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Michael Kühne <sup>1,2,\*†</sup>, Philipp Krisai <sup>1,2†</sup>, Michael Coslovsky <sup>2,3</sup>,  
Nicolas Rodondi<sup>4,5</sup>, Andreas Müller <sup>6</sup>, Jürg H. Beer<sup>7</sup>, Peter Ammann<sup>8</sup>,  
Angelo Auricchio <sup>9</sup>, Giorgio Moschovitis <sup>10</sup>, Daniel Hayoz<sup>11</sup>,  
Richard Kobza <sup>12</sup>, Dipen Shah <sup>13</sup>, Frank Peter Stephan<sup>14</sup>, Jürg Schläpfer<sup>15</sup>,  
Marcello Di Valentino <sup>16</sup>, Stefanie Aeschbacher <sup>1,2</sup>, Georg Ehret <sup>13</sup>,  
Ceylan Eken<sup>1,2</sup>, Andreas Monsch<sup>17</sup>, Laurent Roten <sup>18</sup>,  
Matthias Schwenkglens <sup>19,20</sup>, Anne Springer <sup>1,2</sup>, Christian Sticherling <sup>1,2</sup>,  
Tobias Reichlin <sup>18</sup>, Christine S. Zuern<sup>1,2</sup>, Pascal B. Meyre <sup>1,2</sup>, Steffen Blum <sup>1,2</sup>,  
Tim Sinnecker<sup>21,22</sup>, Jens Würfel <sup>22</sup>, Leo H. Bonati <sup>21</sup>, David Conen <sup>23,\*‡</sup>,  
Stefan Osswald <sup>1,2‡</sup>, and for the Swiss-AF Investigators<sup>¶</sup>

<sup>1</sup>Cardiology/Electrophysiology Division, Department of Medicine, University Hospital Basel, University of Basel, Petersgraben 4, 4031 Basel, Switzerland; <sup>2</sup>Cardiovascular Research Institute Basel, University Hospital Basel, University of Basel, Basel, Switzerland; <sup>3</sup>Clinical Trial Unit Basel, Department of Clinical Research, University Hospital Basel, Basel, Switzerland; <sup>4</sup>Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland; <sup>5</sup>Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; <sup>6</sup>Department of Cardiology, Triemli Hospital Zürich, Zürich, Switzerland; <sup>7</sup>Department of Medicine, Conational Hospital of Baden and Molecular Cardiology, University Hospital of Zürich, Zürich, Switzerland; <sup>8</sup>Department of Cardiology, Kantonsspital St Gallen, St Gallen, Switzerland; <sup>9</sup>Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland; <sup>10</sup>Division of Cardiology, Ospedale Regionale di Lugano, Ente Ospedaliero Cantonale, Lugano, Switzerland; <sup>11</sup>Department of Internal Medicine, HRF—Hôpital Cantonal Fribourg, Fribourg, Switzerland; <sup>12</sup>Department of Cardiology, Luzerner Kantonsspital, Lucerne, Switzerland; <sup>13</sup>Division of Cardiology, Department of Medical Specialities, University Hospital Geneva, Geneva, Switzerland; <sup>14</sup>Department of Cardiology, Bürgerspital Solothurn, Solothurn, Switzerland; <sup>15</sup>Department of Cardiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; <sup>16</sup>Division of Cardiology, Ospedale San Giovanni, Ente Ospedaliero Cantonale, Bellinzona, Switzerland; <sup>17</sup>Memory Clinic, Universitäre Altersmedizin, Felix Platter Spital Basel, University of Basel, Basel, Switzerland; <sup>18</sup>Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; <sup>19</sup>Epidemiology, Biostatistics, and Prevention Institute, University of Zürich, Zürich, Switzerland; <sup>20</sup>Institute of Pharmaceutical Medicine (ECPM), University of Basel, Basel, Switzerland; <sup>21</sup>Department of Neurology and Stroke Center, University Hospital Basel, University of Basel, Basel, Switzerland; <sup>22</sup>Medical Image Analysis Center (MIAC) and Department of Biomedical Engineering, University of Basel, Basel, Switzerland; and <sup>23</sup>Population Health Research Institute, McMaster University, 237 Barton Street East, Hamilton, ON, Canada L8L 2X2

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## Aims

We aimed to investigate the association of clinically overt and silent brain lesions with cognitive function in atrial fibrillation (AF) patients.

## Methods and results

We enrolled 1227 AF patients in a prospective, multicentre cohort study (Swiss-AF). Patients underwent standardized brain magnetic resonance imaging (MRI) at baseline and after 2 years. We quantified new small non-cortical infarcts (SNICs) and large non-cortical or cortical infarcts (LNCCIs), white matter lesions (WML), and microbleeds (Mb). Clinically, silent infarcts were defined as new SNCI/LNCCI on follow-up MRI in patients without a clinical stroke or transient ischaemic attack (TIA) during follow-up. Cognition was assessed using validated tests. The

\* Corresponding authors. Tel: +41 61 265 25 25, Email: [michael.kuehne@usb.ch](mailto:michael.kuehne@usb.ch) (M.K.), Email: [david.conen@phri.ca](mailto:david.conen@phri.ca) (D.C.)

† Equal contribution.

‡ Equal contribution.

¶ A full list of Swiss-AF investigators is provided in the Supplementary material, *Index*.

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mean age was 71 years, 26.1% were females, and 89.9% were anticoagulated. Twenty-eight patients (2.3%) experienced a stroke/TIA during 2 years of follow-up. Of the 68 (5.5%) patients with  $\geq 1$  SNCI/LNCCI, 60 (88.2%) were anticoagulated at baseline and 58 (85.3%) had a silent infarct. Patients with brain infarcts had a larger decline in cognition [median (interquartile range)] changes in Cognitive Construct score [ $-0.12$  ( $-0.22$ ;  $-0.07$ )] than patients without new brain infarcts [ $0.07$  ( $-0.09$ ;  $0.25$ )]. New WML or Mb were not associated with cognitive decline.

### Conclusion

In a contemporary cohort of AF patients, 5.5% had a new brain infarct on MRI after 2 years. The majority of these infarcts was clinically silent and occurred in anticoagulated patients. Clinically, overt and silent brain infarcts had a similar impact on cognitive decline.

### Clinical Trial Registration

ClinicalTrials.gov Identifier: NCT02105844, <https://clinicaltrials.gov/ct2/show/NCT02105844>

### Key question

The incidence of clinically overt and silent brain infarcts, white matter lesions, and microbleeds, and their impact on cognition in atrial fibrillation (AF) patients are not known.

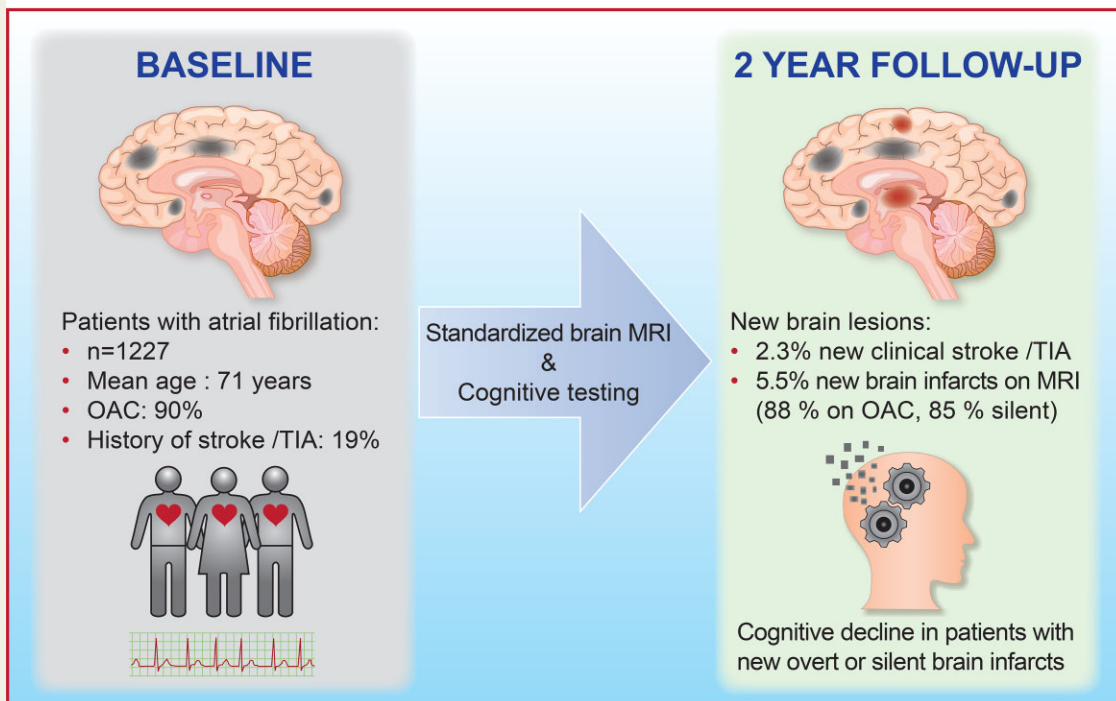
### Key finding

Over 2 years of follow-up, 5.5% of AF patients developed new brain infarcts, with the majority of them being clinically silent and occurring in anticoagulated patients. New clinically overt and silent brain infarcts were similarly associated with cognitive decline.

### Take-home message

In a contemporary cohort of AF patients, new brain infarcts are frequent despite a high anticoagulation rate. Our data suggest that anticoagulation alone may not be sufficient to prevent brain damage and cognitive decline in all AF patients.

## Brain Damage and Change in Cognitive Function in Patients with Atrial Fibrillation



**Structured Graphical Abstract** Brain damage and change in cognitive function in patients with atrial fibrillation.

### Keywords

Atrial fibrillation • Cognitive function • Brain infarction • Oral anticoagulation • Magnetic resonance imaging

## Introduction

Atrial fibrillation (AF) is an important risk factor for death, stroke, heart failure, cognitive dysfunction, and dementia.<sup>1–4</sup> We previously reported data from a cross-sectional analysis where about one in five patients with AF had clinically silent brain infarcts on systematic brain magnetic resonance imaging (MRI).<sup>3</sup> The association of silent brain infarcts with cognitive dysfunction was similar to that of clinical strokes, thus offering a potential explanation for the association between AF and cognitive decline in patients without a previous stroke.<sup>3</sup> AF patients also had a high burden of microbleeds (Mb) and white matter lesions (WML).

Prospective studies are needed to define the incidence of new brain infarcts and other lesions, identify potential mechanisms for their prevention, and study their association with cognitive decline over time. While oral anticoagulation is highly effective in the prevention of clinical stroke and has been associated with lower risk of dementia in patients with AF,<sup>5</sup> prospective data on the development of new brain lesions and their association with cognitive decline in AF patients treated with oral anticoagulation are lacking.

To address these issues, we aimed to investigate the incidence of new brain lesions in a cohort of contemporary AF patients over 2 years of follow-up with pre-defined, systematic brain MRI. We also explored potential predictors of new lesions and assessed the associations of new brain lesions with change in cognitive function.

## Methods

### Patient population

The Swiss Atrial Fibrillation (Swiss-AF) cohort is an ongoing, prospective cohort study at 14 centres in Switzerland.<sup>3,6</sup> The main inclusion criteria were previously documented AF and an age  $\geq 65$  years. For a pre-specified substudy to assess the effect of AF on individuals in the active workforce, a small number of patients aged 45–64 years was enrolled. Exclusion criteria were the inability to give informed consent or secondary AF due to reversible causes. Enrolment of patients with an acute illness was delayed for 4 weeks to allow for resolution of the acute condition. Of the 2415 patients included in Swiss-AF, 672 (27.8%) patients did not undergo baseline MRI because of the presence of a cardiac implantable device or claustrophobia. Eleven (0.5%) patients without complete cognitive testing at baseline, 80 (3.3%) patients with no 2-year follow-up visit, and 425 (17.5%) patients who declined the MRI at the 2-year follow-up visit were excluded. The final study population consisted of 1227 patients (70.4% of the patients with a baseline MRI) (see [Supplementary material online, Figure S1](#)). The study complies with the Declaration of Helsinki, the study protocol was approved by the local ethics committees, and informed written consent was obtained from each participant.

### Clinical variables

At baseline and during yearly in-person study visits, trained study personnel acquired information about patient demographics, prior medical history, interventional and medical treatment, and risk factors by standardized case report forms. Weight and height were directly measured. Body mass index was calculated as weight in kilograms divided

by height in metres squared. The mean of three consecutive blood pressure measurements was used for all analyses. AF was categorized according to guideline recommendations at the time of study inception into paroxysmal, persistent, or permanent.<sup>7</sup> Clinical stroke was defined as a new focal neurological dysfunction with clinical, imaging, or pathological evidence of focal infarction due to ischaemic, haemorrhagic, or undetermined origin. Detailed definitions of stroke subtypes are reported in the [Supplementary material, Index](#). Transient ischaemic attack (TIA) was defined as a new, transient focal neurological dysfunction without evidence of focal infarction. Clinical stroke or TIA during follow-up was reported on pre-defined case report forms and independently adjudicated by two physicians including stroke neurologists using anonymized source documentation (medical records including discharge summaries and imaging reports). Discordant adjudications were resolved by consensus.

### Brain magnetic resonance imaging

Standardized brain MRI images were acquired at the local study centres and centrally analysed by a neuroimaging core lab (Medical Image Analyses Centre, Basel, Switzerland), which is approved for lesion analyses by the EMA/FDA for international clinical Phase III trials.<sup>3</sup> All fluid attenuated inversion recovery (FLAIR) and susceptibility-weighted images were measured at exactly 3 mm of slice thickness. Small non-cortical infarcts (SNCI) were defined as hyperintense lesions  $\leq 20$  mm in diameter on FLAIR on axial sections. Large non-cortical infarcts were defined similar to SNCI but with a diameter  $> 20$  mm. Cortical infarcts were defined as hyperintense lesions of any size on FLAIR involving the cortex. Large non-cortical infarcts and any cortical infarct (LNCCI) were combined into one category. SNCI or LNCCI were considered as silent infarcts in patients without a clinical stroke or TIA between the two MRI imaging studies. Hyperintense WML were identified in either the periventricular or deep white matter region. As the vast majority of longitudinal WML progression in this vascular cohort was expected in increasing confluent lesion volume, we counted new and measured the volume of enlarging  $T_2^*$ -weighted/FLAIR hyperintense lesions. Microbleeds were defined and counted as nodular, strongly hypointense lesions on either  $T_2^*$ -weighted or susceptibility-weighted imaging. Detailed brain MRI imaging descriptions are provided in [Supplementary material online, Appendix](#).

### Cognitive testing

Centrally trained study personnel performed standardized neuro-cognitive testing annually. Neuro-cognitive testing included the Montreal Cognitive Assessment (MoCA),<sup>8</sup> the Trail Making Test (TMT) parts A and B,<sup>9,10</sup> the Digit Symbol Substitution Test (DSST),<sup>11</sup> and the Semantic Fluency Test (SFT). We also used the Swiss-AF Cognitive Construct (CoCo) score for cognitive assessment.<sup>12</sup> The CoCo score is composed of 17 differently weighted combined items from all the above-mentioned individual neuro-cognitive tests. It is a factor score developed for the Swiss-AF study allowing for the quantification of cognitive function and accounting for variance in all items from the full test battery. Detailed test descriptions are provided in [Supplementary material online, Appendix](#).

### Statistical analysis

Detailed description of the statistical methods is provided in [Supplementary material online](#). We used summary statistics to describe baseline characteristics. To estimate the 2-year risk of each of the lesion types, we used logistic regression models, with the presence or absence of lesion type as the outcome. We examined the

associations of a pre-defined set of potential predictors and the risk of lesions, first by adding each potential predictor individually in a univariable logistic regression model, and second by including all predictors simultaneously in a multivariable model. These included age, female sex, active smoking, arterial hypertension, non-paroxysmal AF, diabetes mellitus, prior stroke or TIA, anticoagulation at baseline, and glomerular filtration rate. The process was repeated for each lesion type separately. To correct for potential attrition bias due to missing MRI data from sicker patients, we refitted models while incorporating the stabilized inverse probability of censoring weights (sIPCW).<sup>13</sup> To analyse the effects of lesions on cognitive scores, we used the change in each score from baseline to second follow-up as an outcome variable for linear regression models. Positive numbers reflect improved performance and vice versa. Independent variables in the models included binary variables indicating the presence of a lesion type (e.g. LNCCI) and the natural log-transformed and centred volume of the lesions. Microbleeds were included only as present or absent. For each score, the regression model included the score's value at baseline, as well as age, sex, and education level as covariates.

For all modelling results, we report estimates with 95% confidence intervals (CIs) and asymptotic *P*-values. Due to the exploratory nature of this analysis, *P*-values and CIs are not corrected for multiple testing. All analyses were performed using the statistical software R version 4.0.3.

## Results

Baseline characteristics are shown in [Table 1](#). The mean (standard deviation) age was 71.4 (8.4) years, 320 (26.1%) patients were female, and 652 (53.1%) patients had non-paroxysmal AF. The median [interquartile range (IQR)] CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 3.0 (2.0–4.0). Diabetes mellitus was present in 175 (14.3%), arterial hypertension in 824 (67.2%), a history of heart failure in 228 (18.6%), and a prior stroke or TIA in 235 (19.2%) patients. Nine (0.7%) patients had neurodegenerative disorders, including 6 with parkinsonism and 3 with multiple sclerosis, and 15 (1.2%) patients took neuroleptics. At baseline, 1103 (89.9%) were on anticoagulation and 208 (17.0%) took antiplatelet drugs. Baseline characteristics of excluded patients are shown in [Supplementary material online, Table S1](#). At the 2-year study visit, 1037 (84.7%) were on anticoagulation and 148 (12.1%) were on antiplatelet drugs. Information on use and adherence of other medications are shown in [Supplementary material online, Table S2](#).

## New brain lesions

During follow-up, 28 (2.3%) patients had a clinical stroke (*n* = 19) or TIA (*n* = 9). At least one new SNCI or LNCCI was detected in 68 patients on the 2-year follow-up MRI. Of the 19 patients with a clinical stroke during follow-up, a new brain infarct was identified in 10 patients (53%). In the remaining nine (47%) patients with a clinical stroke and the nine patients with a TIA, no brain infarct on the follow-up MRI was found. Therefore, a total of 86 patients (7%) had a clinical stroke/TIA and/or a newly MRI-detected brain infarct.

The estimated 2-year rate of a new brain infarct (SNCI or LNCCI) was 5.5% (95% CI 4.4–7.0) with a median (IQR) volume of 0.30 (0.12–0.79) mL. Their locations are shown in [Supplementary material online, Table S3](#). These new brain infarcts were clinically silent in 58 (85.3%) patients. The median (IQR)

**Table 1** Baseline characteristics of the study patients (*n* = 1227)

Variable	
Age, years	71.4 (8.4)
Female sex	320 (26.1)
BMI, kg/m <sup>2</sup>	27.7 (4.7)
Highest education	
Basic	131 (10.7)
Medium	584 (47.6)
High	512 (41.7)
Active smoker	85 (6.9)
Non-paroxysmal AF	652 (53.1)
Time since AF diagnosis, years	3.3 (0.9–8.0)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score, points	3.0 (2.0–4.0)
Systolic BP, mmHg	134.9 (17.9)
Diastolic BP, mmHg	78.9 (11.9)
GDS score, points	1.4 (1.7)
Baseline cognitive assessment, points	
MoCA score	25.8 (2.9)
TMT-A score	0.6 (0.2)
TMT-B score	0.2 (0.1)
DSST score	46.7 (14.0)
SFT score	19.7 (5.4)
CoCo score	0.1 (0.5)
Arterial hypertension	824 (67.2)
Diabetes mellitus	175 (14.3)
Prior stroke or TIA	235 (19.2)
Heart failure	228 (18.6)
Coronary heart disease	316 (25.8)
Peripheral artery disease	64 (5.2)
Prior major bleeding	67 (5.5)
GFR, mL/min/1.73 m <sup>2</sup>	62.7 (51.6–75.1)
Baseline brain MRI findings	
SNCI or LNCCI	420 (34.2)
Microbleeds	242 (20.4)
WML volume, mL	7.0 (10.4)
Anticoagulation <sup>a</sup>	1103 (89.9)
VKA	413 (33.7)
DOAC	689 (56.2)
Antiplatelet therapy	208 (17.0)

Values are mean (standard deviation), *n* (%), or median (interquartile range).

The range of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is from 0 to 9 points. A higher score is indicative of a higher risk of stroke.

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CoCo, Cognitive Construct; DSST, Digit Symbol Substitution Test; GDS, Geriatric Depression Scale; GFR, glomerular filtration rate; DOAC, direct oral anticoagulant; LNCCI, large non-cortical or cortical infarcts; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; SFT, Semantic Fluency Test; SNCI, small non-cortical infarcts; TIA, transient ischaemic attack; TMT, Trail Making Test; VKA, Vitamin K antagonist; WML, white matter lesion.

<sup>a</sup>One patient was anticoagulated with low-molecular-weight heparin.

volume of silent infarcts of 0.26 (0.11–0.61) mL was smaller compared with the volume of infarcts in the 10 patients with documented SNCI or LNCCI and an intercurrent clinical stroke/TIA [4.56 (0.26–7.92) mL]. Detailed information about newly detected overt

**Table 2** Occurrence and volume (number for microbleeds) of new brain lesions on brain magnetic resonance imaging after 2 years of follow-up

	Occurrence (n = 1227)	% anticoagulated		Volume (mL)/no. for microbleeds median (IQR)
		Baseline	2-year follow-up	
Patients with overt infarcts (n = 10)				
SNCI or LNCCI	10 (0.8)	90.0	80.0	4.56 (0.26–7.92)
SNCI	4 (0.3)	100	75.0	0.22 (0.16–0.35)
LNCCI	7 (0.6)	85.7	85.7	5.41 (4.56–24.63)
WML	5 (0.4)	100	80	0.13 (0.09–0.30)
Microbleeds <sup>a</sup>	4 (0.3)	75.0	75.0	2 (1–4)
Patients with silent infarcts (n = 58)				
SNCI or LNCCI	58 (4.7)	87.9	87.9	0.26 (0.11–0.61)
SNCI	33 (2.7)	78.8	78.8	0.25 (0.07–0.49)
LNCCI	29 (2.4)	100	100	0.23 (0.11–0.78)
WML	25 (2.0)	88.0	88.0	0.10 (0.05–0.26)
Microbleeds <sup>a</sup>	19 (1.5)	84.2	89.5	1 (1–2)
Patients without infarcts (n = 1159)				
SNCI or LNCCI	–	–	–	–
SNCI	–	–	–	–
LNCCI	–	–	–	–
WML	199 (16.2)	93.0	88.4	96 (45–246)
Microbleeds <sup>a</sup>	113 (9.2)	89.4	89.4	1 (1–2)

Numbers are n (%), mean (standard deviation), or median (interquartile range).

LNCCI, large non-cortical or cortical infarcts; SNCI, small non-cortical infarcts; WML, white matter lesions.

<sup>a</sup>Valid n for microbleeds for all patients, 1192.

and silent brain infarcts and other brain lesions on the 2-year follow-up brain MRI and anticoagulation status at baseline and after 2 years are shown in [Table 2](#) and [Supplementary material online, Table S4](#). Anticoagulation treatment over time and time in therapeutic international normalized ratio range for patients on vitamin K antagonists stratified by the presence or absence of brain infarcts are shown in [Supplementary material online, Figure S2](#) and [Table S5](#), respectively. Similarly, information on anti-arrhythmic therapy, including pulmonary vein isolation, electrocardioversion, and anti-arrhythmic drug therapy, is shown in [Supplementary material online, Table S6](#).

New WML were present in 229 patients (18.7%, 95% CI 16.6–20.9) with a median (IQR) volume of 0.11 (0.05–0.26) mL. New Mb occurred in 136 (11.4%, 95% CI 9.7–13.3) patients with a median (IQR) count of 1 (1–2). The anticoagulation status for patients with new Mb at baseline and after 2 years is shown in [Supplementary material online, Table S7](#). Brain lesion incidences were slightly higher after adjusting for non-randomly missing observations with sIPCW: 6.1% (95% CI 4.8–7.7) for SNCI or LNCCI, 19.0% (95% CI 16.9–21.4) for WML, and 11.9% (95% CI 10.1–14.0) for Mb. Out of 354 patients identified with any new lesion, 284 (80.2%) had only one lesion type and 57 patients (16.1%) had two types (see [Supplementary material online, Table S8](#)).

## Predictors of new brain lesions

Results of regression models to predict new brain lesions are shown in [Table 3](#). In multivariable models, age [odds ratio (OR)

per 10-year increase 1.89 (95% CI 1.30–2.78),  $P=0.001$ ] and a history of prior stroke/TIA [1.95 (95% CI 1.11–3.32),  $P=0.017$ ] were associated with a higher risk of new SNCI or LNCCI. Age [OR per 10-year increase 1.34 (95% CI 1.10–1.65),  $P=0.005$ ] and a history of a prior stroke/TIA [1.53 (95% CI 1.08–2.15),  $P=0.016$ ] were also associated with an increased risk of WML. Age [OR per 10-year increase 1.56 (95% CI 1.20–2.04),  $P<0.001$ ] was associated with an increased risk of new Mb. Regression models weighted by sIPCW and sensitivity analyses replacing arterial hypertension by systolic blood pressure provided similar results (see [Supplementary material online, Tables S9 and S10](#)).

## Cognitive function

The changes in cognitive scores from baseline to the 2-year follow-up visit stratified by the presence or absence of ischaemic brain infarct are shown in [Figure 1](#). We found a decline across most individual tests in patients with an incident SNCI or LNCCI. Patients without incident brain infarcts had an increase of their median (IQR) MoCA score of 1 (–1 to 2) in line with an expected learning effect, while patients with brain infarcts had no change in their MoCA score [0 (–1 to 2)]. As the MoCA score covers several cognitive domains, changes in each individual MoCA subscore are shown in [Supplementary material online, Figure S3](#). Patients with brain infarcts also had a decreased overall efficiency of cognitive operations, shown by a median (IQR) change in their DSST score of –2 (–6 to 2) compared with 1 (–4 to 5) in patients

**Table 3** Logistic regression models for potential predictors of new brain lesions

	Univariable		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
<b>SNCI or LNCCI</b>				
Age, per 10 years	1.94 (1.40–2.72)	<0.001	1.89 (1.30–2.78)	0.001
Female sex	0.66 (0.34–1.18)	0.181	0.54 (0.28–1.00)	0.061
Active smoker	1.59 (0.64–3.37)	0.265	2.31 (0.90–5.24)	0.059
Arterial hypertension	1.38 (0.81–2.46)	0.251	0.99 (0.56–1.81)	0.976
Non-paroxysmal AF	1.12 (0.69–1.85)	0.641	1.03 (0.62–1.72)	0.917
Diabetes mellitus	1.94 (1.05–3.40)	0.027	1.51 (0.79–2.75)	0.193
Prior stroke or TIA	2.12 (1.23–3.57)	0.005	1.95 (1.11–3.32)	0.017
Anticoagulation at baseline	0.83 (0.41–1.93)	0.641	0.63 (0.30–1.51)	0.261
GFR, per 1 mL/min/1.73 m <sup>2</sup>	0.98 (0.97–0.99)	0.004	0.99 (0.97–1.01)	0.218
<b>White matter lesions</b>				
Age, per 10 years	1.37 (1.14–1.64)	<0.001	1.34 (1.10–1.65)	0.005
Female sex	1.12 (0.81–1.54)	0.476	1.10 (0.79–1.52)	0.572
Active smoker	0.93 (0.50–1.61)	0.803	1.07 (0.57–1.90)	0.832
Arterial hypertension	1.40 (1.02–1.94)	0.040	1.19 (0.86–1.67)	0.301
Non-paroxysmal AF	1.25 (0.94–1.67)	0.130	1.21 (0.89–1.63)	0.221
Diabetes mellitus	1.52 (1.03–2.20)	0.031	1.35 (0.90–1.99)	0.136
Prior stroke or TIA	1.67 (1.19–2.33)	0.003	1.53 (1.08–2.15)	0.016
Anticoagulation at baseline	1.50 (0.90–2.64)	0.138	1.21 (0.71–2.15)	0.501
GFR, per 1 mL/min/1.73 m <sup>2</sup>	1.00 (0.99–1.01)	0.715	1.01 (1.00–1.01)	0.208
<b>Microbleeds<sup>a</sup></b>				
Age, per 10 years	1.57 (1.25–1.99)	<0.001	1.56 (1.20–2.04)	<0.001
Female sex	0.89 (0.58–1.33)	0.575	0.80 (0.51–1.21)	0.299
Active smoker	1.04 (0.49–1.97)	0.915	1.47 (0.68–2.89)	0.291
Arterial hypertension	1.22 (0.83–1.81)	0.327	1.13 (0.76–1.71)	0.564
Non-paroxysmal AF	1.51 (1.05–2.20)	0.026	1.45 (0.99–2.12)	0.056
Diabetes mellitus	0.61 (0.32–1.08)	0.109	0.51 (0.27–0.91)	0.032
Prior stroke or TIA	1.14 (0.72–1.75)	0.569	1.13 (0.71–1.76)	0.588
Anticoagulation at baseline	0.80 (0.47–1.45)	0.440	0.66 (0.38–1.22)	0.165
GFR, per 1 mL/min/1.73 m <sup>2</sup>	0.99 (0.98–1.00)	0.017	0.99 (0.98–1.01)	0.389

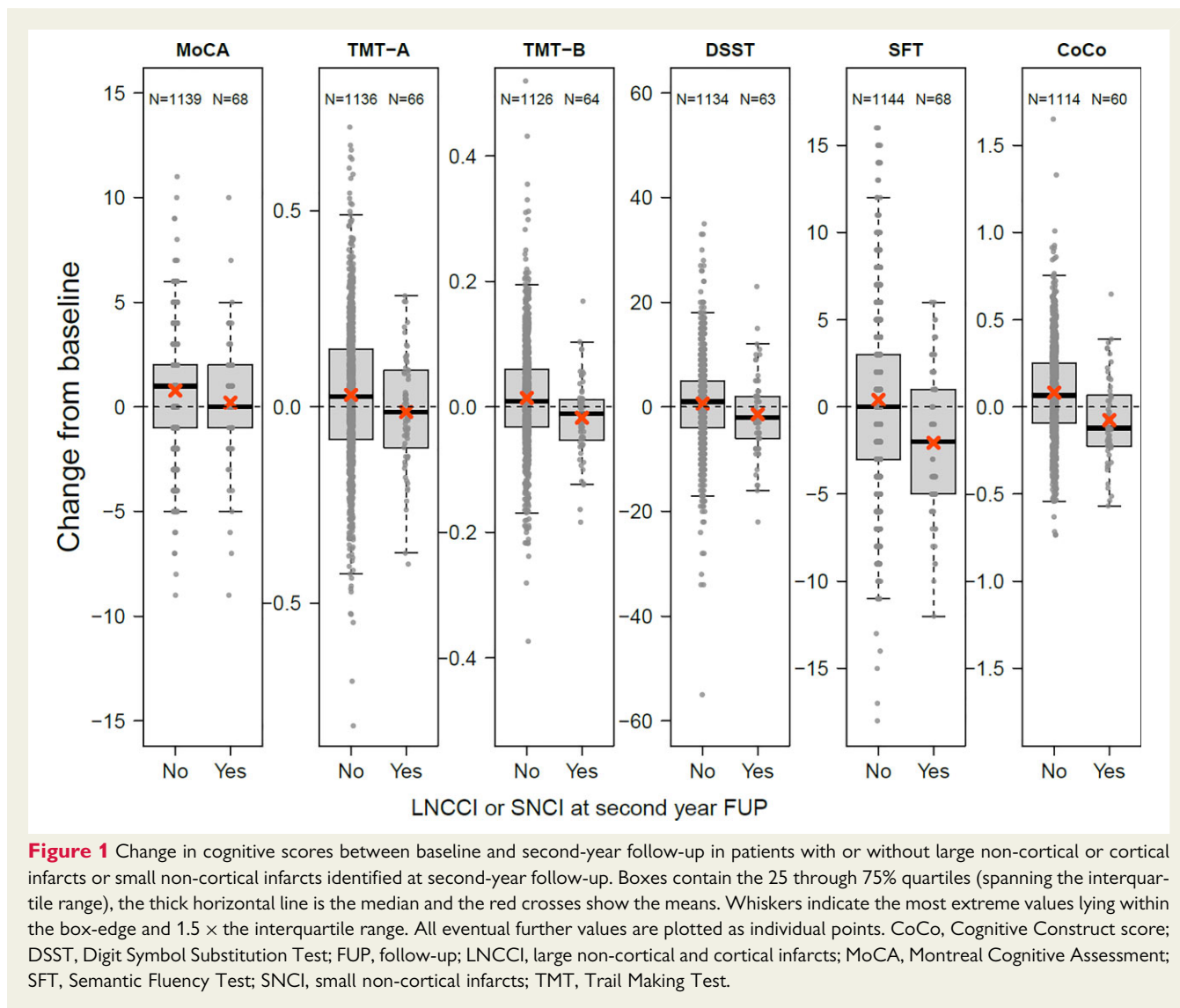
AF, atrial fibrillation; CI, confidence interval; GFR, glomerular filtration rate; LNCCI, large non-cortical infarct or any cortical infarct; OR, odds ratio; SNCI, small non-cortical infarct; TIA, transient ischaemic attack.

<sup>a</sup>n = 1192.

without brain infarcts. Similarly, their semantic memory, language production, and mental flexibility decreased, shown by a median (IQR) change in their SFT score of  $-2$  ( $-5$  to  $1$ ) compared with no change of  $0$  ( $-3$  to  $3$ ) in patients without brain infarcts. These individual test results were also reflected in the median (IQR) CoCo score changes of  $0.07$  ( $-0.09$ ;  $0.25$ ) and  $-0.12$  ( $-0.22$ ;  $-0.07$ ) in patients without and with infarcts, respectively. Changes in cognitive scores further stratified by clinically overt and clinically silent brain infarcts are shown in [Supplementary material online, Figure S4](#).

Patients with and without new WML had similar changes in the MoCA, TMT-B, and CoCo scores, but those with new WML had lower test scores for the TMT-A, DSST, and the SFT (see [Supplementary material online, Figure S5A](#)). Patients with and without new Mb had similar changes in cognitive scores (see [Supplementary material online, Figure S5B](#)).

In a model simultaneously including clinically silent SNCI or LNCCI, clinically overt SNCI or LNCCI, WML, and Mb, while correcting for the baseline CoCo score, age, sex, and education level, the presence of new clinically overt and new clinically silent SNCI or LNCCI were both associated with reductions in the CoCo score ([Figure 2](#)). Their respective beta coefficients (95% CI) were  $-0.23$  ( $-0.44$  to  $-0.01$ ,  $P=0.042$ ) and  $-0.14$  ( $-0.21$  to  $-0.06$ ,  $P<0.0001$ ). Infarct volume was not associated with CoCo score changes during follow-up. Furthermore, neither new WML nor Mb were associated with changes in the CoCo score ([Figure 2](#)). Analyses for the individual cognitive scores are shown in [Supplementary material online, Tables S11–S15](#) and [Figure S6](#). Results were consistent with those obtained from the CoCo score. Sensitivity analyses adjusting for missing values were consistent with the main results (see [Supplementary material online, Table S16](#) and [Figures S7](#) and [S8](#)).

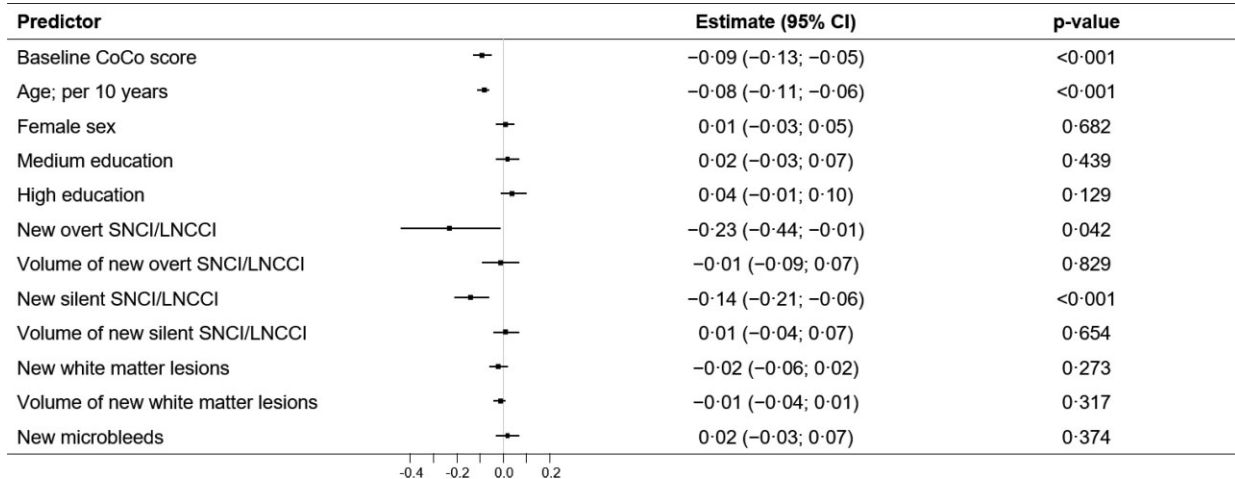


## Discussion

This study prospectively assessed the occurrence of clinically silent and overt brain lesions and their associations with cognitive decline in patients with AF. A brain MRI after 2 years of follow-up in mostly anticoagulated patients revealed new ischaemic brain infarcts in 5.5%, new WML in 18.7%, and new Mb in 11.4%. Nearly 9 out of 10 ischaemic brain infarcts occurred in patients on anticoagulation and were clinically silent. The associations with cognitive decline were similar for new clinically silent and overt brain infarcts despite the larger volume of overt infarcts, and they were independent of other lesion types. In contrast, WML and Mb were not consistently associated with cognitive decline (*Structured Graphical Abstract*).

Our findings support the concept of AF as a cause for vascular dementia caused by predominantly silent brain infarcts.<sup>14</sup> Ischaemic brain infarcts were quite common in our unselected AF population over 2 years of follow-up and the great majority (85%) was clinically silent. Despite being classified as clinically

silent, they were not silent with regard to cognitive decline. Although silent brain infarcts were markedly smaller in volume compared with overt brain infarcts, their effect on cognition was similar. Our results indicate that overt and silent ischaemic brain infarcts may be important mediators of cognitive decline in these patients. While our reported differences in cognitive scores may seem small, they occurred within only 2 years and may increase over time, which will be investigated by our planned long-term follow-up. Subsequently, these differences might develop an important societal impact. For example, a one point difference in the MoCA score has been shown in other cohorts to translate into a 10-year age difference in cognitive function.<sup>15,16</sup> Considering that both AF and cognitive dysfunction are closely related to age, this may constitute a major future public health burden in societies with increasing life spans.<sup>3,17</sup> In contrast to ischaemic brain infarcts, WML and Mb were not consistently and independently associated with cognitive function. However, we found associations of WML with individual cognitive tests evaluating the overall efficiency of cognitive operations and mental flexibility.



**Figure 2** Linear regression model for the change ( $\Delta$ score) in the Cognitive Construct score for patients with 2-year follow-up data ( $n = 1139$ ). LNCCI, large non-cortical and cortical infarcts; SNCI, small non-cortical infarcts.

Our findings are intriguing, as patients were well anticoagulated both at baseline and at 2 years of follow-up, and nearly 90% of brain infarcts occurred in anticoagulated patients. Although anticoagulation is highly effective in reducing cardioembolic strokes in AF patients,<sup>18–20</sup> and is associated with a lower risk of dementia,<sup>5</sup> our data suggest that it might be insufficient to fully prevent the progression of vascular brain injury. Whether some patients may benefit from different, higher doses of anticoagulation or addition of antiplatelet drugs is currently not known and has to be weighed against a higher risk of major bleedings.<sup>21</sup> Especially in patients with small ischaemic, lacunar infarcts that may be primarily due to cerebral small vessel disease and not due to cardioembolism, anticoagulation might be less effective. In addition to antithrombotic treatment, early rhythm control has recently been shown to improve outcomes including a reduction of stroke and death from cardiovascular causes in an AF population with a similar age and CHA<sub>2</sub>DS<sub>2</sub>-VASc score,<sup>22</sup> but the effect of this approach on silent infarcts and cognitive function is unknown.

While we did not find associations of traditional stroke risk factors, including arterial hypertension and diabetes mellitus, with brain lesions, their treatment may still be worthwhile. For example, in our cohort, cross-sectional data showed that hypertension was associated with lower cognition in the presence of WML.<sup>23</sup> It seems biologically plausible that other behavioural and metabolic risk factors likely play a role in AF patients besides the known thrombo-embolic risk factors, considering that modifiable stroke risk factors account for 90% of stroke burden in the general population.<sup>24</sup> However, the extent of risk reduction for overt and silent brain infarcts and its effect on cognitive function in AF patients need to be tested in a randomized trial.

The strengths of our study are the detailed characterization of a large patient population with AF, including systematic brain MRI at baseline and at 2 years of follow-up as well as cognitive assessments. Limitations include the observational nature of our study that does not allow to prove causality. The generalizability to

other patient populations outside of our study and to patients that could not undergo brain MRI due to cardiac devices or competing risks is unclear. We did not have information on the presence of atherosclerosis in brain-supplying arteries. In our study, only a small number of patients had a clinical stroke during follow-up and of those, nine patients did not have an infarct on the follow-up MRI. By counting only brain infarcts detectable on MRI after a 2-year follow-up, we may have underestimated the true event rate in our cohort. As the number of detected brain infarcts was limited, the statistical power to assess predictors may be limited. Furthermore, the low number of infarcts precluded a meaningful analysis of lesion location and cognitive decline. Our analyses adjusting for non-randomly missing observations also indicate that we may have underestimated the true incidence of brain lesions in a general AF population. Finally, we did not have data on time in AF in relation to the start of anticoagulation and on the timing of brain infarcts and change in cognition, which may impact outcomes in our study.

In conclusion, in the Swiss-AF cohort, 5.5% of AF patients developed new brain infarcts after 2 years of follow-up. The great majority (85%) of these infarcts was clinically silent and occurred in anticoagulated patients. New brain infarcts were associated with cognitive decline and this association was similar in patients with clinically overt and silent brain infarcts. These data suggest that anticoagulation alone may not be sufficient to prevent progressive brain damage in all AF patients.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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## Data availability

All data will be shared upon reasonable request to the corresponding author.

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