating Center (MHICC). The MHICC performs regular evaluations of data integration and quality, management and resolution of data discrepancies, tracking of adverse event information, database quality control, and generates reports for principal and co-applicants, study sites, and for committee meetings. At the conclusion of the study, the MHICC will lock the clinical data and perform the final analysis of the trial results.

Statistical analyses

Efficacy data will be analyzed in all randomized subjects (intention-to-treat population), with subjects categorized according to the randomized arm regardless of the treatment actually received. Subjects lost to follow-up before an event will be included in the analysis with their time to event censored when they were last known to be event-free. Statistical analyses will be performed using SAS version 9.4 or higher. All statistical tests will be 2-sided at a significance level of 0.05. No adjustments will be made for multiple testing. No imputation for missing values will be applied. Before all analyses, basic assumptions will be verified, and if they are violated, other models or transformations will be performed. The primary endpoint will be analyzed using a generalized log-rank test, stratified for the phase of the trial (phase I and phase II). Considering that one of the components of the primary outcome, that is, cognitive decline, is assessed yearly, a generalized log-rank test will be performed to account for interval-censored data. The SAS procedure ICLIFETEST will be used as it allows for the estimation of survival functions and statistical testing using nonparametric methods appropriate for interval-censored data. A plot of survival curves will be provided. Secondary endpoints expressed as time-to-event will be similarly analyzed using log-rank tests or generalized log-rank tests as appropriate, with survival curves plotted. In addition to the above, a Cox proportional hazards model will be used to test the consistency of group effects for the primary endpoint, while accounting for clinically important baseline characteristics prespecified in the statistical analysis plan. Again, the statistical approach will be adapted for interval-censored data through the SAS procedure ICPHREG. A mixed-effect model will be performed to investigate the rates of decline using treatment groups, time, and the interaction between treatment groups and time as independent variables. Time will be considered a continuous variable and calculated as the number of days from the date of randomization. Random effects within the model are intercepts and slopes for individual subjects. A time $\times$ treatment group interaction term will assess differences in slopes between groups.

Proposed sample size

BRAIN-AF is an event-driven trial for which the required sample size is estimated to be approximately 3250 (including the 503 patients randomized in phase I) to obtain 609 primary events. These estimates are based on the following assumptions: an additional 3 years of recruitment for phase II, a minimum follow-up of 2 years, 2-tailed α of 0.05, a 1.4% per year study discontinuation rate, 30% cumulative overall noncompliance rate (ie, cessation of study drug, including for new anticoagulation indications), and a 1-year 6.0% overall primary event rate. Calculations were performed using nQuery + nTerim version 2.0.

Planned subgroups analyses

The following subgroups will be considered: age category (ie, < 40 years, between 40 and 55 years, or ≥ 55 years), sex,

MCI at baseline (defined as MoCA < 26) vs no MCI (MoCA ≥ 26), type of AF (ie, paroxysmal, persistent, or permanent), renal function, left atrial volume, depression status (assessed by Beck Depression Inventory-II questionnaire), and vascular disease. Subgroup analyses will be conducted by introducing the subgroup and the treatment groups by subgroup interaction in the planned statistical models.

Data monitoring

The Data and Safety Monitoring Committee (DSMC) comprises 4 members (chair: Dr Kenneth A. Ellenbogen, Dr George Wyse, Dr Kerry L. Lee, and Dr Michael D. Hill). The role of the DSMC is to monitor the progress of the BRAIN-AF trial and ensure that the safety of subjects enrolled in the study is not compromised. The DSMC members will not have any involvement in the BRAIN-AF study, apart from safety monitoring.

Ethics and dissemination

Once the study is completed, the results will be presented at an international conference. A publication in a high-impact journal is planned. The Canadian Heart Rhythm Society will assist in dissemination of the findings, as the principal investigators are members. The members of the executive committee will be responsible for dissemination of the findings through presentations in Canada, the United States, and Europe. Patients who have participated in the study will be informed of the results. Should the results show that anticoagulation in patients at low stroke risk is both safe and effective, the BRAIN-AF team will engage key stakeholders (eg, Canadian Heart Rhythm Society and Canadian Cardiovascular Society) that can enable knowledge dissemination and translation into the clinical realm. Results will be incorporated into clinical practice guidelines for the management of AF.

Baseline characteristics from the internal pilot phase

In the pilot phase of the BRAIN-AF trial, a total of 503 patients (age, 53.1 ± 7.0 years; 23.1% female) were recruited across 42 Canadian centres. Baseline characteristics are summarized in Table 5. The majority of patients had paroxysmal AF (73.3%), and only 3.2% of patients had vascular disease. The mean left ventricular ejection fraction was $60.3\% \pm 6.2\%$, with a left atrial volume of 36.7 ± 19.7 mL. Despite the relatively young age of this AF patient population, 14.5% of patients had MCI at baseline, as defined by a MoCA score of < 26.

Discussion

Several observational studies suggest that AF increases the risk of cognitive decline and dementia. Importantly, this association appears to be independent of manifestation of stroke and several risk factors common to both entities.[6,12] Moreover, the association is strongest in patients younger than 75 years.[6,12] To date, no therapy has been proven effective. Consequently, the World Health Organization declared prevention and treatment of dementia to be a public health priority.[44,45] Simulation studies suggest that delaying the onset of dementia by only 2 years would have a substantial impact on society and health economy.[44,45] Indeed, dementia disorders are typically associated with long prodromal periods characterized by detectible cognitive deficits (so-called MCI) years before the onset of dementia.[46] The pathophysiological link between AF and dementia remains debated.[47] The most convincing pathophysiological mechanism linking AF to cognitive impairment is silent cerebral ischemia due to microembolization, for which OAC should theoretically be effective.[32] Initiating OAC therapy earlier in the disease course (ie, in patients at low risk of stroke) carries the potential to prevent or delay cognitive decline in the AF population. An international consensus statement recently emphasized the urgent need for definitive clinical trials to address neurocognitive outcomes in patients with AF.[48] Indeed, OAC can prevent the majority of ischemic strokes and is now indicated in approximately 75%-80% of patients with AF.[21,49,50] Over time, the threshold to initiate therapy has steadily decreased on the basis of observational studies.[51,52] It is now recommended in patients older than 65 years, men with a **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) score of 1 and women with a score of 2.[49,50] For patients at low risk of stroke, no treatment is currently indicated.[51] In particular, in the absence of vascular disease, ASA is no longer recommended as benefits are not thought to outweigh risks.[53,54] Safer agents can contribute to further lowering the threshold to initiate OAC.[55-58] The BRAIN-AF trial will provide definitive evidence regarding the role of NOACs in this population.

Conclusions

The BRAIN-AF trial compares anticoagulation therapy to standard of care in patients with nonvalvular AF and a low risk of stroke and will help determine the best clinical strategy in this population. The BRAIN-AF trial carries the potential to definitively establish that anticoagulation improves cognitive outcomes in patients with AF at low risk for stroke.

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Disclosures

The authors have no conflicts of interest to disclose.

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