Supplementary methods

Study population

The Swiss Atrial Fibrillation (Swiss-AF) study is a prospective cohort study which has enrolled 2,415 participants with established atrial fibrillation (AF) in 14 centers in Switzerland. The detailed study design and first results have been reported previously.[3,5] Included patients were ≥65 years old and had either paroxysmal AF defined as: self-terminating AF lasting <7 days that does not require cardioversion and that was documented at least twice within the last 60 months; persistent AF defined as AF sustained ≥7 days and/or re-quiring cardioversion, documented within the last 60 months; or permanent AF. Additionally, a smaller group of patients between 45 and 65 years of age was included to assess the effects of AF on actively employed individuals. Patients with a secondary form of AF or unable to provide informed consent were excluded.

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the local ethics committees (Ethikkommission Nordwest- und Zentralschweiz), and written informed consent was obtained from all participants (Trial Registration: ClinicalTrials.gov Identifier, NCT02105844).

Image acquisition

Baseline brain magnetic resonance imaging (MRI) was acquired on either a 1.5 or a 3.0 Tesla scanner, depending on the participating site. The standardized protocol has been described in detail previously.[3,5] Of relevance for the present study, 3D T1-weighted (T1w) magnetization prepared rapid gradient echo (MPRAGE; spatial resolution 1.0×1.0×1.0 mm^3), and 2D axial T2-weighted fluid attenuated inversion recovery (FLAIR; spatial resolution 1.0×1.0×3.0 mm^3) sequences. Out of the 2,415 patients enrolled in Swiss-AF, complete baseline MRI was available in 1,748 patients. The most frequent reason for missing MRI was the presence of an implanted cardiac device (n=461, 69%).

Lesion segmentation

Lesion segmentation was performed on FLAIR images by professional medical image analysts at the Medical Image Analysis Center (MIAC AG, Basel, Switzerland), blinded to clinical and other information, according to in-house standard operating procedures approved for international clinical phase III trials.[6] Board certified neuroradiologists confirmed all ratings. Lesions were classified into large non-cortical or cortical infarcts (LNCCIs) and small non-cortical infarcts (SNCIs). LNCCIs were considered infarcts of potentially embolic origin and included (1) large non-cortical infarcts with a diameter of >20 mm, and (2) cortical infarcts defined as hyperintense lesions on FLAIR involving the cortex irrespective of their size. SNCIs were defined as hyperintense lesions on FLAIR ≤20 mm in diameter assessed on axial sections and not involving the cortex.[7]

Image registration

To prepare images for image co-registration, the patients' brain data were first extracted from the T1w images using FreeSurfer v6.0 (binarization of 'aseg.auto' output from 'recon-all' pipeline; https://surfer.nmr.mgh.harvard.edu/fswiki). Resulting brain masks were dilated slice-by-slice by two voxels since less restrictive brain extraction yielded better results in the later registration. Secondly, corresponding T2w FLAIR white matter hyperintense lesions and LNCCIs were filled on T1w images to minimize their effect on image registration. This was done using the lesion filling algorithm encoded in FSL[5] and masking of the lesion portions in the grey matter.

For image registration (FSL v5.0, FMRIB's Software Library; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki), FLAIR images were first linearly registered to T1w images using FSL (FMRIB's linear registration tool, FLIRT; using defaults settings, 6 degrees of freedom).[8,9] The transformation parameters resulting from this image registration were then applied to the SNCI and LNCCI lesion masks (FLAIR image contrast) using a nearest-neighbor interpolation. At this step, the skull was removed from the FLAIR-to-T1w images using the previously prepared brain masks. Then, FLAIR-to-T1w images were non-linearly registered to an age-specific standard brain template from the BRAINS image bank (https://www.brainsimagebank.ac.uk/; for brains early to mid-seventies; spatial resolution 1.0×1.3×1.0 mm^3) using FSL (FMRIB's non-linear registration tool, FNIRT; settings as specified in the provided configuration file, taking as reference the age-specific brain template).[10] The resulting transformation parameters were then applied to the transformed FLAIR-to-T1w lesion masks again using nearest-neighbor interpolation. The quality assessment of the registration was done by trained and experienced raters. If images showed strong distortions in the registered images, patients were excluded from subsequent analyses. At image registration, 32 patients were excluded, leaving 1,716 patients (98%) for the present analyses.

Spatial lesion distribution and mapping onto vascular territories

The co-registered LNCCI and SNCI lesion masks were overlaid on the age-specific brain template to generate voxel-based le-

sion probability maps. Lesion masks were then projected onto the co-registered MNI Vascular Territories Atlas.[11] Number and volume of lesions within anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories, were computed. Moreover, the percentages of vascular territories affected by LNCCIs or SNCIs (i.e., percentage overlay) were calculated.

Statistical analyses

Infarct counts, volumes, and percentages were reported. We tested if these measures differed within vascular territories of left and right brain hemispheres. The Wilcoxon matched-pair rank test was used to compare median differences of infarct counts, volumes, and percentages within ACA, MCA, and PCA. Only patients having an infarct in this specific vascular territory—either in the left or the right hemisphere—were considered. No correction of *P*-values for multiple testing was performed due to the exploratory nature of the analysis. All statistical analyses were done in R version 3.6.3. (https://www.r-project.org/).

Data availability statement

The patient informed consent forms, as approved by the responsible ethics committee, do not allow the data to be made publicly available. The participants signed a consent form, which states that their data, containing personal and medical information, are exclusively available for research institutions in an anonymized form. Researchers interested in obtaining the data for research purposes can contact the Swiss-AF scientific lead. Contact information is provided on the Swiss-AF website (http://www.swissaf.ch/contact.htm). Authorization of the responsible ethics committee is mandatory before the requested data can be transferred to external research institutions.

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