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ORIGINAL RESEARCH ARTICLE

MRI-Detected Brain Lesions and Cognitive Function in Patients With Atrial Fibrillation Undergoing Left Atrial Catheter Ablation in the Randomized AXAFA-AFNET 5 Trial

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BACKGROUND: We aimed to assess the prevalence of ischemic brain lesions detected by magnetic resonance imaging and their association with cognitive function 3 months after first-time ablation using continuous oral anticoagulation in patients with paroxysmal atrial fibrillation (AF).

METHODS: We performed a prespecified analysis of the AXAFA-AFNET 5 trial (Anticoagulation Using the Direct Factor Xa Inhibitor Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy), which randomized 674 patients with AF 1:1 to uninterrupted apixaban or vitamin K antagonist therapy before first-time ablation. Brain magnetic resonance imaging using fluid-attenuated inversion recovery and high-resolution diffusion-weighted imaging was obtained within 3 to 48 hours after AF ablation in all eligible patients enrolled in 25 study centers in Europe and the United States. Patients underwent cognitive assessment 3 to 6 weeks before ablation and 3 months after ablation using the Montreal Cognitive Assessment (MoCA).

RESULTS: In 84 (26.1%) of 321 patients with analyzable magnetic resonance imaging, high-resolution diffusion-weighted imaging detected at least 1 acute brain lesion, including 44 (27.2%) patients treated with apixaban and 40 (24.8%) patients treated with vitamin K antagonist (P=0.675). Median MoCA score was similar in patients with or without acute brain lesions at 3 months after ablation (28 [interquartile range (IQR), 26–29] versus 28 [IQR, 26–29]; P=0.948). Cerebral chronic white matter damage (defined as Wahlund score ≥4 points) detected by fluid-attenuated inversion recovery was present in 130 (40.5%) patients and associated with lower median MoCA scores before ablation (27 [IQR, 24–28] versus 27 [IQR, 25–29]; P=0.026) and 3 months after ablation (27 [IQR, 25–29] versus 28 [IQR, 26–29]; P=0.011). This association was no longer significant when adjusted for age and sex. Age was associated with lower MoCA scores before ablation (relative risk, 1.02 per 10 years [95% CI, 1.01–1.03]) and 3 months after ablation (relative risk, 1.02 per 10 years [95% CI, 1.01–1.03]).

CONCLUSIONS: Chronic white matter damage as well as acute ischemic lesions detected by brain magnetic resonance imaging were found frequently after first-time ablation for paroxysmal AF using uninterrupted oral anticoagulation. Acute ischemic brain lesions detected by high-resolution diffusion-weighted imaging were not associated with cognitive function at 3 months after ablation. Lower MoCA scores before and after ablation were associated only with older age, highlighting the safety of AF ablation on uninterrupted oral anticoagulation.

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Key Words: anticoagulants ■ atrial fibrillation ■ magnetic resonance imaging

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Clinical Perspective

What Is New?

- Acute ischemic brain lesions or chronic white matter damage detected on magnetic resonance imaging were not associated with cognitive decline at 3 months after first ablation on uninterrupted oral anticoagulation.
- Cognitive dysfunction 3 to 6 weeks before and 3 months after ablation was linked to older age but independent of uninterrupted apixaban or vitamin K antagonist use, which were equally effective in preventing periinterventional acute ischemic brain lesions detected by brain magnetic resonance imaging.

What Are the Clinical Implications?

- Our results highlight the safety of atrial fibrillation ablation with uninterrupted oral anticoagulation with apixaban or a vitamin K antagonist with regard to cognitive dysfunction within 3 months after ablation.
- Research is needed to improve ablation technology to reduce the periprocedural risk of acute ischemic brain lesions, which were detected in 1 of 4 patients in the magnetic resonance imaging substudy of the AXAFA-AFNET 5 trial (Anticoagulation Using the Direct Factor Xa Inhibitor Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy).
- Attention should be paid to optimized therapy of treatable risk factors linked to cognitive decline.

Nonstandard Abbreviations and Acronyms

ACT	activated clotting time
AF	atrial fibrillation
AXAFA-AFNET 5	Anticoagulation Using the Direct Factor Xa Inhibitor Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy
DWI	diffusion-weighted imaging
hrDWI	high-resolution diffusion-weighted imaging
IQR	interquartile range
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
OR	odds ratio
VKA	vitamin K antagonist

Left atrial catheter ablation is an important component of modern rhythm control therapy in patients with atrial fibrillation (AF).[1–3] Clinical trials have shown that catheter ablation could improve left ventricular function in a subset of patients with AF and heart failure.[4,5] However, left atrial catheter ablation is associated with measurable periprocedural risks, including a small risk of periprocedural ischemic stroke.[6–8] Brain magnetic resonance imaging (MRI) using diffusion-weighted imaging (DWI) identifies clinically silent acute brain lesions in 10% to 40% of patients after AF ablation.[6–9] This is concerning because a substantial number of patients require repeated ablation owing to recurrent symptomatic AF and acute brain lesions caused by ablation may contribute to cognitive decline, which is a frequent finding in patients with AF.[1,2,9,10] Because previous randomized ablation trials such as RE-CIRCUIT (Uninterrupted Dabigatran Etexilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation) and VENTURE-AF (A Study Exploring Two Treatment Strategies in Patients With Atrial Fibrillation Who Undergo Catheter Ablation Therapy) did not include an MRI substudy, there is a lack of highly standardized brain MRI data in ablation cohorts using uninterrupted periprocedural oral anticoagulation.[11,12] To quantify the frequency of acute brain lesions in patients undergoing AF ablation receiving high-quality, continuous anticoagulation, and to evaluate the association of periprocedural anticoagulation, MRI-detected brain lesions, and cognitive function, a prespecified MRI substudy was executed as part of the investigator-initiated, multi-center, randomized AXAFA-AFNET 5 trial (Anticoagulation Using the Direct Factor Xa Inhibitor Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy).[7,13]

METHODS

Data Availability Statement

The data will be shared on reasonable request to the AXAFA-AFNET 5 trial sponsor (via axafa@af-net.eu).

Study Design and Study Population

The prospective, parallel-group, 1:1 randomized, open, blinded outcome assessment AXAFA-AFNET 5 trial was conducted in 49 centers from 8 European countries and the United States in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines.[13] The ethical review board of all study centers approved the study protocol and the included MRI substudy. All patients provided written informed consent. Consent to the MRI substudy was optional in study centers able to provide brain MRI after the ablation procedure. An independent data and safety monitoring board monitored the study for safety. All adverse events were adjudicated by an independent end point review committee blinded to study group and international normalized ratio values. The trial sponsor was AFNET (the Atrial Fibrillation Network; www.af-net.eu). The Clinical Research Institute executed the study. From February 2015 to April 2017, 674 patients with symptomatic nonvalvular AF scheduled for a first ablation who had at least 1 established stroke risk factor (age >75 years, heart failure, hypertension, diabetes, previous stroke or transient ischemic attack) and were ≥18 years of age were enrolled.[7] Exclusion criteria can be found in Table S1.

Random Groups and Study Intervention

Patients randomized to apixaban received 5 mg (or 2.5 mg according to label) twice daily before ablation, which was continued during the ablation procedure without interruption. Patients randomized to vitamin K antagonist (VKA) were treated according to local practice routine with warfarin (n=113), phenprocoumon (n=108), or acenocoumarol (n=89), aiming for a target international normalized ratio of 2 to 3.[7,13] Patients could undergo ablation after at least 30 days of continuous anticoagulation. Ablation could be performed earlier if atrial thrombi were excluded by transesophageal echocardiography and patients had at least 2 adjacent apixaban doses or an international normalized ratio ≥1.8 before ablation. The ablation procedure followed current guidelines using either radiofrequency or cryoenergy according to local practice. Throughout the ablation procedure, an activated clotting time (ACT) >300 seconds was targeted.[13]

Study Outcomes and Measures

The primary outcome measure of the AXAFA-AFNET 5 trial was a composite of all-cause death, stroke, or major bleeding events at 3 months after ablation. In patients participating in the MRI substudy, predefined outcomes included the prevalence of clinically silent MRI-detected brain lesions and the effect of ablation-associated clinically overt strokes as well as MRI-detected clinically silent acute brain lesions on cognitive function 3 months after ablation.[13]

Cognition was assessed by the Montreal Cognitive Assessment (MoCA) during a visit at baseline (3–6 weeks before ablation) and 3 months after ablation. MoCA evaluates global cognition by assessing short term memory, visuospatial abilities, executive function, attention, concentration and working memory, language, and orientation to time and place. The test has 30 test items (with a possible score of 0–30 points, with a score ≥26 points being considered normal) and is available in different versions.[14] The level of education was not assessed in the AXAFA-AFNET data set.

Brain MRI

Brain MRIs were performed in eligible patients enrolled at 25 centers in 9 countries using 1.5 or 3 Tesla within 3 to 48 hours after the ablation procedure using a unified protocol defined in an imaging charter. The presence of acute brain lesions was assessed by high-resolution DWI (hrDWI) with 2.5- to 3-mm slice thickness.[7,13] The volume of every single brain lesion was measured by multiplying the individual voxel volume and

Table 1. Baseline Characteristics and Demographics of Study Patients According to Availability of Brain Magnetic Resonance Imaging and Randomization

	No brain MRI (n=293)	Brain MRI (n=333)	*P* value	Brain MRI and VKA (n=165)	Brain MRI and apixaban (n=168)	*P* value
Age, y, median (IQR)	64 (57–69)	64 (58–69)	0.411	64 (59–70)	64 (58–69)	0.430
Female sex, n (%)	99 (34)	109 (33)	0.846	56 (34)	53 (32)	0.728
BMI, kg/m^2, median (IQR)	29 (19–49)	28 (20–42)	<0.01	28 (25–31)	28 (25–30)	0.88
Type of AF, n (%)			0.051			0.756
Paroxysmal	158 (54)	206 (62)		99 (60)	107 (64)	
Persistent	132 (45)	120 (36)		62 (38)	58 (35)	
Longstanding persistent	3 (1)	7 (2)		4 (2)	3 (2)	
CHA_2DS_2-VASc score, median (IQR)	2 (2–3)	2 (1–3)	0.050	2 (2–3)	2 (1–3)	0.224
Older than 75 years, n (%)	28 (10)	26 (8)	0.526	14 (8)	12 (7)	0.801
Previous stroke or TIA, n (%)	19 (6)	28 (8)	0.448	15 (9)	13 (8)	0.805
Hypertension, n (%)	258 (88)	307 (92)	0.108	154 (93)	153 (91)	0.572
Diabetes, n (%)	36 (12)	39 (12)	0.922	19 (12)	20 (12)	0.999
Symptomatic heart failure, n (%)	90 (31)	56 (17)	<0.001	28 (17)	28 (17)	0.999
Vascular disease, n (%)	42 (14)	41 (12)	0.531	22 (13)	19 (11)	0.693
Wahlund score (points), median (IQR)	–	3 (1–5)	NA	3 (1–5)	3 (1–5)	0.930
SF-12 physical component, median (IQR)	45 (39–52)	43 (37–51)	0.103	46 (38–51)	45 (39–52)	0.562
SF-12 mental component, median (IQR)	50 (41–58)	51 (44–58)	0.422	49 (42–58)	51 (41–58)	0.754
Anticoagulation before randomization, n (%)	57 (19)	43 (13)	0.034	38 (23)	5 (3)	<0.001
Antiplatelets before randomization, n (%)	13 (4)	17 (5)	0.839	10 (6)	7 (4)	0.592
Statin before randomization, n (%)	111 (38)	118 (35)	0.581	65 (39)	53 (32)	0.167
MoCA (points), median (IQR)	27 (25–29)	27 (25–29)	0.087	27 (25–28)	27 (25–29)	0.906

Patients who withdrew informed consent were excluded from the analysis. AF indicates atrial fibrillation; BMI, body mass index; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; SF-12, 12-Item Short Form Health Survey; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

the number of positive voxels. If present, the number of brain lesions as well as the total volume of brain lesions was registered for every patient. Fluid-attenuated inversion recovery images with 5- to 6-mm slice thickness were included into the charter to assess the extent of white matter damage using the Wahlund score,[15] defining chronic white matter damage as a Wahlund score ≥4 points. T2*-weighted images with 5- to 6-mm slice thickness were acquired to exclude intracranial bleeding. MRIs were centrally read for new brain lesions in a core laboratory (Neuroscios). Two board-certified neuroradiologists independently assessed all brain MRIs blinded to randomization and clinical information.

Statistics

This analysis followed a predefined statistical analysis plan as described in the Supplemental Material. The analysis population included all patients enrolled in AXAFA who were randomized and underwent catheter ablation. Descriptive statistics for continuous and categorical variables were summarized as means (SDs), medians (25th, 75th percentiles), or counts (percentages), as appropriate. Comparisons between continuous variables were performed using the 2-sample *t* test or Kruskal-Wallis rank sum test depending on normality; comparisons between nominal variables were performed using the Pearson χ^2 test or Fisher exact test, depending on expected cell sizes. Because the current study is a secondary analysis of the AXAFA-AFNET trial, all analyses were exploratory and tested as 2-sided at the nominal 0.05 significance level. A multivariable logistic regression was performed with stepwise elimination procedure for the presence of MRI-detected brain lesions outcome. Models were compared using the Akaike information criterion. The cutoff for variables retained in the multivariable model was set to ≤0.2. No adjustment was made for multiple testing. A post hoc power calculation was performed using the 2-sided Z test with pooled variance. A maximum difference of 12% points (or greater) regarding the proportion of lesions per randomization group could have been detected with 80% power and an α level of 0.05. Regarding the proportion of cognitive decline after 3 months and the presence of acute MRI-detected brain lesions after ablation, a post hoc power calculation revealed 8% power to detect the observed difference between group proportions, which was very small (difference of proportions 0.0260). The association between the Wahlund score and cognitive impairment was assessed, both in a crude analysis and adjusted for age and sex. Potential interaction between age and the Wahlund score was assessed using an interaction term in the model. Statistical analyses were performed with R version 3.4.3.

Table 2. Ablation Characteristics of Study Patients According to Availability of Brain Magnetic Resonance Imaging and Randomization

	No brain MRI (n=293)	Brain MRI (n=333)	*P* value	Brain MRI and VKA (n=165)	Brain MRI and apixaban (n=168)	*P* value
Type of index catheter ablation, n (%)			0.193			0.605
Pulmonary vein isolation	272 (93)	295 (89)		149 (90)	146 (87)	
Pulmonary vein isolation + other ablation	20 (7)	36 (11)		15 (9)	21 (12)	
Other	1 (0)	2 (1)		1 (1)	1 (1)	
Type of ablation energy, n (%)			<0.001			0.716
Radiofrequency	171 (58)	227 (68)		109 (66)	118 (70)	
Cryoenergy	113 (39)	70 (21)		37 (22)	33 (20)	
Other	9 (3)	36 (11)		19 (12)	17 (10)	
Anticoagulation after randomization, n (%)			0.954			<0.001
VKA	144 (49)	165 (50)		165 (100)	0 (0)	
Apixaban	149 (51)	167 (50)		0 (0)	168 (100)	
Use of TEE before ablation, n (%)	259 (88)	286 (86)	0.415	146 (88)	140 (83)	0.233
Randomization to ablation, d, median (IQR)	35 (18–56)	35 (22–47)	0.870	35 (23–49)	35 (21–44)	0.325
ACT during ablation, s, median (IQR)	329 (296–365)	322 (298–359)	0.114	352 (307–368)	325 (290–341)	<0.001
<200 seconds at ≥1 time point measured	49 (17)	80 (24)		34 (21)	46 (27)	
≥200 seconds at all time points measured	45 (15)	40 (12)		10 (6)	30 (18)	
>250 seconds at all time points measured	91 (31)	94 (28)		42 (25)	52 (31)	
>300 seconds at all time points measured	49 (17)	69 (21)		38 (23)	31 (18)	
>350 seconds at all time points measured	43 (15)	37 (11)		29 (18)	8 (5)	
Heparin dose during ablation, IU, median (IQR)	10875 (8000–14126)	12000 (10000–15688)	<0.01	10000 (8000–14000)	14000 (10000–17500)	<0.001
Number of cardioversions during ablation, median (IQR)	0 (0–1)	0 (0–1)	0.279	0 (0–1)	0 (0–1)	0.752
AF or atrial flutter during ablation, n (%)	85 (29)	92 (28)	0.768	41 (25)	51 (30)	0.317

ACT indicates activated clotting time; AF, atrial fibrillation; MRI, magnetic resonance imaging; TEE, transesophageal echocardiogram; and VKA, vitamin K antagonist.

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RESULTS

Baseline Characteristics in the AXAFA-AFNET 5 Brain MRI Substudy

Among 674 patients randomized in the AXAFA-AFNET 5 trial, 634 patients underwent catheter ablation, 444 of which were performed at a study site capable of performing brain MRI. After excluding 108 patients not undergoing brain MRI for medical or technical reasons, 3 patients withdrawing informed consent (Table S2), and 12 patients with unanalyzable MRI, 321 patients were included in the analysis (Figure S1). Of those, 159 were randomized to VKA and 162 to apixaban. Baseline characteristics, demographics, and ablation characteristics of the brain MRI substudy population were similar compared with the total AXAFA study population (Tables 1 and 2) and the AXAFA study population at study sites able to provide brain MRI (Tables S2 and S5). Within the brain MRI cohort, baseline characteristics and demographics were balanced between the apixaban and VKA group (Table 1), with the exception of a higher rate of oral anticoagulation before randomization in the VKA cohort. Ablation characteristics were similar in both cohorts, with the exception of a lower median ACT during ablation and a higher dose of periprocedural heparin in patients randomized to apixaban (Table 2).

Factors Associated With hrDWI-Detected Acute Brain Lesions After Ablation

Brain MRI was carried out with a median delay of 22 hours (interquartile range [IQR], 20–25) after the ablation procedure. hrDWI detected 165 acute brain lesions in 84 (26.1%) patients (Figure). According to univariate analysis, older age, persistent or long-standing persistent AF, higher CHA_2DS_2-VASc score, higher Wahlund score (Table 3), number of cardioversions during the index ablation procedure, and AF or atrial flutter during ablation (Table 4) were associated with MRI-detected acute brain lesions after ablation. In a multivariable logistic regression analysis excluding the CHA_2DS_2-VASc score (including several variables in the model) and the number of cardioversions (because of high correlation with presence of AF or atrial flutter during ablation), age (odds ratio [OR], 1.06 per year [95% CI, 1.03–1.10]), persistent or long-standing persistent AF (OR, 2.47 [95% CI, 1.37–4.46] vs paroxysmal AF), and the presence of AF or atrial flutter during the ablation procedure (OR, 2.47 [95% CI, 1.35–4.53]) remained significant.

Effect of Randomized Treatment on hrDWI-Detected Acute Brain Lesions After Ablation

At least 1 acute ischemic brain lesion was detected by hrDWI in 40 (25.2%) of 159 patients randomized to

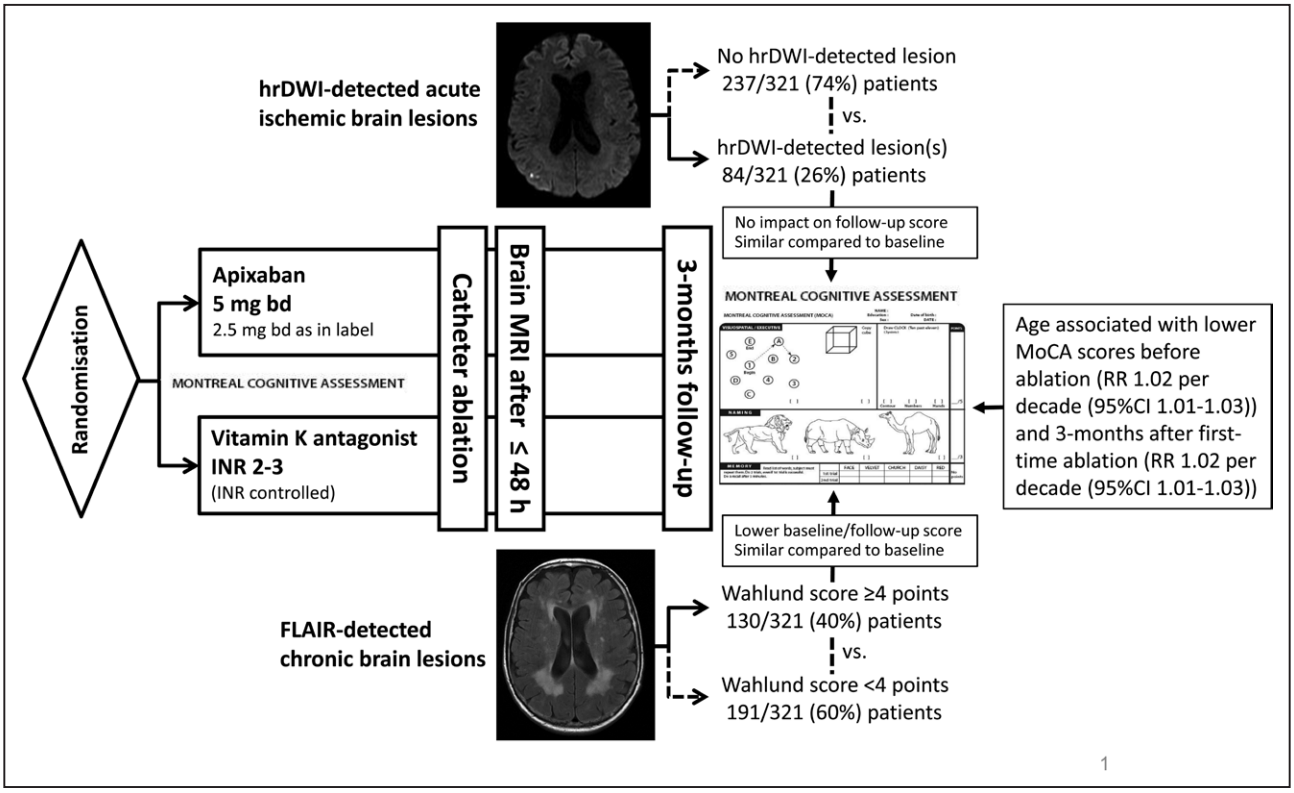

Figure. Study design and the main findings of the AXAFA-AFNET 5 brain MRI substudy.
Illustrative figure demonstrating the study design and the main findings of the AXAFA-AFNET 5 (Anticoagulation Using the Direct Factor Xa Inhibitor Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy) brain magnetic resonance imaging (MRI) substudy. FLAIR indicates fluid-attenuated inversion recovery; hrDWI, high-resolution diffusion-weighted imaging; INR, international normalized ratio; MoCA, Montreal Cognitive Assessment; and RR, relative risk.

Table 3. Baseline Characteristics and Demographics of Study Patients According to hrDWI-Detected Acute Ischemic Brain Lesions or FLAIR-Detected Chronic White Matter Lesions (Assessed by the Wahlund Score)

	No hrDWI lesion (n=237)	hrDWI lesion (n=84)	*P* value	Wahlund score <4 (n=191)	Wahlund score ≥4 (n=130)	*P* value
Age, y, median (IQR)	63 (57–69)	66 (62–72)	<0.001	61 (56–66)	69 (63–73)	<0.001
Female sex, n (%)	75 (32)	30 (36)	0.584	60 (31)	45 (35)	0.632
BMI, kg/m^2, median (IQR)	28 (25–31)	27 (25–30)	0.578	28 (25–31)	27 (25–30)	0.079
Type of AF, n (%)			<0.001			0.281
Paroxysmal	164 (69)	33 (39)		124 (65)	73 (56)	
Persistent	68 (29)	49 (58)		63 (33)	54 (42)	
Longstanding persistent	5 (2)	2 (2)		4 (2)	3 (2)	
CHA_2DS_2-VASc score, median (IQR)	2 (1–3)	3 (2–3)	0.014	2 (1–2.5)	3 (2–4)	<0.001
Older than 75 years, n (%)	14 (6)	12 (14)	0.029	3 (2)	23 (18)	<0.001
Previous stroke or TIA, n (%)	22 (9)	6 (7)	0.710	12 (6)	16 (12)	0.094
Hypertension, n (%)	219 (92)	76 (90)	0.746	181 (95)	114 (88)	0.038
Diabetes, n (%)	26 (11)	12 (14)	0.541	15 (8)	23 (18)	0.012
Symptomatic heart failure, n (%)	35 (15)	21 (25)	0.050	16 (8)	40 (31)	<0.001
Vascular disease, n (%)	33 (14)	7 (8)	0.254	21 (11)	19 (15)	0.428
Wahlund score (points), median (IQR)	2 (1–4)	4 (2–6)	<0.01	1 (0–2)	6 (4–7)	–
SF-12 physical component, median (IQR)	46 (39–53)	44 (39–48)	0.024	46 (41–52)	44 (37–50)	0.029
SF-12 mental component, median (IQR)	49 (41–57)	54 (43–59)	0.048	48 (40–57)	52 (46–57)	0.052
Anticoagulation before randomization, n (%)	30 (13)	11 (13)	0.999	22 (12)	19 (15)	0.518
Statin before randomization, n (%)	85 (35)	27 (32)	0.682	61 (32)	50 (38)	0.277
Antiplatelet before randomization, n (%)	12 (5)	3 (4)	0.798	11 (6)	4 (3)	0.396
MoCA (points), median (IQR)	27 (25–28)	27 (25–29)	0.781	27 (25–29)	27 (24–28)	0.026

AF indicates atrial fibrillation; BMI, body mass index; FLAIR, fluid-attenuated inversion recovery; hrDWI, high-resolution diffusion-weighted imaging; MoCA, Montreal Cognitive Assessment; SF-12, 12-Item Short Form Health Survey; and TIA, transient ischemic attack.

VKA and in 44 (27.1%) of 162 patients randomized to apixaban (*P*=0.753; Table 4), with similar distribution of (total) lesion volume and lesion localization between random groups (Table S3). As depicted in Table S4, there was no significant effect of anticoagulation quality on MRI-detected acute brain lesions after ablation.

The presence or absence of MRI-detected acute brain lesions postablation was not associated with the primary efficacy end point (all-cause death, stroke, or major bleeding events), which was reached in 13 (5.5%) of 236 patients without and 5 (6.0%) of 84 patients with hrDWI-detected brain lesions (*P*=0.999).

Factors Associated With Chronic Brain Lesions Detected by Fluid-Attenuated Inversion Recovery

Fluid-attenuated inversion recovery imaging revealed that a Wahlund score of ≥4 points was present in 130 (40.5%) of 321 patients (Figure). According to univariate analysis, a Wahlund score ≥4 was associated with older age, higher CHA_2DS_2-VASc score, history of hypertension, diabetes, symptomatic heart failure, lower patient-reported physical health (SF-12 [12-Item Short Form Health Survey]) scores, and lower MoCA score at baseline (Table 3).

Association Between MRI-Detected Brain Lesions and Cognition

The MoCA test at baseline (median, 34 days [IQR, 21–46] before the ablation procedure) and 3 months after ablation was available in 319 of 321 patients with analyzable MRI (Figure S1). The distribution of MoCA scores at baseline and 3 months is depicted in Figure S2. The median MoCA test score was not different in patients with or without MRI-detected acute ischemic brain lesions at baseline (27 [IQR, 25–28.5] versus 27 [IQR, 25–28]; *P*=0.781) or at 3 months after the index ablation (28 [IQR, 26–29] versus 28 [IQR, 26–29]; *P*=0.948). Also shown in Table 5, the median difference of baseline to 3 months MoCA test was similar in patients with or without MRI-detected acute ischemic brain lesions. In addition, there was no correlation of lesion number and the MoCA score at 3 months (data not shown).

Compared with patients with a Wahlund score of <4 points, a Wahlund score of ≥4 points was associated with

Table 4. Ablation Characteristics of Study Patients According to hrDWI-Detected Acute Ischemic Lesions

	No hrDWI lesion (n=237)	hrDWI lesion (n=84)	*P* value
Type of index catheter ablation, n (%)			0.103
Pulmonary vein isolation	215 (91)	71 (85)	
Pulmonary vein isolation + other ablation	22 (9)	12 (14)	
Other	0 (0)	1 (1)	
Type of ablation energy, n (%)			0.561
Radio frequency	162 (68)	55 (65)	
Cryoenergy	51 (22)	17 (20)	
Other	24 (10)	12 (14)	
Anticoagulation after randomization, n (%)			0.753
VKA	119 (50)	40 (48)	
Apixaban	117 (50)	44 (52)	
Use of TEE before ablation, n (%)	211 (88)	68 (81)	0.090
Randomization to ablation, d, median (IQR)	35 (23–47)	31 (14–44)	0.138
ACT during ablation, s, median (IQR)	325 (300–362)	315 (297–349)	0.377
<200 at ≥1 time point measured, n (%)	60 (25)	19 (23)	
≥200 at all time points measured, n (%)	25 (11)	14 (17)	
>250 at all time points measured, n (%)	62 (26)	26 (31)	
>300 at all time points measured, n (%)	50 (21)	16 (19)	
>350 at all time points measured, n (%)	28 (12)	8 (10)	
Heparin dose during ablation, IU, median (IQR)	12 000 (10 000–15 625)	13 000 (9 950–16 000)	0.564
Number of cardioversions during ablation, median (IQR)	0 (0–1)	0.5 (0–1)	<0.001
AF or atrial flutter during ablation, n (%)	47 (20)	41 (49)	<0.001

ACT indicates activated clotting time; AF, atrial fibrillation; hrDWI, high-resolution diffusion-weighted imaging; TEE, transesophageal echocardiogram; and VKA, vitamin K antagonist.

a lower median MoCA score at baseline (27 [24–28] vs 27 [IQR 25–29]; *P*=0.026) and at 3 months after the index ablation (27 [IQR 25–29] vs 28 [IQR 26–29]; *P*=0.011). Adjusted for age and sex, this association was no longer significant (baseline MoCA: *P*=0.20; 3-month follow-up MoCA: *P*=0.31). Age was associated with lower MoCA scores before (relative risk, 1.02 per 10 years [95% CI, 1.01–1.03]) and 3 months after ablation (relative risk, 1.02 per 10 years [95% CI, 1.01–1.03]). There was no significant interaction between age and the Wahlund score at baseline (*P*=0.27 for interaction) and 3-month follow-up (*P*=0.53). The alteration of base-

Table 5. Cognitive Performance at Baseline and at 3 Months After Ablation and Change From Baseline to 3 Months According to Presence or Absence of Brain MRI–Detected hrDWI Lesions, Wahlund Score <4 or ≥4, and Randomization (as Treated)

	No hrDWI lesion (n=236)	hrDWI lesions (n=83)	*P* value	Wahlund <4 points (n=190)	Wahlund ≥4 points (n=129)	*P* value	Age <65 years (n=173)	Age ≥65 years (n=146)	*P* value	Apixaban (n=161)	VKA (n=158)	*P* value
MoCA, baseline, median (IQR)	27 (25 to 28)	27 (25 to 28.5)	0.781	27 (25 to 29)	27 (24 to 28)	0.026	27 (25 to 29)	26 (24 to 28)	<0.001	27 (25 to 29)	27 (25 to 28)	0.858
MoCA, 3 months, median (IQR)	28 (26 to 29)	28 (26 to 29)	0.948	28 (26 to 29)	27 (25 to 29)	0.011	28 (26 to 30)	27 (25 to 29)	<0.001	28 (25 to 29)	28 (26 to 29)	0.931
Δ MoCA, median (IQR)	3.4 (–3.4 to 8)	3.5 (0 to 7.9)	0.576	3.4 (–3.3 to 7.6)	3.6 (–3.6 to 8.6)	0.643	3.4 (–3.4 to 7.4)	3.6 (–3.4 to 8.3)	0.386	3.4 (–3.4 to 8.1)	3.4 (–3.4 to 7.6)	0.930

Patients with missing baseline or follow-up Montreal Cognitive Assessment (MoCA) score were excluded. hrDWI indicates high-resolution diffusion-weighted imaging; MRI, magnetic resonance imaging; and VKA, vitamin K antagonist.

line to 3-month MoCA score was not different in patients with or without a Wahlund score of ≥4 points (*P*=0.643; Table 5).

Effect of Randomized Treatment on Cognition After Ablation

The median MoCA test score was similar in the apixaban cohort and VKA cohort at baseline (27 [IQR 25–29] vs 27 [IQR 25–28]; *P*=0.858) and at 3 months after the index ablation (28 [IQR 25–29] vs 28 [IQR 26–29]; *P*=0.931). The alteration in median difference of baseline to 3 months MoCA test did not differ between treatment groups (*P*=0.930; Table 5).

DISCUSSION

AXAFA-AFNET 5 is the largest randomized trial testing the effect of different uninterrupted periprocedural oral anticoagulation therapies on MRI-detected brain lesions after AF ablation.[7] The predefined analysis of available brain MRIs revealed several important findings.[13] First, hrDWI-detected acute brain lesions were found in 26% of all patients who had an analyzable MRI. Second, there was no effect of randomized anticoagulation treatment on hrDWI-detected acute brain lesions after ablation or on cognitive function at 3 months after ablation, as similarly reported for the primary outcome measure.[7] Third, cognitive function as well as the composite of all-cause death, stroke, or major bleeding events at 3 months postablation was not related to hrDWI-detected acute brain lesions after ablation. Fourth, the presence of hrDWI-detected acute brain lesions after ablation was linked to older age, persistent or long-standing persistent AF, and the presence of AF or atrial flutter during the ablation procedure. Fifth, older age was the only factor associated with lower MoCA scores at baseline and at 3 months after first-time ablation, highlighting the safety of AF ablation with uninterrupted oral anticoagulation. The extent of chronic white matter damage in the brain (assessed by the MRI-based Wahlund score),[15] which was more often found in elderly patients with cardiovascular risk factors,[16,17] was linked to lower MoCA scores at baseline and at 3 months after ablation. However, this association was lost after adjusting for age and sex.

Because 1 of 4 patients had at least 1 MRI-detected acute ischemic brain lesion despite uninterrupted oral anticoagulation and periprocedural heparinization, dislodgment of ablation debris and air embolism may substantially contribute to brain embolization. Further research is warranted aiming to improve ablation technology. Considering that the AXAFA-AFNET 5 MRI substudy used a higher spatial resolution (2.5–3 mm slice thickness) than previous studies, our results are in line with results of the randomized ELIMINATE-AF trial (A Prospective, Randomized, Open-Label, Blinded Endpoint Evaluation Parallel Group Study Comparing Edoxaban vs VKA in Subjects Undergoing Catheter Ablation of Non-valvular Atrial Fibrillation). In ELIMINATE-AF, 177 of 632 patients (28%) with AF underwent brain MRI (using a DWI slice thickness of 4–5 mm) within 4±2 days after ablation.[8] DWI-detected acute brain lesions were present in 16 (14%) patients who received edoxaban and 5 (10%) patients who received VKA. However, our results differ from those of a multicenter registry of 29 patients undergoing left atrial catheter ablation using periprocedural apixaban, which reported no DWI-detected acute brain lesion.[18]

Despite several strengths of this prespecified substudy of a randomized multicenter study (MRI core laboratory, near complete follow-up, and prespecified statistical analysis plan), there are limitations that must be considered. Although it included >50% of all AXAFA study participants, the substudy was not specifically powered to detect any differences regarding MRI-detected brain lesions or cognitive function. Furthermore, consent to the MRI substudy was optional, which might have included an additional selection bias. Because single brain MRIs within 3 to 48 hours after ablation were examined, we cannot rule out that acute brain lesions may have occurred up to 14 days before the ablation procedure and during the 3 months of follow-up. Despite the fact that using a DWI slice thickness of 2.5 to 3 mm is a high-quality standard of spatial resolution, lesions with a diameter of <2.5 mm might have been missed. Changes in cognitive function were analyzed at 3 months after ablation and therefore reflect short-term outcomes only. Furthermore, despite using different versions of the validated MoCA test, learning bias imparted by serial testing cannot be excluded. In addition, subtle cognitive impairment may have gone unnoticed using no extensive battery of neurocognitive tests.[14] Although baseline characteristics, anticoagulation treatment, and ablation procedures did not show differences, unmeasured confounders of cognitive function (such as the level of education and location of brain lesions[16]) may be unbalanced. Furthermore, it is difficult from a pathologic perspective to determine whether any specific lesion constellation (number, size, and location) will contribute to cognitive decline because other coexisting pathologies and clinical resilience may contribute to cognitive decline.[16] The observed lower median ACT during ablation in the apixaban cohort (despite a higher mean dose of intravenous heparin) is a well-known phenomenon.

MRI-detected acute ischemic brain lesions as well as chronic white matter damage are found in a relevant proportion of patients after first-time catheter ablation for paroxysmal AF. MRI-detected brain lesions after ablation were not associated with cognitive function at 3 months after the index procedure. We observed an association between old age and lower MoCA scores

before and after ablation, highlighting the safety of AF ablation with uninterrupted oral anticoagulation. The AXAFA-AFNET 5 trial revealed no differences between uninterrupted apixaban or VKA on the prevalence of hrDWI-detected acute brain lesions after ablation or cognition at 3 months after ablation.

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Supplemental Material

Supplemental Statistical Analysis Plan

Figures S1 and S2

Tables S1–S5

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