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Letter to the Editor

# Biomarkers, Clinical Variables, and the $CHA_2DS_2$-VASc Score to Detect Silent Brain Infarcts in Atrial Fibrillation Patients

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## Dear Sir:

Silent brain infarcts are associated with cognitive dysfunction similar to overt strokes in af (AF) patients.[1] Brain magnetic resonance imaging (bMRI) is needed to detect silent infarcts and initiate secondary prevention, but is unfeasible in all patients. We therefore investigated the associations of biomarkers, clinical variables and the $CHA_2DS_2$-VASc score with silent brain infarcts to non-invasively identify high-risk patients.

The Swiss Atrial Fibrillation (Swiss-AF) cohort is a prospective, multicenter study, that enrolled patients with previously documented AF and age ≥65 years (subset aged 45 to 65 years was included).[1] The study complies with the Declaration of Helsinki, the study protocol was approved by the local ethics committees (approval number 2014-067) and informed written consent was obtained from each participant. Of 2,415 enrolled patients, we excluded 479 (19.8%) with a history of stroke or transient ischemic attack (TIA) to analyze only silent brain infarcts, 658 (27.2%) without standardized bMRI and 381 (15.8%) without complete biomarker assessment, leaving 1,140 patients. Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA) (maximum score 30 points, higher scores indicating better cognition, one point was added if formal education ≤12 years).[2] A 12-lead electrocardiogram (ECG) was performed at enrolment. Details on biomarker selection are provided in the Supplementary material.[3-12] Large non-cortical infarcts were defined as hyperintense lesions on fluid attenuated inversion recovery (FLAIR) >20 mm in diameter on axial sections without cortical involvement. Cortical infarcts as hyperintense lesions of any size on FLAIR involving the cortex. Large non-cortical and any cortical infarct (LNCCIs) were combined into one category and chosen as the primary outcome as LNCCI were the only brain lesions independently associated with cognitive dysfunction.[1]

Biomarkers and LNCCI volumes were log-transformed. To investigate associations of biomarkers with LNCCI presence and volume, we standardized (z-score) all biomarkers in crude, age/sex-adjusted and multivariable (adjusted for prespecified vari-

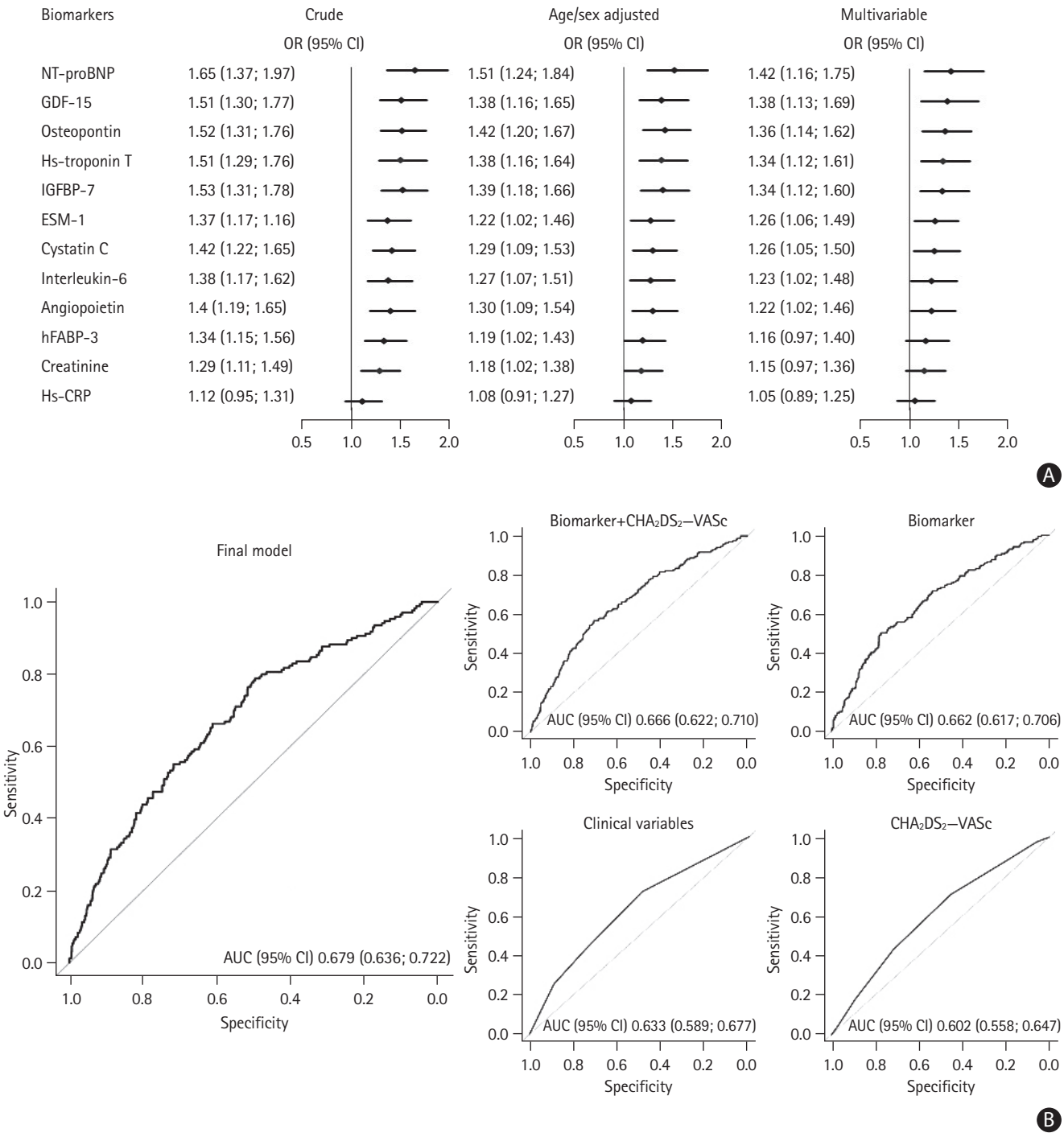


**Figure 1.** (A) Separate logistic regression models for the relations of biomarker and large non-cortical and any cortical infarct (LNCCI). (B) Area under the curve (AUC) to diagnose LNCCI for different models. OR, odd ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; GDF-15, growth differentiation factor-15; IGFBP-7, insulin-like growth factor-binding protein-7; ESM-1, endothelial cell-specific molecule-1; hFABP-3, heart fatty-acid-binding protein-3; hs-CRP, high-sensitivity C-reactive protein.

ables) models. To maximize the area under the curve (AUC) for diagnosing silent LNCCIs, a biomarker combination was selected by backward selection from a model containing all biomarkers and the $CHA_2DS_2$-VASc score as a continuous variable. Similar backward selection was repeated for clinical variables and a combination of clinical variables and biomarkers. Clinical variables included sex, age, body mass index, active smoking, arterial hypertension, prior heart failure, diabetes, vascular disease, and presence of AF on a 12-lead ECG. We then compared the AUCs of the biomarkers, the $CHA_2DS_2$-VASc score, the clini-


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cal variables, and their combinations. The final model with the highest AUC, a combination of biomarker and clinical variables, was internally validated based on 1,000 simulations using bootstrap with replacement. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) or R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) (registration-URL: http://www.clinicaltrials.gov; unique identifier: NCT02105844).

Mean±standard deviation age was 72.1±8.7 years, 836 (73.3%) patients were male and 445 (45.9%) had paroxysmal AF. LNCCI were present in 170 (14.9%) patients and median volume was 492 $mm^3$ (interquartile range [IQR], 144 to 3,510). All biomarkers except for creatinine, high-sensitivity C-reactive protein, and heart fatty-acid-binding protein-3 (hFABP-3) were individually associated with present LNCCI (Figure 1A). Levels of hs-troponinT (β=0.33; 95% confidence interval [CI], 0.02 to 0.64; *P*=0.04) and angiopoietin-2 (β=0.33; 95% CI, 0.03 to 0.63; *P*=0.03) were also associated with LNCCI volumes.

AUCs for all different models are shown in Figure 1B (details in Supplementary material). The combination of hs-troponinT, osteopontin, hFABP-3, vascular disease, and AF on the ECG had the highest AUC of 0.679 (95% CI, 0.636 to 0.722) for LNCCI and was therefore selected as the final model. Individual odds ratios (ORs) were 1.31 (95% CI, 1.06 to 1.62; *P*=0.01 for hs-troponinT), 1.38 (95% CI, 1.12 to 1.70; *P*=0.002 for osteopontin), 0.82 (95% CI, 0.65 to 1.04; *P*=0.10 for hFABP-3), 1.76 (95% CI, 1.24 to 2.51; *P*=0.002 for vascular disease), and 1.64 (95% CI, 1.16 to 2.32; *P*=0.005 for AF on the ECG). Internal validation showed an AUC of 0.662 (IQR, 0.643 to 0.682).

The AUC for vascular disease and AF on the ECG alone was 0.633 (95% CI, 0.589 to 0.677; *P*=0.001 compared to the final model) and their respective ORs were 2.10 (95% CI, 1.50 to 2.96; *P*<0.0001) and 1.95 (95% CI, 1.40 to 2.72; *P*<0.0001). The biomarker combination of hs-troponinT, N-terminal pro-B-type natriuretic peptide (NT-proBNP), osteopontin, and hFABP-3 had an AUC of 0.662 (95% CI, 0.617 to 0.706; *P*=0.16 compared to the final model), without any significant improvement by adding the $CHA_2DS_2$-VASc score. Individual ORs were 1.33 (95% CI, 1.07 to 1.64; *P*=0.009 for hs-troponinT), 1.34 (95% CI, 1.08 to 1.66; *P*=0.008 for NT-proBNP), 1.34 (95% CI, 1.08 to 1.66; *P*=0.007 for osteopontin), and 0.80 (95% CI, 0.63 to 1.02; *P*=0.07 for hFABP-3). The AUC and OR for the $CHA_2DS_2$-VASc score alone were 0.602 (95% CI, 0.558 to 0.647; *P*=0.0002 compared to the final model) and 1.28 (95% CI, 1.14 to 1.44; *P*<0.0001), respectively.

Risk quartiles based on the final model showed increasing LNCCI prevalence from 7.4%, 8.8%; 16.8% to 26.7% and decreasing MoCA scores from 26.3, 26.3; 25.3 to 24.8 points over increasing quartiles (*P*<0.0001 for both).

We comprehensively assessed the associations of clinical parameters, biomarkers, and the $CHA_2DS_2$-VASc score with silent brain infarcts. Approximately one out of four AF patients in the highest risk quartile, based on the final model, had a silent brain infarct. Thus, our risk model identifies a high-risk population for bMRI screening. Once silent brain lesions are confirmed, these patients might benefit from initiation or adjustment of anticoagulation, reduction in AF-burden,[13] and treatment of traditional stroke risk factors.[14] Randomized trials are needed to establish the impact of those interventions on cognitive decline related to silent infarcts. Strengths of our study include the large sample size, a wide biomarker array and detailed patient characterization. Limitations are unclear generalizability to patients with transient AF forms, cardiac devices and a history of stroke/TIA.

In conclusion, the combination of hs-troponinT, osteopontin, hFABP-3, vascular disease, and AF on the ECG had the highest discriminatory ability to diagnose clinically silent LNCCIs.

## Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2021.02068.

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# Supplementary material

## Biomarker assessment

Biomarkers were selected based on biological plausibility, prior literature and availability. We included biomarkers of inflammation and oxidative stress,[3-5] myocardial injury and strain,[5-8] vascular damage,[9,10] renal dysfunction,[11] and cerebral damage.[12]

C-reactive protein (CRP) and interleukin-6 were both positively associated with an inflammatory, prothrombotic state and CRP was additionally shown to directly related to stroke risk.[3,4] Growth differentiation factor-15 was associated with stroke-related death among with troponinT and N-terminal prohormone of brain natriuretic peptide (NT-proBNP).[5,6] Moreover, NT-proBNP is released into the serum after acute ischaemic stroke, as are heart-fatty acid binding proteins (hFABPs).[8] As a marker for left atrial dilatation, insulin-like growth factor-binding protein-7 (IGFBP-7) was shown to be positively associated with left atrial size.[7] Renal markers were included, as renal insufficiency is known to influence the efficacy of anticoagulants in atrial fibrillation patients.[11] As vascular markers, angiopoietin-2 was shown to be upregulated after cerebral artery occlusion in an experimental model and endothelial cell-specific molecule-1 (ESM-1) plays a crucial role in vascular permeability after ischemic stroke.[9,10] Osteopontin acts as a direct marker of cerebral damage after ischemic stroke and was therefore also included in our analyses.[12]

## Detailed description for Figure 1B

Receiver operating curves are displayed, showing the accuracy of the models to diagnose large non-cortical and cortical infarcts. Final model (area under the curve [AUC], 0.679; 95% confidence interval [CI], 0.636 to 0.722) includes hs-troponin T, osteopontin, heart fatty-acid binding protein 3, vascular disease, and atrial fibrillation on the electrocardiogram (ECG). Biomarker model (AUC, 0.662; 95% CI, 0.617 to 0.706; $P$=0.16 compared to the final model) includes hs-troponin T, NT-proBNP, heart fatty-acid binding protein 3, and osteopontin. The addition of the $CHA_2DS_2$-VASc score to the biomarker combination did not improve the AUC of 0.666 (95% CI, 0.622 to 0.710; $P$=0.29 compared to the final model). Clinical variables (AUC, 0.633; 95% CI, 0.589 to 0.677; $P$=0.001 compared to the final model) include vascular disease and atrial fibrillation on the ECG. The CHA2DS2-VASc score alone had an AUC of 0.602 (95% CI, 0.558 to 0.647; $P$=0.0002 compared to the final model).


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