Stroke

CLINICAL AND POPULATION SCIENCES

Biomarker, Imaging, and Clinical Factors Associated With Overt and Covert Stroke in Patients With Atrial Fibrillation

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BACKGROUND: Atrial fibrillation is a major risk factor for stroke and silent brain infarcts. We studied whether a multimodal approach offers additional insights to the CHA_2DS_2-VASc score in predicting stroke or new brain infarcts on magnetic resonance imaging (MRI) over a 2-year follow-up.

METHODS: Swiss-AF is a prospective, multicenter cohort study of patients with known atrial fibrillation. We included patients with available brain MRI both at enrollment and 2 years later. The dates of the baseline and follow-up visits ranged from March 2014 to November 2020. The primary outcome was assessed 2 years after baseline and was defined as a composite of clinically identified stroke or any new brain infarct on the 2-year MRI. We compared a multivariable logistic regression model including prespecified clinical, biomarker, and baseline MRI variables to the CHA_2DS_2-VASc score.

RESULTS: We included 1232 patients, 89.8% of them taking oral anticoagulants. The primary outcome occurred in 78 patients (6.3%). The following baseline variables were included in the final multivariate model and were significantly associated with the primary outcome: white matter lesion volume in milliliters (adjusted odds ratio [aOR], 1.91 [95% CI, 1.45–2.56]), NT-proBNP (N-terminal pro-B-type natriuretic peptide; aOR, 1.75 [95% CI, 1.20–2.63]), GDF-15 (growth differentiation factor-15; aOR, 1.68 [95% CI, 1.11–2.53]), serum creatinine (aOR, 1.50 [95% CI, 1.02–2.22]), IL (interleukin)-6 (aOR, 1.37 [95% CI, 1.00–1.86]), and hFABP (heart-type fatty acid–binding protein; aOR, 0.48 [95% CI, 0.31–0.73]). Overall performance and discrimination of the new model was superior to that of the CHA_2DS_2-VASc score (C statistic, 0.82 [95% CI, 0.77–0.87] versus 0.64 [95% CI, 0.58–0.70]).

CONCLUSIONS: In patients with atrial fibrillation, a model incorporating white matter lesion volume on baseline MRI and selected blood markers yielded new insights on residual stroke risk despite a high proportion of patients on oral anticoagulants. This may be relevant to develop further preventive measures.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: brain ■ creatinine ■ humans ■ infarction ■ risk factors

One in 3 patients at the age of 55 years will develop atrial fibrillation (AF) later in life. AF increases the risk of stroke up to 5×.[1] On an individual basis, the risk of stroke is estimated primarily by the CHA_2DS_2-VASc score, which encompasses congestive heart failure, hypertension, age, diabetes, history of stroke,

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
aOR	adjusted odds ratio
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
BIOSIGNAL	Biomarker Signature of Stroke Aetiology
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcomes Study
CROMIS-2	Clinical Relevance of Microbleeds in Stroke Study
GDF-15	growth differentiation factor-15
hFABP	heart-type fatty acid–binding protein
IL	interleukin
MRI	magnetic resonance imaging
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OAC	oral anticoagulant
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
REGARDS	Reasons for Geographic and Racial Differences in Stroke

vascular disease, and sex category.[2] Adding high-sensitivity cardiac troponin-I to the CHA_2DS_2-VASc score improves its accuracy for stroke as shown in 14 821 patients with AF enrolled in the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation).[3] In the same cohort, the age, biomarkers, clinical history stroke score—consisting of age, NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity cardiac troponin-I, prior stroke/transient ischemic attack—had an even higher C index of 0.68 for stroke. Traditionally, the end point of risk scores is clinically overt stroke, defined in ARISTOTLE as "sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery."[4] On the contrary, covert or silent brain infarcts are detected only via brain imaging, the gold standard being magnetic resonance imaging (MRI). These are neither benign nor rare: in our cohort of 1737 patients with AF, brain infarcts were present on cross-sectional brain MRI among 22% of patients, most of them with no clinical history of stroke or transient ischemic attack, and were associated with lower scores on the Montreal Cognitive Assessment test.[5] Over 2 years of follow-up, new brain infarcts occurred in 5.5% of patients with AF, with the majority of them being clinically silent and occurring in anticoagulated patients, and were associated with cognitive decline.[6] Understanding the contributors of residual stroke risk despite oral anticoagulants (OACs) is crucial to start and individualize preventive measures.

In this prospective cohort study of patients with AF, we sought to identify clinical variables, MRI variables, and blood markers at baseline associated with brain infarcts or clinical stroke over a follow-up of 2 years. We then compared the diagnostic accuracy of a model consisting of clinical variables, baseline MRI variables, and blood markers with CHA_2DS_2-VASc—a score including clinical variables only—in the prediction of new brain infarcts or clinical stroke.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patients

The Swiss-AF study is an ongoing prospective cohort study across 14 centers in Switzerland since 2014. The local ethics committees approved the study protocol, and written informed consent was obtained from all participants. The detailed methodology had been described previously.[6,7] Briefly, we included patients who were ≥45 years of age with a history of documented AF and had both a baseline and a follow-up MRI 2 years later. We excluded patients with secondary forms of AF, that is due to a temporary condition that resolves over time (eg, AF after an infection or an operation), and those unable to provide informed consent.

Baseline Clinical Measures

Clinical and demographic information was obtained through standardized case report forms. Weight and height were directly measured, and body mass index was calculated as weight in kilograms divided by height in meters squared. AF was classified into paroxysmal, persistent, and permanent AF according to recommended definitions.[7]

Biomarkers

Biomarker selection and assessment has been described previously. We selected biomarkers of inflammation and oxidative stress, myocardial injury and strain, vascular damage, renal impairment, and cerebral damage.[8] At the baseline study visit, nonfasting venous blood samples were collected and centrifuged. Plasma samples were aliquoted and stored at −80 °C in a central biobank. The list of biomarkers assessed is reported in Table 1.

Brain MRI

The MRI acquisition protocol has been described previously.[5] MRI was acquired on a 1.5T or 3.0T scanner. The standardized protocol included a 3-dimensional T1-weighted magnetization-prepared rapid gradient echo, a 2-dimensional axial fluid-attenuated inversion recovery, and 2-dimensional axial diffusion-weighted imaging sequence with whole brain coverage and without interpolation. In addition, either a 2-dimensional axial susceptibility-weighted imaging or a 2-dimensional axial T2*-weighted (spatial resolution of 1.0, 1.0, and 3.0 mm^3) sequence was applied. All brain MRI scans were analyzed

Table 1. Overview of All Variables at Baseline, Overall, and by the Presence of the Primary End Point (Clinically Overt/Covert Stroke at 2-Year Follow-Up)

	Overall	No primary end point	Primary end point	*P* value	Missing, %
n	1232	1154	78		
Age at baseline, y; mean (SD)	71.4 (8.3)	71.2 (8.4)	75.0 (7.2)	<0.001	0
Sex: female, %	321 (26.1)	306 (26.5)	15 (19.2)	0.199	0
Congestive heart failure, %	230 (18.7)	211 (18.3)	19 (24.4)	0.237	0
Other cardiovascular disease (ie, CAD or PAD), %	343 (27.8)	309 (26.8)	34 (43.6)	0.002	0
Arterial hypertension, %	494 (40.1)	462 (40.0)	32 (41.0)	0.957	0
Hypercholesterolemia, %	102 (8.8)	96 (8.8)	6 (8.0)	0.972	5.7
Diabetes, %	177 (14.4)	161 (14.0)	16 (20.5)	0.152	0
History of stroke or TIA, %	237 (19.2)	211 (18.3)	26 (33.3)	0.002	0
CHA_2DS_2-VASc score, median (IQR)	3 (2–4)	3 (2–4)	4 (3–5)	<0.001	0
CHA_2DS_2-VASc score ≥2 points, %	1020 (82.8)	946 (82.0)	74 (94.9)	0.006	0
AF type: nonparoxysmal, %	656 (53.2)	612 (53.0)	44 (56.4)	0.645	0
Smoking status (active smoker at baseline), %	85 (6.9)	77 (6.7)	8 (10.3)	0.328	0
Type of anticoagulant, %				0.516	0
None	125 (10.1)	116 (10.1)	9 (11.5)		
VKA	414 (33.6)	384 (33.3)	30 (38.5)		
NOAC	693 (56.2)	654 (56.7)	39 (50.0)		
Biomarker levels					
High-sensitivity cardiac troponin T, pg/mL; median (IQR)	12.1 (8.5–18.6)	12.0 (8.4–18.1)	17.4 (10.3–26.2)	0.001	5.4
NT-proBNP, pg/mL; median (IQR)	460.1 (151.5–1146.9)	444.0 (144.7–1093.9)	1104.6 (377.6–2131.4)	<0.001	5.7
Osteopontin, ng/mL; median (IQR)	16.1 (12.5–22.2)	16.0 (12.4–21.9)	19.3 (14.4–26.2)	0.001	5.6
hFABP, ng/mL; median (IQR)	33.6 (27.7–42.5)	33.7 (27.7–42.3)	33.5 (28.0–44.3)	0.690	5.4
Serum neurofilament light chain, pg/mL; median (IQR)	37.0 (25.8–53.4)	36.5 (25.6–52.0)	44.0 (33.3–69.1)	0.001	2.0
Non-HDL cholesterol, mmol/L; mean (SD)	3.3 (1.0)	3.3 (1.0)	3.1 (1.1)	0.082	5.7
hsCRP, mg/L; median (IQR)	1.5 (0.8–3.5)	1.5 (0.8–3.4)	1.8 (1.1–5.4)	0.044	3.3
Creatinine, µmol/L; median (IQR)	97.0 (84.0–114.0)	96.0 (84.0–112.0)	106.0 (86.0–126.5)	0.017	1.5
Cystatin C, mg/L; median (IQR)	1.2 (1.1–1.5)	1.2 (1.1–1.5)	1.3 (1.1–1.6)	0.001	1.6
GDF-15, pg/mL; median (IQR)	1373.5 (971.2–2035.7)	1347.4 (962.1–1957.7)	1870.8 (1329.4–2862.6)	<0.001	5.4
IL-6, pg/mL; median (IQR)	3.6 (2.5–5.4)	3.5 (2.5–5.2)	4.8 (3.1–7.4)	<0.001	18.6
ANG-2, ng/mL; median (IQR)	2.5 (1.8–3.7)	2.4 (1.8–3.6)	3.0 (2.0–5.0)	0.005	5.4
ESM-1, ng/mL; median (IQR)	2.1 (1.7–2.6)	2.1 (1.7–2.6)	2.3 (1.8–2.7)	0.250	0.8
IGFBP-7, ng/mL; median (IQR)	175.2 (156.1–204.1)	174.2 (155.4–202.4)	189.7 (161.3–228.9)	0.006	5.4
Brain MRI characteristics					
Presence of LNCCI or SNCI at baseline, %	424 (34.4)	375 (32.5)	49 (62.8)	<0.001	0
Volume of WML at baseline, mean (SD)	7041.1 (10428.8)	6519.4 (9496.9)	14759.7 (17994.3)	<0.001	0
Presence of MB at baseline, %	244 (20.4)	218 (19.4)	26 (36.1)	0.001	3.1

AF indicates atrial fibrillation; ANG-2, angiopoietin-2; CAD, coronary artery disease; ESM-1, endothelial cell–specific molecule-1; GDF-15, growth differentiation factor-15; HDL, high-density lipoprotein; hFABP, heart-type fatty acid–binding protein; hsCRP, high-sensitivity C-reactive protein; IGFBP-7, insulin-like growth factor–binding protein-7; IL-6, interleukin-6; IQR, interquartile range; LNCCI, large noncortical or cortical infarct; MB, microbleed; MRI, magnetic resonance imaging; NOAC, non-vitamin K-antagonist oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral arterial disease; SNCI, small noncortical infarct; TIA, transient ischemic attack; VKA, vitamin K antagonist; and WML, white matter lesion.

centrally in a specialized imaging core laboratory (Medical Image Analysis Centre, Basel, Switzerland). Fluid-attenuated inversion recovery hyperintense lesions not meeting the criteria for brain infarcts were identified as white matter lesions. Microbleeds were identified and counted as nodular, strongly hypointense lesions on either T2*-weighted or susceptibility-weighted imaging. T2-weighted volumes of white matter lesions were segmented and quantified semiautomatically using Amira (Mercury Computer Systems, Inc, Chelmsford, MA). Lesions with a central fluid-attenuated inversion recovery hypointense core were segmented in total without differentiating between hyperintense and hypointense lesion areas. Expert raters of MRI scans were unaware of patient characteristics. Board-certified neuroradiologists confirmed all ratings.

End Points

The primary end point was a composite of clinically overt or covert stroke detected in the 2-year MRI compared with the baseline MRI. Overt stroke was defined as symptoms compatible with a focal cerebral ischemia over the 2-year follow-up period. Covert stroke was defined as a new brain infarct in the 2-year MRI compared with the baseline MRI, without symptoms compatible with a focal cerebral ischemia over the 2-year follow-up period. On MRI, brain infarcts were classified into 2 groups. One group encompassed small noncortical infarcts appearing as hyperintense lesions on axial fluid-attenuated inversion recovery sections, ≤20 mm in diameter and located in the white matter, internal or external capsule, deep brain nuclei, thalamus, or brain stem but not in the cortex.[8] The second group encompassed large noncortical infarcts (>20 mm in diameter) and any cortical infarcts regardless of their size—brain infarcts often referred as nonlacunar in clinical practice.

Statistical Analysis

Baseline characteristics were stratified by the presence or absence of a new brain infarct on follow-up MRI at 2 years compared with the baseline MRI or new clinical stroke during the 2-year follow-up (primary end point). Categorical variables are presented as frequencies and percentages. For normally distributed continuous variables, we present the mean and SD; for variables with a (highly) skewed distribution, the median and interquartile range. We compared differences across groups with Wilcoxon rank-sum tests for continuous variables or χ^2 tests for categorical ones. Lesion volumes were summarized by their median (interquartile range) given their skewed distribution. To estimate the probability of the primary end point, we fitted and compared 2 logistic regression models: the first model contained only the CHA_2DS_2-VASc score as explaining variable, and the second model contained baseline clinical, MRI, and biomarker variables and was adjusted for variables selected with backward selection based on Akaike Information Criterion. The Akaike Information Criterion uses the log-likelihood as a comparative measure of goodness of fit with the number of estimated parameters as a penalty to overfitting. To bootstrap the model, we resampled the complete case data set for all clinical, biomarker, and MRI predictors 10000× and refitted the null and full models. We then performed bidirectional selection based on the Akaike Information Criterion, presenting the probability of times that each predictor was selected. To address the risk of model overfitting, we computed multivariate models with forward variable selection. We then assessed and compared overall performance, discrimination, and calibration of the 2 models. We assessed model performance with the Brier score, which ranges from 0 (perfect model) to 0.25 (noninformative model). Model discrimination measures was assessed using the area under the receiver operating characteristic curve with 95% CI using the DeLong method.[9] Model calibration was assessed by plotting the observed versus predicted rates of the primary end point. All analyses were performed on an available data basis and conducted using R, version 4.0.3. (R Core Team, 2018, R Foundation, Vienna, Austria).

RESULTS

Overall, 2415 patients were included in Swiss-AF and 1183 were excluded, mainly because they had a contraindication to MRI due to an implanted cardiac device or claustrophobia (flowchart in Figure S1). In the present analysis, we included 1232 patients with AF, 26.1% of whom were women. Mean age was 71.4 years; history of stroke or transient ischemic attack was present in 19.2%; median CHA_2DS_2-VASc score was 3 points; and OAC was taken by 89.8%. Baseline MRI revealed a brain infarct in 34.4%, ≥1 microbleeds in 20.4%, and a mean white matter lesion volume of 7.0 cm^3 (SD, ±10.4 cm^3). Table 1 summarizes baseline characteristics and biomarker levels.

At 2-year follow-up, the primary outcome—overt or covert stroke since baseline—occurred in 78 patients (78/1232 patients, 6.3%). Most of these strokes were covert (59/78 patients, 75.6%), that is, were detected only on follow-up MRI, not via clinical exam. An additional 10 patients (10/78 patients, 12.8%) experienced a clinically symptomatic stroke with a corresponding brain infarct; 9 patients (9/78 patients, 11.5%) experienced a clinically symptomatic stroke without any visible brain infarct. Of all new brain infarcts visible on follow-up MRI, the majority were small noncortical infarcts (38/69, 55.1%; Figure 1). The MRI field strength—1.5T or 3.0T—did not influence the detection rate of brain infarcts, neither at baseline nor at the 2-year follow-up (Tables S1 and S2).

Baseline variables are reported in Table 1. Patients with a primary outcome event were older (75.0 [SD, ±7.2] versus 71.2 [SD, ±8.4] years; $P<0.001$), more often had coronary heart disease or peripheral artery disease (43.6% versus 26.8%; $P=0.002$), and had higher CHA_2DS_2-VASc scores (4 [IQR, 3–5] versus 3 [IQR, 2–4]; $P<0.001$). There was no significant difference in the frequency of OAC intake (88.5% versus 90.0%; $P=0.52$). On baseline MRI, patients with the primary outcome had more often a brain infarct (62.8% versus 32.5%; $P<0.001$), larger white matter lesion volumes (14.8 [SD, ±18.0] versus 6.5 [SD, ±9.5] cm^3; $P<0.001$), and a higher frequency of cerebral microbleeds (36.1% versus 19.4%; $P=0.001$). All univariate comparisons of blood marker levels are reported in Table 1.

The full multivariable logistic regression model is reported in Table 2. The multivariable logistic regression model with variables selected by backward selection using the Akaike Information Criterion is reported in Table 3, by forward selection in Table S3. The following baseline variables—all log-transformed—were associated with the primary outcome in the multivariable model: white matter lesion volume in milliliters (adjusted odds ratio [aOR], 1.91 [95% CI, 1.45–2.56]), NT-proBNP (aOR, 1.75 [95% CI, 1.20–2.63]), IL (interleukin)-6 (aOR, 1.37 [95% CI, 1.00–1.86]), serum creatinine (aOR, 1.50 [95% CI, 1.02–2.22]), GDF-15 (growth differentiation factor-15; aOR, 1.68 [95% CI, 1.11–2.53]), and hFABP (heart-type fatty acid–binding protein; aOR, 0.48 [95% CI, 0.31–0.73]). Bootstrapped

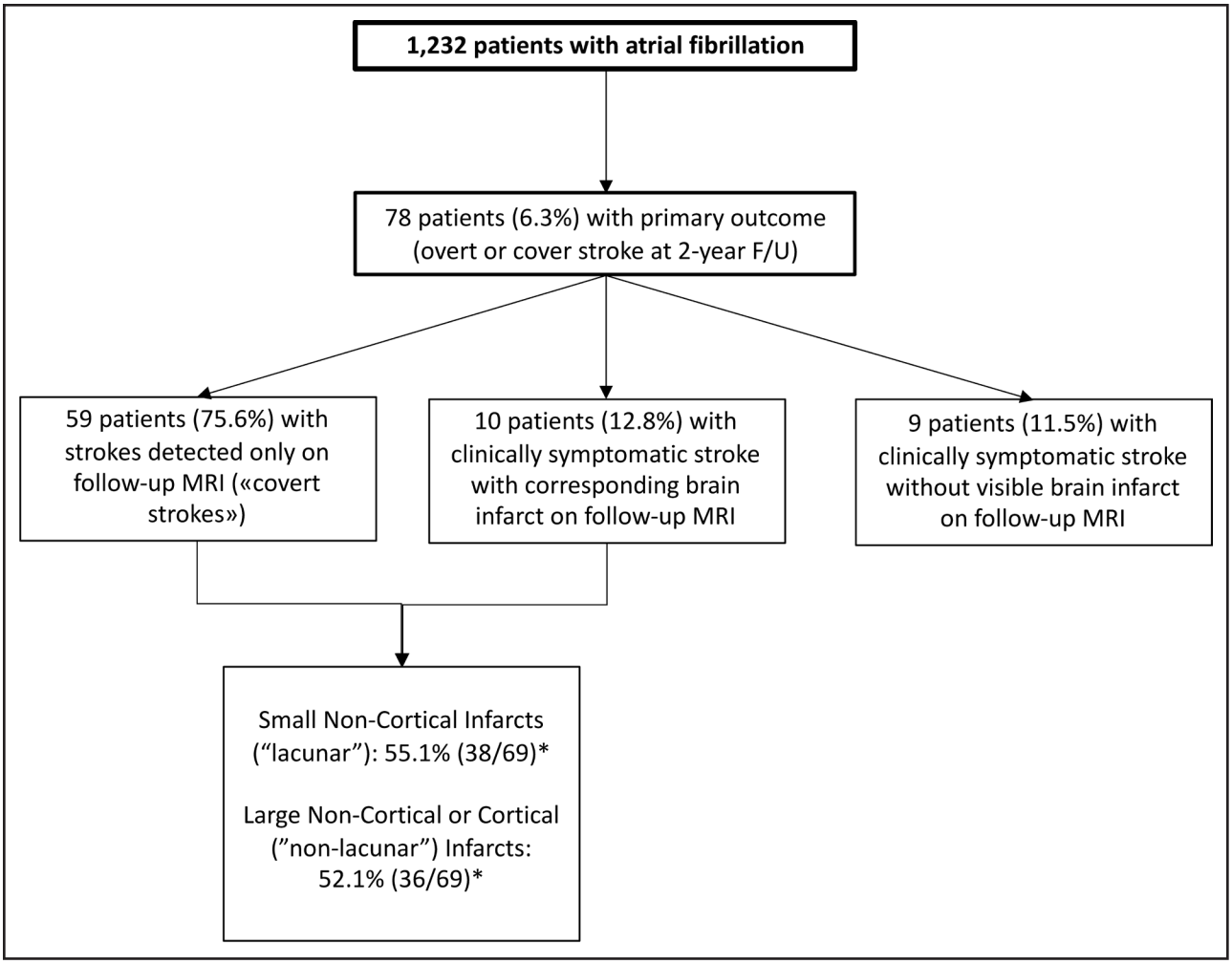

Figure 1. Primary end points.
F/U indicates follow-up; and MRI, magnetic resonance imaging. *Not mutually exclusive.

results are presented in Table S4. A sensitivity analysis with a model including the CHA_2DS_2-VASc score but not its components is presented in Tables S5 through S7 and in Figure S2. The 3 predictors that were selected most times in the refitted models were white matter lesion volume (100% times selected), hFABP (92% times selected), and N-proBNP (89% times selected). The following variables were not selected in the final backward model for the primary end point: clinical variables, baseline serum neurofilament light chain, baseline brain infarcts, or microbleeds on MRI.

Greater diagnostic performance and accuracy was seen for the multivariable model in Table 3 compared with the CHA_2DS_2-VASc score, as indicated by higher area under the receiver operating characteristic curve and a lower Brier score (area under the receiver operating characteristic curve$_{\text{multivariate model}}$, 0.82 [95% CI, 0.77–0.87]; Brier score, 0.054 versus area under the receiver operating characteristic curve$_{\text{CHA2DS2-VASc}}$, 0.64 [95% CI, 0.58–0.70]; Brier score, 0.059; Figure 2). In 5-fold internal cross-validation of the backward selected model, repeated 10×, the average area under the receiver operating characteristic curve was 0.73 (95% CI, 0.60–0.85). Plots of predicted versus observed probabilities showed good calibration for both the multivariable model and the CHA_2DS_2-VASc score (Figure 3).

DISCUSSION

In this prospective Swiss-AF cohort study, we found that the risk of stroke was increased among patients with larger volumes of white matter lesion on baseline MRI or higher baseline blood levels of NT-proBNP, IL-6, creatinine, and GDF-15. A model including these and other variables offered greater diagnostic accuracy than the CHA_2DS_2-VASc score.

Although 90% of the study participants were on OAC, the 2-year rate of clinically overt strokes was 1.5%, which is in line with the reported 2.4% rate over a median follow-up ranging between 1.8 and 2.8 years in the pivotal randomized trials testing NOACs for stroke prevention in AF.[10] The residual stroke risk suggests alternative stroke

Table 2. Multivariable Adjusted ORs for All Clinical, Biomarker, and Magnetic Resonance Imaging Predictors Plus Age at Baseline and Sex Estimated From a Logistic Regression Model for the Presence of Either Clinically Overt or Covert Stroke at 2-Year Follow-Up

	OR (95% CI)
Age at baseline, y	1.03 (0.97–1.08)
Sex (female vs male)	0.66 (0.27–1.56)
Medical history	
Congestive heart failure	0.85 (0.41–1.68)
Other cardiovascular disease (ie, coronary or peripheral artery disease)	1.38 (0.72–2.59)
Arterial hypertension (uncontrolled vs normotension)	1.16 (0.63–2.14)
Hypercholesterolemia	2.52 (0.54–10.60)
Diabetes	0.87 (0.38–1.91)
History of stroke or TIA	1.69 (0.84–3.34)
AF type (nonparoxysmal vs paroxysmal)	0.68 (0.36–1.31)
Smoking status (active smoker at baseline)	1.28 (0.36–3.86)
Type of anticoagulant (vitamin K antagonist vs none)	0.63 (0.23–1.99)
Type of anticoagulant (non–vitamin K antagonist vs none)	0.74 (0.27–2.29)
MRI findings	
Presence of LNCCI or SNCI at baseline	1.61 (0.83–3.19)
ln(volume of white matter lesions at baseline)	1.85 (1.39–2.53)
Presence of microbleeds at baseline	1.82 (0.96–3.40)
Blood biomarkers	
ln(high-sensitivity cardiac troponin T)	1.02 (0.63–1.60)
ln(NT-proBNP)	1.91 (1.15–3.29)
ln(osteopontin)	0.67 (0.38–1.16)
ln(hFABP)	0.50 (0.31–0.80)
ln(serum neurofilament light chain)	0.95 (0.70–1.42)
Non-HDL cholesterol	1.10 (0.74–1.65)
ln(high-sensitivity C-reactive protein)	0.94 (0.66–1.33)
ln(creatinine)	1.44 (0.84–2.46)
ln(cystatin C)	1.02 (0.49–2.13)
ln(GDF-15)	1.74 (1.02–2.94)
ln(IL-6)	1.45 (0.99–2.11)
ln(angiopoietin-2)	1.12 (0.72–1.74)
ln(endothelial cell–specific molecule-1)	0.85 (0.60–1.19)
ln(insulin-like growth factor–binding protein-7)	0.90 (0.55–1.48)

All variables are entered in the multivariate model. AF indicates atrial fibrillation; GDF-15, growth differentiation factor-15; HDL, high-density lipoprotein; hFABP, heart-type fatty acid–binding protein; IL-6, interleukin-6; LNCCI, large noncortical or cortical infarct; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; SNCI, small noncortical infarct; and TIA, transient ischemic attack.

mechanisms other than AF, such as cerebral small vessel disease. Two findings from our study back this thesis. First, most observed brain infarcts were unlikely to have been caused by cardiogenic embolism as they are small and restricted to the white matter (not cortical, lacunar). Second, baseline volume of white matter disease—an MR-imaging marker of small vessel disease—was significantly associated with the primary end point. In line with our findings, a report from the prospective cohort study CROMIS-2 (Clinical Relevance of Microbleeds in Stroke Study) showed that the presence and severity of small vessel disease significantly increased the risk of recurrent ischemic stroke despite OAC in patients with AF ($HR_{\text{presence of SVD}}$, 1.89 [95% CI, 1.01–3.53]; P=0.046; $HR_{\text{per point increase}}$, 1.33 [95% CI, 1.04–1.70]; P=0.023).[11] In the RENo multicenter registry (Causes and Risk Factors of Cerebral Ischemic Events in Patients With Nonvalvular AF Treated With NOACs for Stroke Prevention), the contribution of small vessel disease to recurrent ischemic stroke among patients with AF taking NOAC was 10.4%.[12] In our multivariate model, serum neurofilament light chain levels—a biomarker of axonal injury—were not associated with the primary end point, likely because of collinearity with white matter disease volume.

The association between the proinflammatory IL-6 and the primary end point suggests that inflammation contributes to incident stroke. A case-cohort study culled from the REGARDS study (Reasons for Geographic and Racial Differences in Stroke) showed that IL-6 doubled the risk of incident ischemic stroke after adjusting for cardiovascular risk factors and demographic variables ($HR_{\text{IL-6 quartile 4 versus 1}}$, 2.0 [95% CI, 1.2–3.1]).[13] A causal effect of IL-6 signaling on ischemic stroke has been strongly suggested by 2 Mendelian randomization studies. Here, genetic proxies for downregulated IL-6 signaling were associated with significant odds reduction for any ischemic stroke ranging from 2.25% to 11.0%. The ischemic stroke subtype whose risk was reduced most and consistently across both studies was small vessel stroke (odds ratio, 0.71 [95% CI, 0.59–0.86] and 0.95 [95% CI, 0.92–0.98]).[14,15] These findings support that IL-6 signaling blockade may represent a potential therapeutic target to reduce the risk of ischemic stroke. Supporting this view, a secondary analysis from CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) demonstrated that the cardiovascular preventive benefit of IL-1β inhibition was associated with the reduction of IL-6 levels; residual cardiovascular risk was proportional to IL-6 levels after treatment.[16]

Higher creatinine levels were associated with a higher risk of overt and covert stroke. An association between renal impairment and different MRI markers of small vessel disease was detected in a meta-analysis of 17 studies of patients without stroke (odds ratio, 2.33 [95% CI, 1.80–3.01]). Renal impairment was associated with covert brain infarcts (odds ratio, 2.44 [95% CI, 1.59–3.74]).[17] Because higher creatinine remained significantly associated with the primary end point even after adjusting for the volume of white matter disease, pathways other than white matter disease are likely to link renal impairment to the primary end point. Proposed underlying mechanisms beyond shared established traditional risk factors include uremia-related nontraditional

Table 3. ORs for the Clinical, Biomarker, and MRI Predictors Selected by Backward Selection Using Akaike Information Criterion Estimated From a Logistic Regression Model for the Presence of Either Clinically Overt or Covert Stroke at 2-Year Follow-Up

	OR (95% CI)
Hypercholesterolemia	2.92 (0.91–8.03)
History of stroke or TIA	1.68 (0.87–3.19)
ln(NT-proBNP)	1.75 (1.20–2.63)
ln(osteopontin)	0.68 (0.43–1.05)
ln(hFABP)	0.48 (0.31–0.73)
ln(creatinine)	1.50 (1.02–2.22)
ln(GDF-15)	1.68 (1.11–2.53)
ln(IL-6)	1.37 (1.00–1.86)
Presence of LNCCI or SNCI at baseline	1.70 (0.88–3.32)
ln(volume of white matter lesion at baseline)	1.91 (1.45–2.56)
Presence of microbleeds at baseline	1.70 (0.92–3.09)

GDF-15 indicates growth differentiation factor-15; hFABP, heart-type fatty acid–binding protein; IL-6, interleukin-6; LNCCI, large noncortical or cortical infarct; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; SNCI, small noncortical infarct; and TIA, transient ischemic attack.

risk factors, such as oxidative stress, and dialysis-specific factors, such as cerebral hypoperfusion.[18]

The association between NT-proBNP and the primary end point is in line with a study with 1172 patients with AF under oral anticoagulation and international normalized ratio between 2.0 and 3.0, where—over a median follow-up of 2.76 years—NT-proBNP was associated with the risk of stroke (adjusted hazard ratio, 2.71 [95% CI, 1.54–4.75]).[19] The link between NT-proBNP levels and stroke was corroborated by secondary analyses from RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) and ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation).[20,21] Among 1759 patients with ischemic stroke, higher midregional pro-atrial natriuretic peptide (MR-proANP) levels were associated with newly detected AF, AF burden, and recurrent ischemic stroke over 1-year follow-up as shown in the multicenter BIOSIGNAL study (Biomarker Signature of Stroke Aetiology).[22] Thus, among patients with AF, both NT-proBNP and MR-proANP (the latter in patients with a history of stroke) may help identifying patients at higher residual risk of stroke despite OAC.

GDF-15 is a stress-induced cytokine and a marker of oxidative stress and inflammation, expressed in different organs including the brain.[23] Our observed association between GDF-15 and incident stroke confirms and expands published data. In a prospective study with 3562 outpatients, higher GDF-15 blood concentrations were associated with a higher stroke risk over a follow-up of 6.6 years. The association remained significant after adjusting for NT-proBNP and high-sensitivity cardiac troponin T (hs-TnT). AF was,

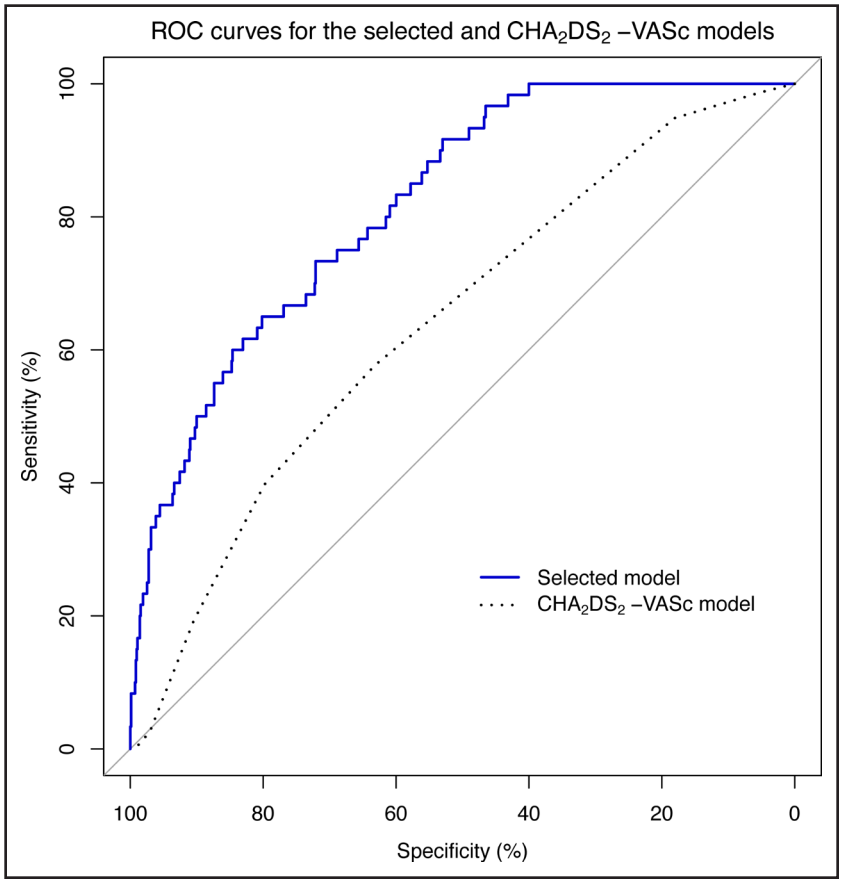

Figure 2. Receiver operating characteristic (ROC) curves for the full clinical–magnetic resonance imaging–biomarker backward selected model compared with the CHA_2DS_2-VASc score for the primary end point.
The area under the curve of the selected model is 0.82 (95% CI, 0.77–0.87) and that of the CHA_2DS_2-VASc score is 0.64 (95% CI, 0.58–0.70).

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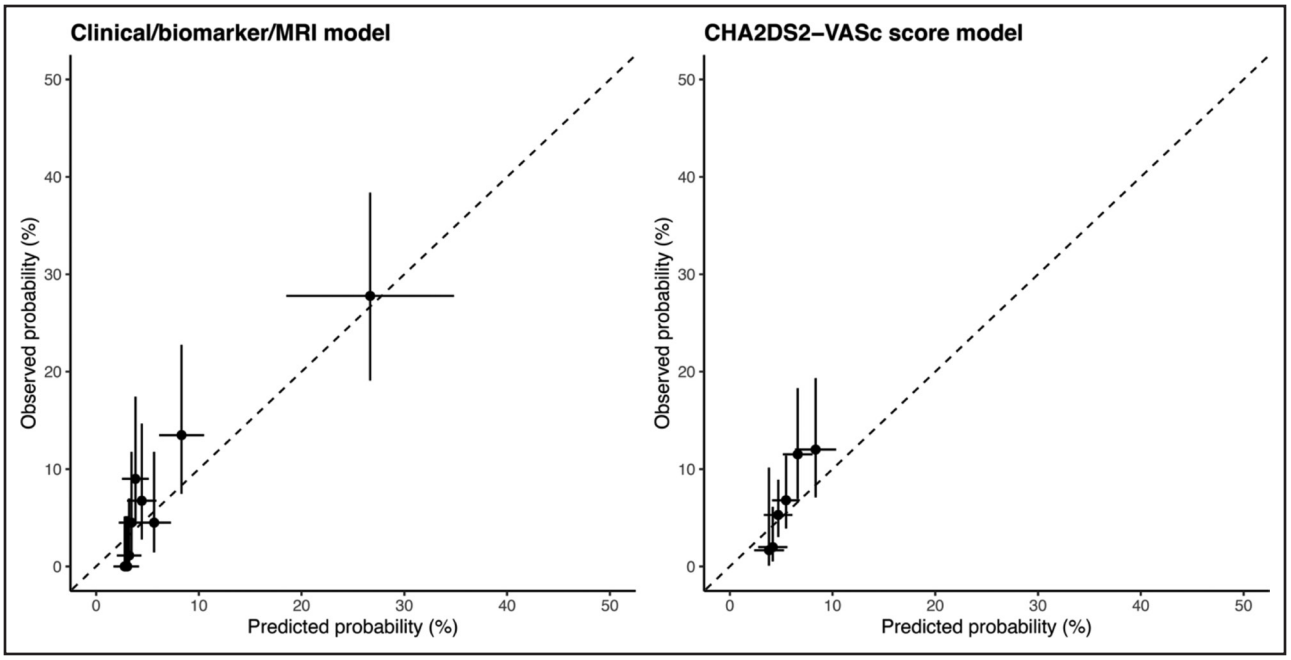

Figure 3. Observed vs predicted rates of the primary end point for the backward selected logistic regression model and the CHA_2DS_2-VASc score.

Each point represents a decile of predicted probabilities. The vertical and horizontal lines span the CI for the observed and predicted probabilities, respectively. The dashed line represents perfect agreement of observations and predictions. MRI indicates magnetic resonance imaging.

however, rare in this cohort (3.8%).[24] In the ARISTOTLE trial, all patients had AF and were taking OACs. GDF-15 was associated with stroke incidence over a median follow-up of 1.9 years. As opposed to our study—after adjusting for NT-proBNP and cardiac troponin—GDF-15 was not significantly associated with stroke anymore. Differently from our study, ARISTOTLE assessed strokes that were clinically overt, as reflected in the lower stroke rate (1.9% versus 3.15% per year in our cohort), reducing statistical power in ARISTOTLE to detect an association after adjusting for cardiac biomarkers.[23] Moreover, in our study, most incident strokes were subcortical: rather than cardioembolism, microangiopathy was likely the stroke pathogenesis. GDF-15 was associated with white matter hyperintensity volumes in the Framingham Offspring Study.[25]

Higher levels of hFABP were associated with a lower risk of the primary end point in our study. This finding was unexpected, as higher levels of hFABP—a blood marker of myocardial injury—were associated with higher odds of detecting covert brain infarcts at baseline in the same cohort.[8] The reasons for this discrepancy remain unclear, and we cannot rule out a chance finding.

Three-fourths of primary end point events were covert, that is, were not detected clinically but on follow-up MRI only. Since covert brain infarcts contribute to cognitive decline, strategies reducing the residual ischemic risk are likely not only to reduce clinically overt stroke but also to preserve cognitive function.[6]

The discriminatory ability of the CHA_2DS_2-VASc score observed in this study for new brain infarcts at 2 years was higher than for brain infarcts on baseline MRI reported previously (0.64 [95% CI, 0.58–0.70] versus 0.60 [95% CI, 0.56–0.65], respectively).[8]

Strengths of our study are the prospective design with inclusion of a large, well-characterized cohort of patients with established AF, undergoing brain MRI at baseline and at 2 years. We acknowledge limitations. First, there is the inevitable selection bias of patients able to undergo a brain MRI. Second, the rate of primary end point events is relatively low, which limits statistical power. To assess the risk of model overfitting, we fitted multivariate models with forward selection and bootstrapped the results; the results substantially overlap with those of the backward selection model, mitigating the concern of overfitting. Third, on MRI, we did not assess basal ganglia perivascular spaces, one of the MRI markers of small vessel disease. Fourth, the study lacked a control group with people having similar comorbidities but without AF, making it difficult to estimate what proportion of the observed stroke end points can be attributed to AF itself. In a recent cohort study of patients with AF experiencing ischemic stroke despite OAC, stroke etiologies other than cardioembolism were observed in 24% of patients, the most common competing mechanism being large artery atherosclerosis followed by small vessel disease.[26] Finally, since other ethnic groups—such as Asians—tend to have a higher incidence of both ischemic and hemorrhagic stroke than White Europeans,[27] ethnical diversity in the study cohort would have increased the generalizability of the results.

In conclusion, despite OAC, there is still a relevant residual risk of overt and covert strokes in mostly anticoagulated patients with AF. Independent factors contributing to this risk are the volume of white matter disease, inflammation, renal impairment, and residual cardioembolism. Development of pharmacological and nonpharmacological strategies to address these factors may reduce the risk of stroke beyond OAC and control of traditional risk factors alone.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7
Figures S1–S2

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