Relationships of Overt and Silent Brain Lesions with Cognitive Function in Patients with Atrial Fibrillation

David Conen[a,b,c], MD, MPH; Nicolas Rodondi[d,e], MD, MAS; Andreas Müller[f], MD; Juerg H. Beer[g], MD; Peter Ammann[h], MD; Giorgio Moschovitis[i], MD; Angelo Auricchio[j], MD, PhD; Daniel Hayoz[k], MD; Richard Kobza[l], MD; Dipen Shah[m], MD; Jan Novak[n], MD; Jürg Schläpfer[o], MD; Marcello Di Valentino[p], MD; Stefanie Aeschbacher[a,b], PhD; Steffen Blum[a,b], MD; Pascal Meyre[a,b], MD; Christian Sticherling[a,b], MD; Leo H. Bonati[q], MD; Georg Ehret[m], MD; Elisavet Moutzouri[d,e], MD; Urs Fischer[r], MD, MSc; Andreas U. Monsch[s], PhD; Christoph Stippich[t], MD; Jens Wuerfel[u], MD; Tim Sinnecker[q,u], MD; Michael Coslovsky[b], PhD; Matthias Schwenkglenks[v], MPH; Michael Kühne[a,b], MD*; Stefan Osswald[a,b], MD*; for the Swiss-AF study investigators[†]

* Contributed equally, shared last authors

† A list of all Swiss-AF investigators is provided in the Supplemental material

[a] Cardiology Division, Department of Medicine, University Hospital Basel, Switzerland
[b] Cardiovascular Research Institute Basel, Switzerland
[c] Population Health Research Institute, McMaster University, Hamilton, Canada
[d] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
[e] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[f] Department of Cardiology, Triemli Hospital Zurich, Switzerland
[g] Departement of Medicine, Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zurich, Switzerland
[h] Department of Cardiology, Kantonsspital St. Gallen, Switzerland
[i] Department of Cardiology, Ospedale Regionale di Lugano, Switzerland
[j] Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland
[k] Department of Internal Medicine, HFR-Hôpital Cantonal Fribourg, Switzerland
[l] Department of Cardiology, Luzerner Kantonsspital, Switzerland
[m] Cardiology, Department of Medical Specialties, University Hospital Geneva, Switzerland
[n] Department of Cardiology, Bürgerspital Solothurn, Switzerland
[o] Department of Cardiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[p] Department of Cardiology, Ospedale San Giovanni, Bellinzona, Switzerland
[q] Department of Neurology and Stroke Center, University Hospital Basel, University of Basel, Switzerland
[r] Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[s] Memory Clinic, Universitäre Altersmedizin, Felix Platter Spital Basel, University of Basel, Switzerland
[t] Department of Neuroradiology, University Hospital Zurich, Switzerland
[u] Medical Image Analysis Center (MIAC AG) and Department of Biomedical Engineering, University Basel, Switzerland
[v] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland

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Twitter handle: @CRIBasel

Suggested tweet: Patients with #AFib have a high burden of clinically silent cerebral infarcts, and they are associated with worse cognitive function. Read more in #JACC.

Address for correspondence:
David Conen MD MPH
Population Health Research Institute
Barton Street East
Hamilton Ontario, Canada
Phone: +1 905 522-1155
Fax: +1 905 521 6068
Email: Conend@mcmaster.ca

Abstract

Background: Patients with atrial fibrillation (AF) have an increased risk of cognitive decline, potentially due to clinically unrecognized vascular brain lesions.

Objectives: To assess the relationships between cognitive function and vascular brain lesions in AF patients.

Methods: Patients with known AF were enrolled in a multicenter study in Switzerland. Brain magnetic resonance imaging (MRI) and cognitive testing using the Montreal Cognitive Assessment (MoCA) were performed in all participants. Large non-cortical or cortical infarcts (LNCCIs), small non-cortical infarcts (SNCIs), microbleeds and white matter lesions (WML) were quantified by a central core laboratory. Clinically silent infarcts were defined as infarcts on brain MRI in patients without a clinical history of stroke or transient ischemic attack (TIA).

Results: We included 1737 patients with a mean age of 73±8 years (28% women, 90% on oral anticoagulation). On MRI, LNCCIs were found in 387 patients (22%), SNCIs in 368 (21%), microbleeds in 372 (22%) and WMLs in 1715 (99%). Clinically silent infarcts among the 1390 patients without a history of stroke/TIA were found in 201 (LNCCI; 15%) and 245 (SNCI; 18%), respectively. The MoCA score was 24.7±3.3 and 25.8±2.9 in those with and without LNCCIs on brain MRI ($p<0.001$). The difference in MoCA score remained similar when only clinically silent LNCCIs were considered (24.9±3.1 versus 25.8±2.9, $p<0.001$). In a multivariable regression model including all vascular brain lesion parameters, LNCCI volume was the strongest predictor for a reduced MoCA ($\beta=-0.26$, 95% confidence interval, -0.40 to -0.13, $p<0.001$).

Conclusions: AF patients have a high burden of LNCCIs and other brain lesions on systematic brain MRI screening, the majority being clinically silent. LNCCIs were associated with worse

cognitive function, even among patients with clinically silent infarcts. Our findings raise the question of MRI screening in AF patients.

Condensed abstract:

Patients with atrial fibrillation (AF) have an increased risk of cognitive dysfunction, potentially due to clinically unrecognized vascular brain lesions. We performed systematic brain MRIs and cognitive testing in 1737 patients. The overall prevalence of cerebral infarcts was 22%. The prevalence of silent infarcts in patients without a history of stroke or transient ischemic attack was 15%. Cognitive function was significantly worse in those with cerebral infarcts, and this difference was similar in those with overt or silent brain infarcts. Thus, AF patients have a high burden of silent cerebral infarcts, and these infarcts were associated with worse cognitive function.

Keywords: Atrial fibrillation, Cognitive dysfunction, Silent cerebral infarcts, Microbleeds, White matter lesions

Abbreviations

AF	Atrial fibrillation
MRI	Magnetic resonance imaging
SNCI	Small non-cortical infarct
LNCCI	Large non-cortical infarcts or cortical infarct
MoCA	Montreal Cognitive Assessment
TIA	Transient ischemic attack

Introduction

The prevalence of atrial fibrillation (AF) in the general population is increasing rapidly (1). Patients with AF are at high risk of adverse events. While the relationships of AF with death, stroke and congestive heart failure have been known for many years (2,3), more recent evidence suggests that patients with AF also face an increased risk of cognitive dysfunction and dementia (4,5). This growing awareness is reflected by a recent publication of an international expert consensus paper on this topic (6).

Meta-analyses suggest that part of the association between AF and dementia is explained by the higher stroke risk among AF patients, but the risk of dementia was also increased in AF patients without a clinical history of stroke (5). Clinically unrecognized (silent) cerebral infarcts, microbleeds or other brain lesions may explain this association, but systematic investigations in patients with AF are currently lacking. Microbleeds are of particular interest, as patients with AF usually need lifelong oral anticoagulation for stroke prevention (7). Although prior studies did not show a consistent trend of more microbleeds among patients using oral anticoagulation, its use among patients with a significant burden of microbleeds remains controversial (8-10).

The aim of the current study was to assess the relationships of clinically known and unknown (silent) vascular brain lesions detected on brain magnetic resonance imaging (MRI) with cognitive function in a large sample of patients with AF. We focused on large infarcts and infarcts involving the brain cortex, which may origin from embolic mechanisms and as such represent AF-related sequelae. We also considered imaging markers of cerebral small vessel pathology, which share vascular risk factors with AF, including white matter disease, small non-cortical infarcts and microbleeds (11). Both cerebral small vessel disease and embolic stroke are key mechanisms underlying the development of vascular dementia (12).

Methods

Study design and participants

The Swiss Atrial Fibrillation (Swiss-AF) study is an ongoing prospective cohort study that enrolled 2415 patients between 2014 and 2017 across 14 centers in Switzerland. The detailed methodology has been described previously (13). Patients were eligible for Swiss-AF if they had a history of documented AF and if they were 65 years or older. In addition, we aimed to enroll 10-15% of patients aged between 45 and 65 years to assess the effects of AF on individuals in the active workforce. We excluded patients with secondary forms of AF and patients who were unable to provide informed consent. Patients with an acute illness within the last 4 weeks could only be enrolled once the acute episode had resolved.

Of the 2415 patients enrolled in Swiss-AF, 667 did not have a brain MRI at baseline. The main reason for a missing brain MRI was the presence of a cardiac device (n=461; 69%). Other reasons included further contraindications to perform an MRI or claustrophobia of the patient. An additional 11 patients did not undergo cognitive testing, leaving 1737 participants for the present analysis. The local ethics committees approved the study protocol and written informed consent was obtained from all participants.

Clinical measures

Information on personal characteristics, risk factors, co-morbidities, antithrombotic treatment and other factors was obtained through standardized case report forms. Weight and height were directly measured and body mass index calculated as weight in kilograms divided by height in meters squared. At baseline, three consecutive blood pressure measurements were obtained, and the mean of the last two were used in all analyses. We classified AF into paroxysmal, persistent and permanent AF according to recommended definitions (7).

Brain magnetic resonance imaging

Brain MRI was acquired on a 1.5 or 3.0 Tesla scanner. The standardized protocol included a 3D T1 weighted (T1w) Magnetization Prepared Rapid Gradient Echo (MPRAGE; spatial resolution 1.0x1.0x1.0 mm^3), a 2D axial Fluid Attenuated Inversion Recovery (FLAIR; spatial resolution 1.0x1.0x3.0 mm^3), and 2D axial Diffusion weighted imaging (DWI; spatial resolution 1.0x1.0x3.0 mm^3) sequence with whole brain coverage and without interpolation. In addition, either a 2D axial Susceptibility weighted imaging (SWI; spatial resolution 1.0x1.0x3.0 mm^3) or a 2D axial T2* weighted (spatial resolution of 1.0x1.0x3.0 mm^3) sequence was applied.

All brain MRI's were analyzed centrally in a specialized imaging core laboratory (Medical Image Analysis Centre, Basel, Switzerland). MRI's were analyzed by blinded expert raters unaware of personal characteristics or cognitive function. They marked and segmented lesions in a standardized fashion using an in-house procedure approved for international clinical studies. Board certified neuro-radiologists confirmed all ratings. Small non-cortical infarcts (SNCI) were defined as hyperintense lesions on FLAIR ≤20 mm in diameter on axial sections and not involving the cortex, consistent with ischemic infarction in the territory of a perforating arteriole (located in the white matter, internal or external capsule, deep brain nuclei, thalamus or brainstem) (11). We did not further differentiate between small non-cortical infarcts and lacunes based on the presence or absence of a central fluid-filled cavity. Large non-cortical infarcts were non-cortical infarcts with a diameter >20 mm. Cortical infarcts were defined as hyperintense lesions on FLAIR involving the cortex irrespective of their size and whether or not they also involved subcortical areas. For the present analysis we differentiated between (A) SNCIs and (B) large non-cortical infarcts or cortical infarcts (LNCCIs). Hyperintense white matter lesions were graded using the Fazekas scale, and at least moderate disease was defined as a score ≥2 in either the periventricular or the deep white matter region (14). Perivascular spaces were identified,

differentiated by their tubular morphology and subsequently excluded. FLAIR hyperintense lesions not meeting the criteria mentioned above were identified as white matter lesions. Microbleeds were identified and counted as nodular, strongly hypointense lesions on either T2*w or SWI. T2w volumes of non-cortical and cortical infarcts as well as white matter lesions were segmented and quantified semi-automatically using Amira (Mercury Computer Systems Inc., Chelmsford, USA). Lesions with a central FLAIR-hypointense core were segmented in total without differentiating between hyper- and hypointense lesion areas.

Cognitive testing

All study personnel was centrally trained to perform a standardized neurocognitive assessment. The Montreal Cognitive Assessment (MoCA) evaluates visuospatial and executive functions, confrontation naming, memory, attention, language and abstraction (15). Patients can obtain a maximum of 30 points, with higher scores indicating better cognitive function. One point was added to the total test score if the patient had 12 years or less of formal education.

Statistical analysis

Baseline characteristics were stratified by the presence or absence of a clinical history of stroke or transient ischemic attack (TIA) and presented as mean ± standard deviation for continuous variables or as counts (percentages) for nominal variables. We compared differences across groups with Wilcoxon's rank-sum tests or Chi-square tests, as appropriate. Silent cerebral infarcts were defined as cerebral infarcts (LNCCIs or SNCIs) on brain MRI in patients without a history of stroke or TIA. Lesion volumes were indicated as median (interquartile range) given their skewed distribution.

As history of stroke/TIA is a key predictor of lower cognitive function, we repeated all main analyses in patients without a history of stroke/TIA. To assess the associations of vascular

brain lesion parameters with MoCA score values and to adjust for potential confounders, we constructed linear mixed effects regression models in which study center was included as a random intercept to account for potential differences across study centers. We first fitted univariable models using log-transformed and centered vascular brain lesion parameters (or counts for microbleeds) as MoCA score predictors. Separate models were constructed for each brain lesion parameter. Univariable models were adjusted for a pre-defined set of covariates, including age, sex, body mass index, education level, smoking status, history of hypertension, history of diabetes, AF type and use of oral anticoagulation. Finally, we constructed a combined multivariable model including all structural brain lesion parameters in a single model. We performed two sensitivity analyses, one that additionally adjusted the combined model for a history of cardioversion or left atrial ablation, and one adjusting for time since first AF diagnosis. Finally, to examine the independence of SNCI and LNCCI, we performed two additional analyses in which we excluded patients who had both SNCIs and LNCIs on brain MRI.

MoCA scores were compared across different strata and subgroups using likelihood ratio tests between mixed effects models with and without the stratum as single predictor. In all models, we included dummy indicators representing the presence or absence of each vascular brain lesion type, in addition to the actual volume or count measurement. Visual model diagnostics were performed, and no major violations of model assumptions of homogeneity and normally distributed residuals were detected. The microbleed count was truncated at 20, and three outliers were given a count of 20 to minimize their influence on the associations. All analyses were performed on an available data basis and conducted using R version 3.5.1 (R Core Team, 2018); mixed effects models were constructed using the nlme package (16).

Results

Baseline characteristics are shown in **Table 1**. Mean age was 73±8 years, 28% of participants were women, 90% were anticoagulated at the time of study enrollment (54% non-vitamin K antagonists, 36% vitamin K antagonists), and 18% were on antiplatelet therapy. Patients with a history of stroke/TIA were older, had a higher prevalence of hypertension and diabetes and they were more often on oral anticoagulation.

Prevalence and size of vascular brain lesions detected on brain MRI are shown in **Table 2**. At least one LNCCI was detected in 22% of participants, with a median volume of 1623 mm^3. SNCIs were observed in 21% (median volume 63 mm^3). The overlap between LNCCI and SNCI was small, 80% of patients with SNCIs had no LNCCI, and 75% of patients with LNCCI had no SNCI, such that 37% of the study population had either LNCCIs or SNCIs. Microbleeds in 22% (median count 1) and white matter lesions in 99% (volume 3918 mm^3). The extent of white matter lesions was at least moderate in 54% of participants. When patients with a history of stroke/TIA were excluded, 201 of 1390 (15%) participants had evidence of a silent LNCCI (volume 525 mm^3), and 245 (18%) had evidence of a silent SNCI (volume 57 mm^3) (**Table 2**).

Comparisons of MoCA scores between patients with and without a specific vascular brain lesion are shown in **Figure 1** and in Table S1. The least square mean MoCA was 24.9 (95% confidence interval [CI], 24.3 to 25.5) and 25.9 (95% CI, 25.3 to 26.5) among patients with and without an LNCCI on brain MRI ($p<0.001$). The MoCA was 25.0 (95% CI, 24.4 to 25.6) versus 25.9 (95% CI, 25.3 to 26.4) in patients with and without an SNCI ($p<0.001$), and 25.4 (95% CI, 24.7 to 26.0) versus 25.8 (95% CI, 25.2 to 26.4) in patients with and without microbleeds ($p=0.07$). When patients with a clinical history of stroke or TIA were excluded, the MoCA score difference between patients with or without silent LNCCI (25.1 [95% CI, 24.4 to

25.7] versus 26.0 [25.4 to 26.5], p<0.001), with or without silent SNCI (25.1 [95% CI, 24.5 to 25.7] versus 26.0 [95% CI, 25.4 to 26.5], p<0.001), and with or without microbleeds (25.5 [95% CI, 24.9 to 26.2] versus 25.9 [95% CI, 25.3 to 26.5], p=0.15) remained of similar magnitude.

In univariable regression models, LNCCI volume on brain MRI was significantly related to MoCA scores, with larger infarct volumes predicting lower MoCA scores (β=-0.28, [95% CI, -0.42 to -0.13], p<0.001) (**Table 3**). A similar finding was observed with white matter lesion volume (β=-0.38, [95% CI, -0.49 to -0.28], p<0.001), and presence of at least moderate white matter lesions (β=-0.99 [95% CI, -1.27 to -0.72], p<0.001). There was no significant association with SNCI volume or microbleed count. In multivariable models, LNCCI count and volume as well as presence of at least moderate white matter lesions (β=-0.40 [95% CI, -0.68 to -0.11], p=0.007) remained strongly associated with lower MoCA scores (**Table 3**). Coefficients of all covariates included in the multivariable models are presented in Table S2. In a combined multivariable model including all vascular brain lesion parameters, LNCCI count and volume were the strongest predictors of the MoCA score (**Table 3**, and Table S3). When we excluded patients with a history of stroke/TIA, presence of LNCCI (β=-0.53, [95% Cl, -0.94 to -0.12], p=0.012), LNCCI volume (β=-0.18, [95% Cl, -0.39 to 0.02], p=0.072) and presence of at least moderate white matter lesions (β=-0.46, [95% CI, -0.77 to -0.16], p=0.003) remained associated with the MoCA score (**Table 3**, and Tables S4 and S5). Sensitivity analyses with models including covariates for a baseline history of cardioversion and left atrial ablation, or time since first AF diagnosis provided very similar results (Tables S6 to S9). Excluding patients with both SNCIs and LNCCIs on brain MRI also provided similar results (Tables S10 and S11).

Stratified MoCA score results are shown in **Figure 2**. The overall mean MoCA score was 25.5±3.1. It was 24.7±3.7 and 25.6±2.9 among patients with and without a clinical history of

stroke ($p<0.001$). MoCA scores also differed across strata of age, AF type, hypertension, diabetes, oral anticoagulation, and CHA_2DS_2-VASc score, but not sex. Patients with permanent AF had lower MoCA scores than patients with paroxysmal or persistent AF, a finding that persisted in multivariable models (Table S2). The same subgroups were assessed for differences in brain lesion parameters (Table S12). Larger LNCCI volumes were observed in patients with permanent AF, higher CHA_2DS_2-VASc scores, and those with a history of stroke, hypertension, or diabetes. Oral anticoagulation with either non-vitamin K antagonists or vitamin K antagonists was not associated with a higher microbleed count compared to no anticoagulation. Higher CHA_2DS_2-VASc scores were associated with significantly higher infarct and white matter lesion volumes, but lower microbleed counts (Table S12).

Discussion

Several important findings emerged from this comprehensive analysis of vascular brain lesions and cognitive function in AF patients. First, participants had a substantial burden of vascular brain lesions detected on systematic brain MR imaging: 22% and 21% had evidence of a previous LNCCI and SNCI, respectively. Second, among patients without a history of stroke/TIA, 15% and 18% still had evidence of a previous clinically silent LNCCI and SNCI, respectively. Thus, most of the observed lesions were clinically silent. Third, these findings were observed in a population with a high prevalence of oral anticoagulation at the time of brain MRI. Fourth, patients with an LNCCI had a lower cognitive function than those without LNCCI. The magnitude of this difference was similar for patients with silent infarcts, and similar to the effect of a previous stroke. Fifth, SNCI volume, white matter lesion volume and microbleed count were not independently associated with cognitive function in a combined multivariable model including all lesion types. Finally, anticoagulation was not related to a higher microbleed count.

Comparing the prevalence of brain MRI lesions across studies is difficult, because of differences in definitions and technologies. Nevertheless, the infarct prevalence of 37% in our study seems to be higher than in the general population, where the infarct prevalence was 31%. In addition, the great majority of these infarcts were small (17). Another study found that the presence of clinically silent infarcts on brain MRI approximately doubled the risk of dementia and led to a steeper decline in cognitive function (18).

In order to understand the relationships between AF and cognitive impairment, we specifically assessed imaging markers of vascular pathologies known to be associated with vascular dementia, which is the most common cause of dementia following Alzheimer's disease. Vascular dementia is a heterogeneous disorder caused by a variety of mechanisms (12), the most

important of which are infarction of the brain cortex (multi-infarct dementia) and cerebral small vessel disease. When we corrected the impact of the different lesions types on cognition for each other, we found that only LNCCI was significantly associated with a significantly lower MoCA score. The magnitude of the difference was similar when only silent infarcts in patients without a history of stroke/TIA were considered. In contrast, none of the imaging markers of small vessel disease, including white matter lesions, SNCI and microbleeds, were associated with cognitive imparirment in the combined multivariable model. Therefore, silent LNCCIs but not small vessel disease may explain the association between AF and dementia in the absence of clinically overt strokes (**Central illustration**) (5).

While a 1-point MoCA score difference may seem small on an absolute scale, it is similar to a 10-year age difference or the presence of hypertension or diabetes (**Figure 2**). We therefore expect such a difference to be relevant from a clinical and societal perspective. As the majority of brain infarcts were clinically silent and observed in patients without a history of stroke/TIA, our data raise the issue of brain MRI screening in patients with AF. Future studies should develop risk scores for AF patients that identify subgroups of AF patients who may benefit from brain imaging to better guide antithrombotic treatment in a cost-efficient manner. It is intriguing that permanent AF was associated with a lower MoCA score independent of covariates and brain lesion volumes (Table S3), suggesting that the arrhythmia itself or associated treatments may have a direct effect on cognition. This supports findings from a prior study showing worse cognition in AF patients without evidence of brain infarcts on MRI (19).

Oral anticoagulation effectively prevents stroke in patients with AF (20). Although our cross-sectional analysis cannot address the question of whether the cerebral infarcts occurred before or after initiation of oral anticoagulation, it nevertheless raises the issue that

anticoagulation might not be sufficient to prevent a significant number of silent infarcts, especially those caused by mechanisms other than cardiac embolism. A combination of aspirin and low-dose rivaroxaban was significantly better than aspirin alone for stroke prevention among patients with stable vascular disease but without AF (21). Whether such a treatment strategy may also benefit patients with AF is currently unknown. Finally, both history of hypertension and diabetes were significantly associated with lower MoCA scores in multivariable analyses, suggesting that the high prevalence of cardiovascular risk factors in patients with AF may also contribute to the occurrence of overt and silent cerebral lesions.

Although its detailed histopathological correlates still need to be investigated, microbleeds are considered to be small bleedings in the brain (22). Patients with microbleeds have an increased risk of stroke and intracranial hemorrhage (23,24). In our study with a high prevalence of anticoagulation use, 22% of participants had microbleeds. This prevalence is similar to that in elderly individuals from the general population (25), or patients with ischemic stroke (26). Anticoagulation use was not associated with a higher microbleed count and microbleed count was not associated with cognitive function. This is in agreement with data showing that aspirin and apixaban had a similar impact on the incidence of microbleeds (27). Currently available data therefore suggest that anticoagulation is safe in most patients with microbleeds, although it remains controversial whether there is a subgroup of patients with a high microbleed burden who should not be anticoagulated despite their high stroke risk (28,29).

Strengths of this study include the large sample size of very well-characterized AF patients, including the availability of brain MRI and cognitive testing. A potential limitation includes the cross-sectional design of this analysis, precluding the assessment of causality or directionality of effect. Participants in our study were mostly white and all were enrolled in the

compulsory Swiss health insurance system. Whether our data are applicable to other population groups or settings remains to be determined. Finally, our study included only AF patients, and it is unclear how the prevalence of vascular brain lesions compares with that of other sample populations.

In conclusion, in this large study of well treated AF patients we found a high burden of vascular brain lesions on systematic brain MRI screening. Most of these lesions were previously unrecognized. Our analyses show that the presence of overt or silent LNCCIs on MRI have a similar impact on cognitive function as overt strokes, suggesting that they may explain at least part of the increased risk of cognitive dysfunction in this patient population. On the other hand, microbleeds were not significantly associated with cognitive function. Finally, the value of routine MRI scanning and cognitive function testing for better risk stratification of AF patients should be assessed in further studies.

Clinical perspectives

Competency in medical knowledge 1: our study shows that most brain infarcts observed in patient with AF are clinically silent. A large number of silent and overt lesions were observed despite the fact that 90% of the patients were taking oral anticoagulation at the time of the brain MRI.

Translational outlook 1: Future studies should evaluate whether and which AF patients may benefit from brain MRI screening. They should also address the question about the optimal antithrombotic treatment to prevent silent infarcts in patients with AF.

References

1. Krijthe BP, Kunst A, Benjamin EJ et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J 2013;34:2746-51.
2. Conen D, Chae CU, Glynn RJ et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA 2011;305:2080-7.
3. Chatterjee NA, Chae CU, Kim E et al. Modifiable Risk Factors for Incident Heart Failure in Atrial Fibrillation. JACC Heart Fail 2017;5:552-560.
4. Thacker EL, McKnight B, Psaty BM et al. Atrial fibrillation and cognitive decline: a longitudinal cohort study. Neurology 2013;81:119-25.
5. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med 2013;158:338-46.
6. Dagres N, Chao TF, Fenelon G et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice? Heart Rhythm 2018: Advance online publication.
7. Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-2429.
8. Horstmann S, Mohlenbruch M, Wegele C et al. Prevalence of atrial fibrillation and association of previous antithrombotic treatment in patients with cerebral microbleeds. Eur J Neurol 2015;22:1355-62.
9. Saito T, Kawamura Y, Sato N et al. Non-vitamin k antagonist oral anticoagulants do not increase cerebral microbleeds. J Stroke Cerebrovasc Dis 2015;24:1373-7.
10. Akoudad S, Darweesh SK, Leening MJ et al. Use of coumarin anticoagulants and cerebral microbleeds in the general population. Stroke 2014;45:3436-9.
11. Wardlaw JM, Smith EE, Biessels GJ et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet neurology 2013;12:822-38.
12. O'Brien JT, Thomas A. Vascular dementia. Lancet 2015;386:1698-706.
13. Conen D, Rodondi N, Mueller A et al. Design of the Swiss Atrial Fibrillation Cohort Study (Swiss-AF): structural brain damage and cognitive decline among patients with atrial fibrillation. Swiss Med Wkly 2017;147:w14467.
14. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149:351-6.
15. Nasreddine ZS, Phillips NA, Bedirian V et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005;53:695-9.
16. Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team. nlme: Linear and Nonlinear Mixed Effects Models. R package version 31-137 2018: https://CRAN.R-project.org/package=nlme.
17. Price TR, Manolio TA, Kronmal RA et al. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Stroke 1997;28:1158-64.

18. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215-22.
19. Knecht S, Oelschlager C, Duning T et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J 2008;29:2125-32.
20. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
21. Eikelboom JW, Connolly SJ, Bosch J et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;377:1319-1330.
22. van Veluw SJ, Charidimou A, van der Kouwe AJ et al. Microbleed and microinfarct detection in amyloid angiopathy: a high-resolution MRI-histopathology study. Brain 2016;139:3151-3162.
23. Charidimou A, Karayiannis C, Song TJ et al. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology 2017;89:2317-2326.
24. Wilson D, Ambler G, Shakeshaft C et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. Lancet neurology 2018;17:539-547.
25. Poels MM, Vernooij MW, Ikram MA et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. Stroke 2010;41:S103-6.
26. Charidimou A, Shakeshaft C, Werring DJ. Cerebral microbleeds on magnetic resonance imaging and anticoagulant-associated intracerebral hemorrhage risk. Front Neurol 2012;3:133.
27. O'Donnell MJ, Eikelboom JW, Yusuf S et al. Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. Am Heart J 2016;178:145-50.
28. Diener HC, Selim MH, Molina CA, Greenberg SM. Embolic Stroke, Atrial Fibrillation, and Microbleeds: Is There a Role for Anticoagulation? Stroke 2016;47:904-7.
29. Charidimou A, Shoamanesh A, Al-Shahi Salman R et al. Cerebral amyloid angiopathy, cerebral microbleeds and implications for anticoagulation decisions: The need for a balanced approach. Int J Stroke 2018;13:117-120.

Figure Legends

Figure 1. Least square mean MoCA score according to the presence or absence of a specific vascular brain abnormality. A) All patients; B) Patients without a history of stroke or transient ischemic attack. Least square means were obtained from linear mixed effects models that included covariates for the presence versus absence of a specific damage and damage volume (count for microbleeds), and study center as random intercept. MoCA: Montreal Cognitive Assessment; SNCI: small non-cortical infarcts; LNCCI: large non-cortical or cortical infarcts; Faz: Fazekas scale.

Figure 2. MoCA score across predefined strata.

Data are mean ± standard deviation. P values represent overall differences across strata and were obtained from linear mixed effects models with each strata variable as predictor and study center as random intercept. MoCA: Montreal Cognitive Assessment; NOAC: non-vitamin K antagonist; VKA: vitamin K antagonist.

Central Illustration. Potential relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation.

Abbreviations: TIA=transient ischemic attack; SNCI=Small Non-cortical Infarcts; LNCCI=Large Non-cortical or Cortical Infarcts; WML=White Matter Lesion.

Table 1 Baseline characteristics

Characteristic	All patients (N=1737)	No history of stroke/TIA (N=1390)	History of stroke/TIA (N=347)	p-value*
Age, y	73±8	72±9	75±7	<0.001
Female sex, No. (%)	477 (28)	369 (27)	108 (31)	0.10
Body-mass index, kg/m^2	27.7±4.8	27.8±4.8	27.3±4.7	0.10
Blood pressure, mmHg	135±19 / 79±12	135±18 / 79±12	135±19 / 78±12	0.69 / 0.12
History of hypertension, No. (%)	1197 (69)	939 (68)	258 (74)	0.017
History of diabetes mellitus, No. (%)	265 (15)	197 (14)	68 (20)	0.015
Smoking status, No. (%)				0.73
Current	168 (10)	138 (10)	30 (9)	
Past	871 (50)	697 (50)	174 (50)	
Never	695 (40)	552 (40)	143 (41)	
Education level†, No. (%)				0.43
Basic	203 (12)	157 (11)	46 (13)	
Middle	850 (49)	677 (49)	173 (50)	
Advanced	684 (39)	556 (40)	128 (37)	
Atrial fibrillation type, No. (%)				0.012
Paroxysmal	797 (46)	623 (45)	174 (50)	
Persistent	524 (30)	442 (32)	82 (24)	
Permanent	416 (24)	325 (23)	91 (26)	
History of coronary artery disease, No. (%)	462 (27)	363 (26)	99 (29)	0.40
History of clinical stroke, No. (%)	230 (13)	0 (0)	230 (66)	-

History of TIA, No. (%)	159 (9)	0 (0)	159 (46)	-
History of heart failure, No. (%)	376 (22)	295 (21)	81 (23)	0.44
History of major bleeding, No. (%)	97 (6)	72 (5)	25 (7)	0.18
CHA_2DS_2-VASc score	3.3±1.7	2.8±1.4	5.3±1.3	<0.001
Oral anticoagulation, No. (%)	1560 (90)	1236 (89)	324 (93)	0.019
Non-vitamin K antagonists	929 (54)	741 (53)	188 (54)	0.82
Vitamin K antagonists	631 (36)	495 (36)	136 (39)	0.24
Antiplatelet therapy, No. (%)	309 (18)	237 (17)	72 (21)	0.12

Data are means ± SD or counts (percentages). TIA: transient ischemic attack.

* P value compares patient with and without a history of stroke/TIA. P values were obtained from Wilcoxon's rank-sum tests for continuous variables and chi-square tests for categorical variables.

† Basic education: ≤6 years (less than compulsory education curriculum); middle education: 6 to ≤12 years (high school or similar); advanced education: ≥12 years (college or university degree).

Table 2 Prevalence of vascular brain lesions detected on brain magnetic resonance imaging

Characteristic	Prevalence	Volume, mm^3	Counts
All patients (N=1737)			
Small non-cortical infarcts	368 (21)	63 [30-163]	1 [1-3]
Large non-cortical or cortical infarcts	387 (22)	1623 [255-7314]	1 [1-2]
Microbleeds	372 (22)	-	1 [1-2]
White matter lesions	1715 (99)	3918 [1439-9783]	23 [11-41]
Fazekas scale ≥2	928 (54)		
Patients without a history of stroke or TIA (N=1390)			
Small non-cortical infarcts	245 (18)	57 [30-141]	2 [1-3]
Large non-cortical or cortical infarcts	201 (15)	525 [162-3396]	1 [1-2]
Microbleeds	272 (20)	-	1 [1-2]
White matter lesions	1372 (99)	3512 [1323-8669]	21 [10-40]
Fazekas scale ≥2	694 (50)		

Data are counts (percentages) or median [interquartile range]. TIA: transient ischemic attack.

Table 3 Linear mixed effect models assessing the relationships of MoCA score with vascular brain lesion parameters

	Presence of damage type			Volume/count		
Predictor of interest	**β coefficient**	**95% CI**	**p value**	**β coefficient**	**95% CI**	**p-value**
All patients						
Small non-cortical infarcts						
Univariable	-0.87	(-1.22, -0.53)	<0.001	-0.15	(-0.41, 0.10)	0.24
Multivariable	-0.43	(-0.76, -0.10)	0.010	-0.11	(-0.35, 0.13)	0.38
Combined*	-0.32	(-0.67, 0.03)	0.072	-0.15	(-0.39, 0.10)	0.24
Large non-cortical or cortical infarcts						
Univariable	-1.02	(-1.35, -0.69)	<0.001	-0.28	(-0.42, -0.13)	<0.001
Multivariable	-0.66	(-0.97, -0.34)	<0.001	-0.26	(-0.39, -0.12)	<0.001
Combined*	-0.64	(-0.97, -0.31)	<0.001	-0.26	(-0.40, -0.13)	<0.001
Microbleeds						
Univariable	-0.39	(-0.81, 0.03)	0.07	0.03	(-0.09, 0.14)	0.66
Multivariable	-0.03	(-0.42, 0.36)	0.88	0.04	(-0.07, 0.14)	0.52
Combined*	0.02	(-0.37, 0.41)	0.93	0.08	(-0.03, 0.19)	0.16
White matter lesions						
Univariable	-0.59	(-1.99, 0.81)	0.41	-0.38	(-0.49, -0.28)	<0.001
Multivariable	0.14	(-1.20, 1.47)	0.84	-0.12	(-0.23, -0.01)	0.028
Combined*	0.43	(-0.92, 1.78)	0.53	-0.06	(-0.18, 0.05)	0.29
Fazekas scale ≥2						
Univariable	-0.99	(-1.27, -0.72)	<0.001			

Multivariable	-0.40	(-0.68, -0.11)	0.007			
Patients without a history of stroke or TIA						
Small non-cortical infarcts						
Univariable	-0.85	(-1.24, -0.46)	<0.001	-0.16	(-0.48, 0.16)	0.33
Multivariable	-0.44	(-0.82, -0.07)	0.021	-0.09	(-0.39, 0.21)	0.54
Combined†	-0.35	(-0.76, 0.05)	0.09	-0.05	(-0.36, 0.25)	0.74
Large non-cortical or cortical infarcts						
Univariable	-0.90	(-1.32, -0.48)	<0.001	-0.21	(-0.42, -0.00)	0.06
Multivariable	-0.58	(-0.98, -0.18)	0.004	-0.19	(-0.39, 0.01)	0.06
Combined†	-0.53	(-0.94, -0.12)	0.012	-0.18	(-0.39, -0.02)	0.07
Microbleeds						
Univariable	-0.35	(-0.84, 0.13)	0.15	-0.01	(-0.17, 0.15)	0.93
Multivariable	0.02	(-0.43, 0.48)	0.92	-0.01	(-0.16, 0.14)	0.94
Combined†	0.06	(-0.40, 0.52)	0.81	0.03	(-0.12, 0.19)	0.66
White matter lesions						
Univariable	-0.58	(-2.05, 0.89)	0.44	-0.35	(-0.46, -0.24)	<0.001
Multivariable	0.14	(-1.26, 1.54)	0.85	-0.10	(-0.22, 0.02)	0.11
Combined†	0.41	(-1.03, 1.85)	0.57	-0.04	(-0.17, 0.09)	0.57
Fazekas scale ≥2						
Univariable	-1.01	(-1.31, -0.72)	<0.001			
Multivariable	-0.46	(-0.77, -0.16)	0.003			

MoCA: Montreal Cognitive Assessment; Results are from linear mixed effects models, taking into account the effect of study center. Vascular brain lesion volumes are centered on the mean natural-log transformed volumes. Models include, for each damage type, an indicator of the presence of the damage alongside the measurement of volume or, for microbleeds, count. Multivariable models are adjusted for age, sex, history of hypertension, smoking status, history of diabetes, body mass index, AF type, education level, oral anticoagulation (yes, no). Coefficients of all covariates are presented in the appendix, pages 6 and 9. The combined multivariable model includes all vascular brain lesion variables. Coefficients of all covariates from the combined model are presented in the appendix, pages 7 and 10.

* The combined model included 1677 patients.

† The combined model included 1344 patients.

No. of patients with microbleeds=1682; No of patients with microbleeds without a history of stroke or TIA=1348