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RESEARCH LETTER

Pattern of Atrial Fibrillation and Cognitive Function in Young Patients With Atrial Fibrillation and Low $CHADS_2$ Score: Insights From the BRAIN-AF Trial

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Atrial fibrillation (AF) has been associated with cognitive impairment and dementia even in the absence of stroke, and independently from shared comorbidities.[1] Patients with persistent AF seem to have lower global cognitive abilities than individuals with paroxysmal AF.[2,3] Whether this association is explained by AF burden or shared cofactors is uncertain. Left atrial (LA) enlargement, which is commonly associated with AF, has also been linked with an increased risk of stroke and cognitive impairment in patients with or without AF.[4] Here, we sought to investigate the association between AF subtype, that is, paroxysmal AF versus nonparoxysmal (persistent or permanent) AF, LA volume (LAV), and cognition in low stroke-risk AF patients.

We conducted this analysis in patients participating in the internal pilot phase of the BRAIN-AF trial (Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02387229).[5] This trial assesses whether rivaroxaban (15 mg daily) reduces the composite outcome of stroke/transient ischemic attack or neurocognitive decline in patients with AF at low risk for stroke, when compared with placebo. We used the Montreal Cognitive Assessment (MoCA) score to assess various cognitive domains (visuospatial-executive, naming, attention, language, abstraction, memory, and orientation). Depression status was assessed using the Beck Depression Inventory-II. All questionnaires were performed before randomization. The study was approved by the local research ethics board. All participants gave their written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Of 503 patients enrolled in the internal pilot phase, 195 had complete echocardiographic data. Of these, 135 had paroxysmal AF (69.2%). Mean age was 53 years, 42 (21.5%) were women, 185 (94.9%) White, 35 (17.9%) with sleep apnea, 9 (4.6%) from vascular disease, and 37 (19%) from dyslipidemia. Forty-four (22.6%) consumed ≥10 alcoholic drinks/wk and 120 (61.5%) did not meet physical activity recommendations (150 minutes of physical activity/wk). Per inclusion/exclusion criteria, no individual suffered from history of stroke/transient ischemic attack, heart failure, diabetes, hypertension, or valvular AF. The CHA_2DS_2-VASc score was 0 in 148 (75.9%), 1 in 45 (23.1%), and 2 (1.0%) in 2 patients.

A hierarchical multiple regression analysis tested whether AF-related characteristics (AF subtype, LAV, LA anterior-posterior diameter, and left ventricular ejection fraction) predicted the MoCA score. Only AF-related characteristics significant in univariable analyses were included in the model (AF subtypes and LAV). In the first step of multiple regression all covariates were included. Sex and body mass index were included because they differed significantly between AF groups, whereas age, education, and depressive symptoms were included because of substantive

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BRAIN-AF	Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation
LA	left atrium
LAV	left atrial volume
MoCA	Montreal Cognitive Assessment

knowledge of their association with cognitive decline. In the second step, we introduced AF subtypes and LAV. A first-order interaction variable (AF group×LAV) was introduced in the third step. If the interaction term accounted for significantly more variance, a moderation analysis was run using the PROCESS add-on v3.3 for SPSS.

Compared with nonparoxysmal AF, paroxysmal AF patients had a significantly lower LAV (32.8 versus 45.5 mL, $P<0.001$), were mostly male (91.7% versus 72.6%, $P=0.003$), and had a lower body mass index (28.6 versus 30.6 kg/m^2, $P=0.012$). After correction for age, sex, body mass index, years of education, and depressive symptoms, nonparoxysmal AF was associated with a lower global MoCA score ($P=0.03$) and visuospatial-executive subscore ($P=0.02$, Figure [A]). After including LAV as a moderator in the model, AF group was no longer significant, leaving the interaction term (LAV×AF group) as the only significant predictor of MoCA score. A larger LAV significantly moderated the global MoCA difference observed between paroxysmal and nonparoxysmal AF (Figure [B]). Specifically, having LAV one SD higher than average (or 56.2 mL) predicted a lower global MoCA score by 1.29 points, ($P<0.01$) in the nonparoxysmal group than those with paroxysmal AF. In sensitivity analyses that excluded the 15 (7.7%) patients who received oral anticoagulation before randomization, results remained unchanged.

Mechanisms proposed to explain AF-related cognitive dysfunction include silent brain infarcts, cerebral hypoperfusion, inflammation, brain atrophy, microhemorrhage, and genetic factors. A much higher incidence of silent brain infarcts has been detected by imaging in AF versus matched non-AF patients; thus, the leading mechanistic hypothesis is that subclinical ischemic events underlie cognitive decline. Furthermore, LA enlargement has been associated with increased risk of spontaneous echo contrast and embolic events. In conjunction with the data here, this finding supports the microembolization mechanism. These data are subjected to several limitations. The sample size is relatively small and the cross-sectional design does not allow an analysis of how cognitive scores change over time as a function of AF burden.

Nevertheless, this study reveals that in low-risk AF patients, nonparoxysmal AF is associated with lower cognitive function scores when compared with paroxysmal, and that larger LAV moderates this cognitive deficit observed in nonparoxysmal AF. This association may be explained by a higher risk of thromboembolism and may have clinical implications. Future confirmatory studies are required to better understand the influence of, and interaction between, AF burden and LAV on cognition.

ARTICLE INFORMATION

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REFERENCES

1. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. *J Am Coll Cardiol.* 2019;73:612–619. doi: 10.1016/j.jacc.2018.10.077
2. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, Bergamasco L, Boffano C, Valentini MC, Cesarani F, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol.* 2013;62:1990–1997. doi: 10.1016/j.jacc.2013.05.074
3. Chen LY, Agarwal SK, Norby FL, Gottesman RF, Loehr LR, Soliman EZ, Mosley TH, Folsom AR, Coresh J, Alonso A. Persistent but not paroxysmal atrial fibrillation is independently associated with lower cognitive function: ARIC study. *J Am Coll Cardiol.* 2016;67:1379–1380. doi: 10.1016/j.jacc.2015.11.064
4. Karadag B, Ozyigit T, Ozben B, Kayaoglu S, Altuntas Y. Relationship between left atrial volume index and cognitive decline in elderly patients with sinus rhythm. *J Clin Neurosci.* 2013;20:1074–1078. doi: 10.1016/j.jocn.2012.10.021
5. Rivard L, Khairy P, Talajic M, Tardif JC, Nattel S, Bherer L, Black S, Healey J, Lanthier S, Andrade J, et al. Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation (BRAIN-AF): methods and design. *Can J Cardiol.* 2019;35:1069–1077. doi: 10.1016/j.cjca.2019.04.022

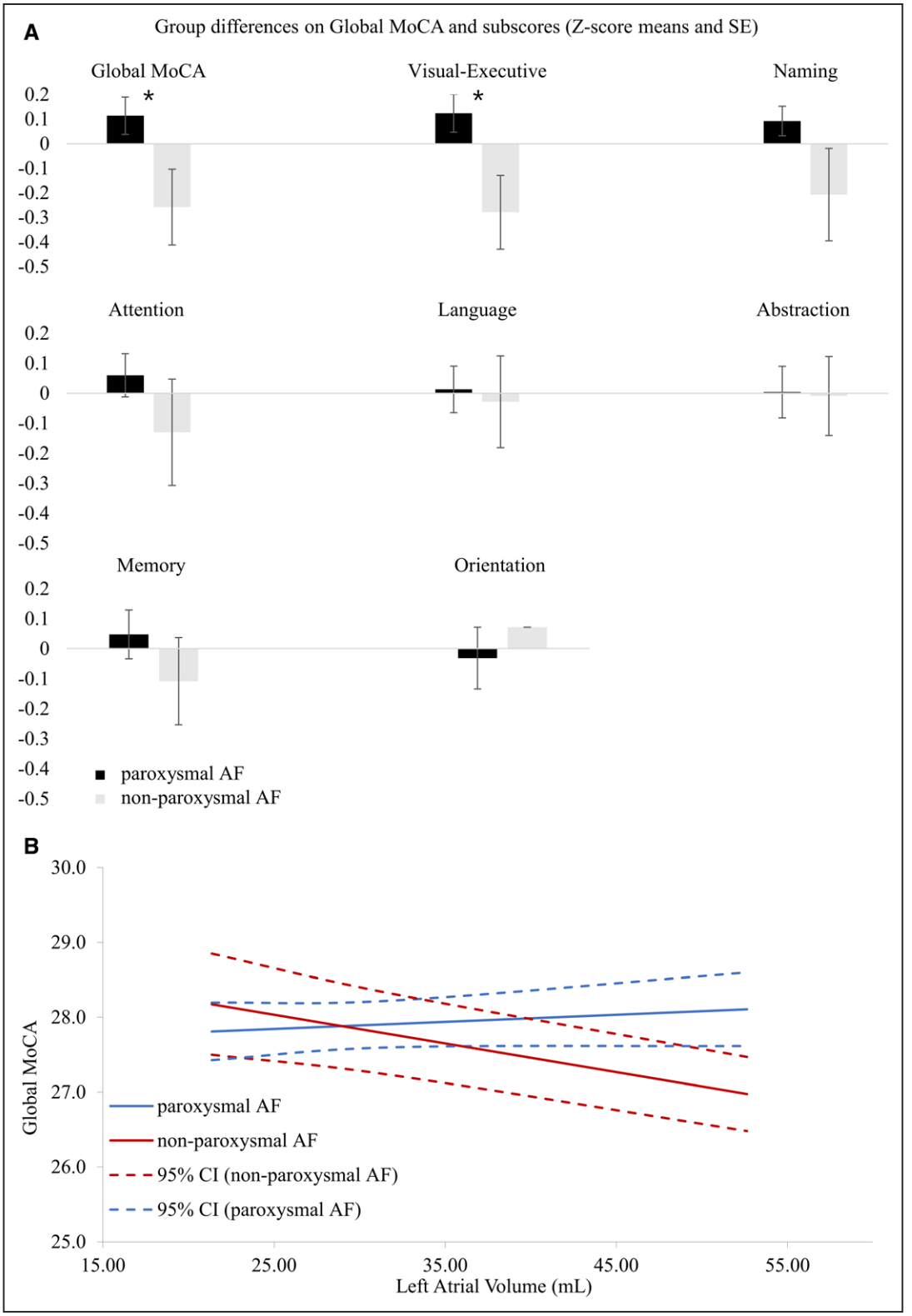

Figure. Differences between paroxysmal vs. non-paroxysmal atrial fibrillation (AF) and conditional effects of left atrial volume on Montreal Cognitive Assessment (MoCA) scores

A, Bar graphs of group differences between paroxysmal vs nonparoxysmal AF on MoCA scores. Shown are bar graphs for mean *Z* score transformed global MoCA scores and subscores in patients with paroxysmal (black) and nonparoxysmal (gray) AF. The error bars indicate standard errors. Significant differences (*P<0.05) between groups were observed for the global MoCA score and visuospatial-executive subscore. **B**, Conditional effects of left atrial volume on global MoCA scores.