# Hypertension

## WHITE MATTER LESIONS

# Blood Pressure and Brain Lesions in Patients With Atrial Fibrillation

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**ABSTRACT:** The association of blood pressure (BP) and hypertension with the presence of different types of brain lesions in patients with atrial fibrillation is unclear. BP values were obtained in a multicenter cohort of patients with atrial fibrillation. Systolic and diastolic BP was categorized in predefined groups. All patients underwent brain magnetic resonance imaging and neurocognitive testing. Brain lesions were classified as large noncortical or cortical infarcts, small noncortical infarcts, microbleeds, or white matter lesions. White matter lesions were graded according to the Fazekas scale. Overall, 1738 patients with atrial fibrillation were enrolled in this cross-sectional analysis (mean age, 73 years, 73% males). Mean BP was 135/79 mm Hg, and 67% of participants were taking BP-lowering treatment. White matter lesions Fazekas ≥2 were found in 54%, large noncortical or cortical infarcts in 22%, small noncortical infarcts in 21%, and microbleeds in 22% of patients, respectively. Compared with patients with systolic BP <120 mm Hg, the adjusted odds ratios (95% CI) for Fazekas≥2 was 1.25 (0.94–1.66), 1.41 (1.03–1.93), and 2.54 (1.65–3.95) among patients with systolic BP of 120 to 140, 140 to 160, and ≥160 mm Hg (P for linear trend<0.001). Per 5 mm Hg increase in systolic and diastolic BP, the adjusted β-coefficient (95% CI) for log-transformed white matter lesions was 0.04 (0.02–0.05), P<0.001 and 0.04 (0.01–0.06), P=0.004. Systolic BP was associated with small noncortical infarcts (odds ratios [95% CI] per 5 mm Hg 1.05 [1.01–1.08], P=0.006), microbleeds were associated with hypertension, but large noncortical or cortical infarcts were not associated with BP or hypertension. After multivariable adjustment, BP and hypertension were not associated with neurocognitive function. Among patients with atrial fibrillation, BP is strongly associated with the presence and extent of white matter lesions, but there is no association with large noncortical or cortical infarcts.

Hypertension is one of the most important cardiovascular risk factors and strongly associated with major cardiovascular events, such as atrial fibrillation (AF), congestive heart failure, myocardial infarction, and stroke.[1–4] AF and hypertension often coexist and the prevalence of both conditions is expected to increase in the future.[5,6] AF is a risk factor of cognitive impairment and dementia, independent of clinical stroke.[7,8] AF may contribute to vascular dementia either by causing embolic strokes or via shared risk factors for small vessel disease, such as hypertension or diabetes. However, the relationship of hypertension with various types of brain lesions observed in patients with AF is poorly understood.

Brain parenchymal damage, especially white matter lesions (WML), is frequently detected on brain magnetic resonance imaging (bMRI), mainly in elderly individuals.

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## Novelty and Significance

### What Is New?

- Blood pressure (BP) and hypertension are associated with white matter lesions but not with large noncortical or cortical infarcts in patients with atrial fibrillation (AF).
- BP and hypertension are not associated with neurocognitive function after multivariable adjustment.

### What Is Relevant?

- Optimal BP control is important to potentially prevent brain lesions in patients with atrial fibrillation.

### Summary

Among patients with atrial fibrillation, BP is strongly associated with the presence and extent of white matter lesions, but there is no association with large noncortical or cortical infarcts. Whether more aggressive BP control may prevent different types of brain lesions in patients with atrial fibrillation has to be investigated.

## Nonstandard Abbreviation and Acronyms

| | |
|---|---|
| **AF** | atrial fibrillation |
| **bMRI** | brain magnetic resonance imaging |
| **BP** | blood pressure |
| **LNCCI** | large noncortical or cortical infarcts |
| **MoCA** | Montreal Cognitive Assessment |
| **SNCI** | small noncortical infarcts |
| **Swiss-AF** | Swiss Atrial Fibrillation Cohort Study |
| **WML** | white matter lesions |

The prevalence and volume of different clinical and subclinical brain lesions has been reported to be significant both in patients with and without AF.[9–11] In the general population, increased blood pressure (BP) was associated with the occurrence and the progression of WML.[12–14] In elderly individuals, hypertension was not only associated with WML, but also with MRI-detected subclinical brain infarcts.[10] In a small study of patients with lacunar strokes, a positive association was found between ambulatory BP and cerebral microbleeds.[15] Although smaller studies exist in different patient groups without AF,[10,12–15] the association between BP and clinical and subclinical brain lesions has never been investigated thoroughly in patients with AF. Whether hypertensive patients with AF show a different pattern of brain lesions compared to normotensive patients with AF is unknown. The generalizability of the current evidence in general populations to patients with AF is not clear and patients with AF might have a different susceptibility for brain lesions due to several reasons. First, patients with AF often suffer from multiple comorbidities and have a high risk of brain lesions due to AF and other cardiovascular comorbidities. Second, AF per se might be a risk modifier regarding BP-related brain lesions for example due to high beat-to-beat BP variability or cerebral hypoperfusion. In addition, the majority of patients with AF are on oral anticoagulation for stroke prevention. However, its effect on the association between BP and brain lesions is unknown. Finally, the shape of the association between BP and brain lesions in patients with AF is unclear. Therefore, the aim of this analysis was to investigate brain lesion types according to BP and BP control in an unselected cohort of patients with AF.

## METHODS

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

Data of the ongoing, prospective, observational, multicenter Swiss-AF (Swiss Atrial Fibrillation Cohort Study) were used for this cross-sectional analysis. The study design of the Swiss-AF study was published previously.[16] In brief, patients ≥65 years with documented AF were enrolled in 14 study centers in Switzerland between 2014 and 2017. A group of 250 patients with AF <65 years were enrolled, as indicated in the study protocol. Exclusion criteria were short episodes of AF (eg, after cardiac surgery, or severe sepsis), any acute illness within the past 4 weeks, or inability to sign the informed consent. The study protocol was approved by the local Ethics committee. Written informed consent was obtained from all patients and the study was conducted in accordance with the Helsinki declaration.

Of 2415 patients enrolled in this study, 667 patients had to be excluded due to missing bMRI (mainly due to the presence of a cardiac device or claustrophobia), 5 patients due to a missing MRI sequence (fluid-attenuated inversion recovery), and 5 patients due to missing BP measurement, resulting in the 1738 patients used for this analysis.

### BP and Hypertension

Systolic and diastolic BP was measured 3× in a supine position after 5 minutes of rest using a validated device. For this analysis, the mean of all available BP measurements was used. If only 2 or 1 BP measurements were available, we used the mean of 2 or even a single measurement (n=2 with 2 and n=4 with only one BP measurement). Hypertension was defined according to current guidelines,[17,18] and all definitions are presented in Table S1 in the Data Supplement.

## Other Study Variables

Information on cardiovascular risk factors, lifestyle factors, medical history, and medication was assessed using standardized questionnaires. Weight and height were taken and body mass index was calculated as the ratio of the weight in kg and the height in m$^2$. Smoking status was categorized into current, former, or never smoking. Educational status was classified according to the highest degree achieved. To assess neurocognitive function, the Montreal Cognitive Assessment (MoCA) score, the Trail Making Test (part A and B), the Semantic Fluency Test, and the Digit Symbol Substitution Test were performed in all patients. In brief, the validated MoCA score is scaled from 0 (worse) to 30 (best) and is representing global cognitive functioning. Patients with <12 years of education receive an additional point if they have <30 points. Details regarding the methodology of the other cognitive tests are presented in Table S2.[19–24]

## Brain Magnetic Resonance Imaging

A bMRI without application of contrast agents was obtained according to a standardized protocol in all eligible study patients. The standardized protocol included a sagittal 3-dimensional T-weighted magnetization-prepared rapid gradient echo (spatial resolution 1.0×1.0×3.0 mm$^3$), an axial 2-dimensional fluid-attenuated inversion recovery (spatial resolution 1.0×1.0×3.0 mm$^3$), and an axial 2-dimensional diffusion-weighted imaging (spatial resolution 1.0×1.0×3.0 mm$^3$) sequence with whole-brain coverage, no gaps and without interpolation. All bMRI data were sent to and analyzed in a specialized imaging core laboratory (Medical Imaging Analysis Center AG, Basel, Switzerland). The scans were analyzed by blinded expert raters. Brain lesions were marked and segmented in a standardized fashion using an in-house procedure approved for international clinical studies. Board-certified neuroradiologists confirmed all ratings.

The Fazekas scale was used to grade hyperintense white matter lesions. A score of ≥2 in either the periventricular or the deep white matter was defined as at least moderate disease.[25] Ischemic brain lesions were classified as large noncortical or cortical infarcts (LNCCI) or small noncortical infarcts (SNCI). Large noncortical infarcts are defined as noncortical infarcts >20 mm. Cortical infarcts are defined as hyperintense lesions on fluid-attenuated inversion recovery involving the cortex independent of the size of the lesion. Both lesion types in combination are defined as LNCCI. SNCIs are defined as noncortical infarcts<20 mm.[26] The cause of LNCCI and SNCI cannot be proven based on the bMRI. However, in general, LNCCIs might represent embolic lesions, whereas SNCI might correspond to microvascular brain damage. Microbleeds were identified and counted as nodular, hypointense lesion on either T2*-weighted or susceptibility-weighted imaging.

## Statistical Analysis

Baseline characteristics were stratified by groups of systolic BP (<120, 120−140, 140−160, and ≥160 mm Hg) and hypertension categories (normotension, controlled hypertension, and uncontrolled hypertension). Continuous data are presented as mean±SD or median (interquartile range) and categorical data as numbers (percentages). Continuous and categorical data were compared across categories using ANOVA, Kruskal-Wallis tests or χ$^2$ tests, as appropriate.

To assess the associations of BP and hypertension with the prevalence of vascular brain lesions, multivariable-adjusted logistic regression analyses were performed using the presence of Fazekas score ≥2, LNCCI, SNCI, or microbleeds as the outcome variable. In a second step, the association of BP and hypertension with the volume of brain lesions was calculated using multivariable-adjusted linear regression analysis. Due to the skewed distribution, the volumes of the respective brain lesions were log-transformed. Results are presented as odds ratios (OR) or β-coefficients with the corresponding 95% CI, and 2-sided P-values were calculated. The volume of microbleeds was not quantified due to an expected blooming effect of the volume when using the current methods. All regression analyses were adjusted for age and sex. A second model was additionally adjusted for educational status, body mass index, smoking status, diabetes, history of stroke, history of heart failure, and history of coronary heart disease, AF type, oral anticoagulation, and antithrombotic treatment. When using BP as the predicting variable, we additionally adjusted the models for antihypertensive treatment (yes/no).

The association of BP and hypertension with the MoCA score and the other neurocognitive tests was calculated using multivariable-adjusted linear regression models. Subgroup analysis for the presence or absence of the respective brain lesion was done for the association of BP or hypertension with the MoCA score. The model was adjusted as described above. We tested interacting effects of lesion presence and BP or hypertension by including the respective interaction terms in the models.

P values were not corrected for multiple comparisons due to the exploratory nature of this analysis. All analyses were performed with R version 3.5.2 (2018-12-20; R Core Team, 2019).

# RESULTS

## Baseline Characteristics

Baseline characteristics stratified by systolic BP categories and hypertension are presented in Table 1 and Table S3, respectively. The mean age of the population was 73±8 years, and 73% were male. Mean SBP and DBP were 135±19 and 79±12 mm Hg, respectively, and 1158 (67%) patients were on antihypertensive treatment. A history of stroke was present in 230 (13%) patients. Across increasing systolic BP categories, patients were older, more often female, and had a higher CHA$_2$DS$_2$-VASc score. The prevalence of recurrent falls across systolic BP categories was not different, even when looking at patients with low systolic BP (Table 1 and Table S4). Normotension, controlled hypertension and uncontrolled hypertension according to the criteria of the European Society of Cardiology were present in 387 (22%), 642 (37%), and 709 patients (41%), respectively (Table S3).

## Prevalence and Volume of Brain Lesions

On the bMRI, 99% of the patients presented WMLs, 54% had a Fazekas score ≥2, 22% had LNCCIs, 21% SNCIs and 22% microbleeds. In patients without a history of stroke or transient ischemic attack, 50% had a

**Table 1. Baseline Characteristics Stratified by Blood Pressure Categories**

| | Overall | Systolic blood pressure | | | | P value |
|---|---|---|---|---|---|---|
| | | <120 mm Hg | 120–140 mm Hg | 140–160 mm Hg | ≥160 mm Hg | |
| | n=1738 | n=355 (20.4%) | n=740 (42.6%) | 469 (27.0%) | 174 (10.0%) | |
| Age, y | 72.5±8.4 | 71.3±8.9 | 71.8±8.4 | 73.7±7.8 | 75.0±7.7 | <0.001 |
| Sex, male | 1262 (72.6) | 270 (76.1) | 559 (75.5) | 327 (69.7) | 106 (60.9) | <0.001 |
| Body mass index, kg/m$^2$ | 27.7±4.7 | 27.5±4.7 | 27.9±4.9 | 27.6±4.5 | 26.9±4.8 | 0.04 |
| Smoking status, % | | | | | | 0.75 |
| Current | 131 (7.5) | 31 (8.7) | 56 (7.6) | 34 (7.2) | 10 (5.7) | |
| Past | 840 (48.4) | 175 (49.3) | 365 (49.4) | 218 (46.5) | 82 (47.1) | |
| Never | 765 (44.1) | 149 (42.0) | 318 (43.0) | 216 (46.0) | 82 (47.1) | |
| Systolic BP, mm Hg | 135.1±18.5 | 111.2±7.0 | 129.8±5.8 | 148.5±5.6 | 170.3±9.7 | … |
| Diastolic BP, mm Hg | 78.5±11.9 | 69.0±9.1 | 77.0±8.8 | 84.0±11.3 | 89.1±13.3 | … |
| Antihypertensive treatment, % | 1155 (66.5) | 192 (54.1) | 487 (65.8) | 337 (71.9) | 139 (79.9) | <0.001 |
| No. of antihypertensive drugs | | | | | | 0.05 |
| 1 | 203 (16.9) | 34 (9.6) | 89 (12.0) | 60 (12.8) | 20 (11.5) | |
| 2 | 374 (31.2) | 39 (11.0) | 163 (22.0) | 119 (25.4) | 53 (30.5) | |
| ≥3 | 578 (48.2) | 119 (33.5) | 235 (31.8) | 158 (33.7) | 66 (37.9) | |
| History of stroke, % | 230 (13.2) | 47 (13.2) | 102 (13.8) | 58 (12.4) | 23 (13.2) | 0.92 |
| History of diabetes, % | 271 (15.6) | 47 (13.2) | 111 (15.0) | 81 (17.3) | 32 (18.4) | 0.29 |
| History of heart failure, % | 378 (21.8) | 104 (29.3) | 147 (19.9) | 92 (19.6) | 35 (20.1) | 0.002 |
| History of cardiovascular disease, % | 463 (26.6) | 106 (29.9) | 206 (27.8) | 124 (26.4) | 27 (15.5) | 0.004 |
| CHA$_2$DS$_2$-VASc Score | 3.3±1.7 | 3.1±1.8 | 3.2±1.7 | 3.5±1.7 | 3.8±1.6 | <0.001 |
| AF type, % | | | | | | 0.85 |
| Paroxysmal | 795 (45.7) | 153 (43.0) | 335 (45.3) | 221 (47.1) | 86 (49.4) | |
| Persistent | 543 (31.2) | 117 (33.0) | 232 (31.4) | 140 (29.9) | 54 (31.0) | |
| Permanent | 400 (23.0) | 85 (23.9) | 173 (23.4) | 108 (23.0) | 34 (19.5) | |
| Oral anticoagulation, % | 1566 (90.1) | 314 (88.5) | 663 (89.6) | 427 (91.0) | 162 (93.1) | 0.32 |
| Antiplatelet drugs, % | 96 (5.5) | 21 (5.9) | 46 (6.2) | 26 (5.5) | 3 (1.7) | 0.13 |
| Recurrent falls, % | 117 (6.7) | 25 (7.0) | 40 (5.4) | 34 (7.2) | 18 (10.3) | 0.11 |

Data are n (%) or mean±SD. Groups were compared using χ$^2$ tests or Kruskal-Wallis Tests, as appropriate. AF indicates atrial fibrillation; and BP, blood pressure.

Fazekas score ≥2, 15% had LNCCIs, 18% SNCIs and 20% microbleeds. As an example, the bMRI of 2 different patients with AF is presented in Figure 1, showing one patient with few brain lesions (Fazekas <2) and one patient with multiple brain lesions (Fazekas ≥2, SNCI, and LNCCI). There was a linear increase of the prevalence of Fazekas ≥2, SNCIs, and microbleeds as well as volume of WML across systolic BP categories (P value for all <0.02; Table 2 and Figure 2). However, the prevalence and volume of brain lesions did not differ across categories of diastolic BP (Table 2). The prevalence and volume of WMLs, LNCCIs, SNCIs, and microbleeds stratified by hypertension are presented in Table S5.

## Association of BP and Hypertension With White Matter Lesions

The multivariable-adjusted ORs for Fazekas≥2 among patients with systolic BP of 120 to 140, 140 to 160 and ≥160 mm Hg were 1.25 (0.94–1.66), 1.41 (1.03–1.93),

and 2.54 (1.65–3.95), compared with patients with a systolic BP <120 mm Hg (P<0.001). In addition, we found an association between continuous BP and Fazekas ≥2. Per 5 mm Hg increase in systolic and diastolic BP, the odds of Fazekas ≥2 increased by 7% (OR [95% CI], 1.07 [1.03–1.10], P<0.001 and 1.07 [1.02–1.12], P=0.005, respectively; Table 3). There was a linear increase in WML volume across systolic and diastolic BP categories (P value for trend <0.001 for systolic and P value for trend 0.004 for diastolic BP; Table 3 and Figure 3). Results of the association between hypertension and WML are presented in Table S6.

## Association of BP and Hypertension With Large Noncortical or Cortical Infarcts, Small Noncortical Infarcts, and Microbleeds

Associations of BP and hypertension with the presence and volume of LNCCIs are presented in Tables S7 and S8. No association was found between systolic and
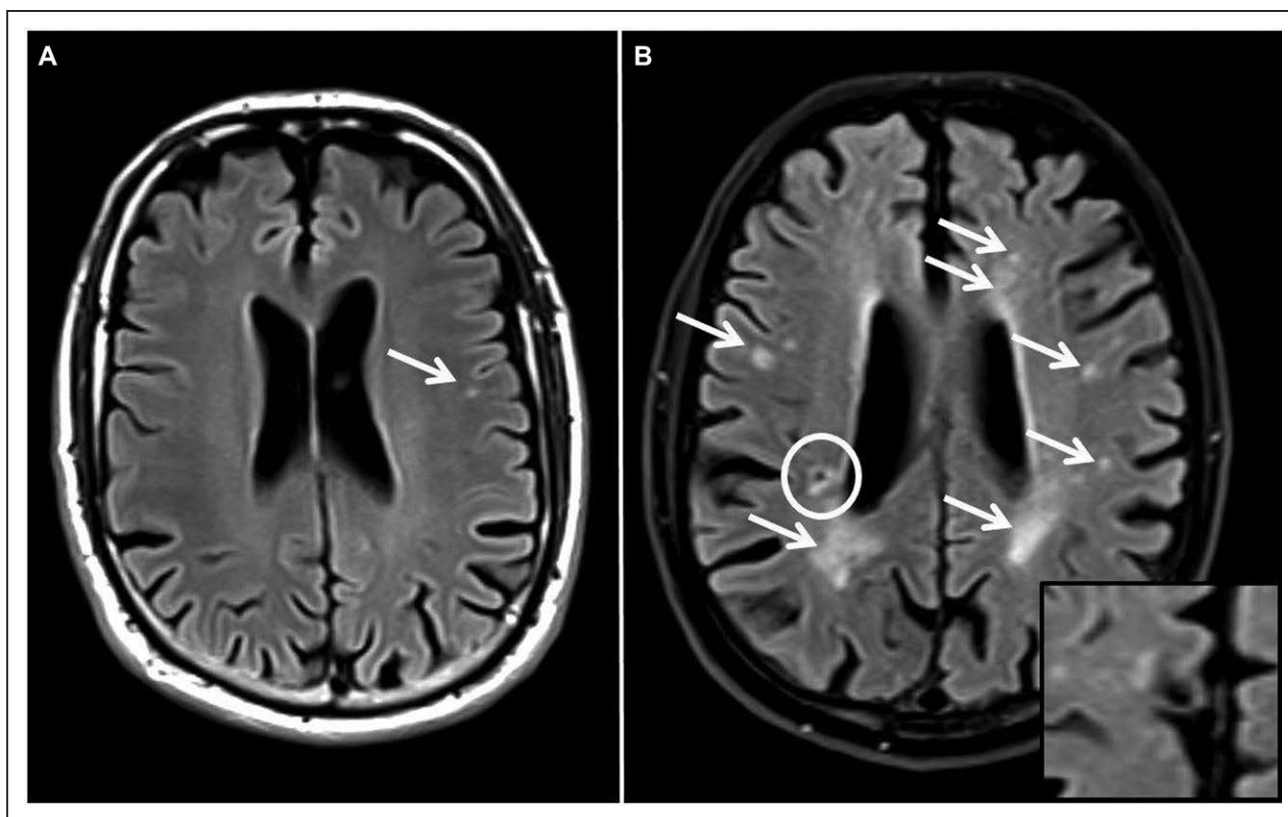
**Figure 1. Brain magnetic resonance imaging (fluid-attenuated inversion recovery) of 2 different patients with atrial fibrillation.**
**A**, Normotensive man, 72 y old with a small amount of white matter lesions (Fazekas score <2, arrows). **B**, Uncontrolled hypertensive man, 74 y old with white matter lesions inferior (Fazekas score ≥2, arrows), lacunar lesions (circle), and cortical infarcts (**right** bottom).

diastolic BP and the presence and volume of LNCCIs. In addition, the presence and volume of LNCCI was not associated with controlled and uncontrolled hypertension, compared with normotensive patients. Systolic BP was associated with the presence of SNCI (OR [95% CI] per 5 mm Hg 1.05 [1.01−1.08], $P$=0.006), as shown in Table S9. Compared with patients with a systolic BP <120 mm Hg, the multivariable-adjusted OR (95% CI) for patients with a systolic BP of 120 to 140, 140 to 160, and ≥160 mm Hg was 1.07 (0.76−1.51), 1.31 (0.91−1.90), and 1.89 (1.20−2.97), respectively ($P$ for linear trend=0.003). However, we found no consistent relationship between BP and hypertension with volume of SNCI (Tables S9 and S10). Finally, the presence of microbleeds was associated with hypertension (Table S11) but not with either systolic or diastolic BP (Table S12).

## BP and Neurocognitive Function

Across increasing categories of BP, the mean MoCA score was different for diastolic ($P$=0.006) but not for systolic BP ($P$=0.10). Results of the Digit Symbol Substitution Test, Trail Making Test A, and Trail Making Test B were different across systolic and diastolic BP categories (Table S13). Using multivariable-adjusted

regression models, we found no association between BP and neurocognitive function when using the MoCA score or the other neurocognitive tests as the outcome variables (Table S14). There was an interaction of the association between hypertension and the MoCA score for the presence/absence of Fazekas≥2 ($P$ for interaction=0.007), with an inverse association in patients with a Fazekas≥2, but no association in patients with a Fazekas<2. None of the other interaction analyses were significant (Table S15).

## DISCUSSION

In this cross-sectional analysis of patients with AF, we identified several important results. First, most patients with AF (78%) had either controlled (37%) or uncontrolled hypertension (41%) and only few patients were normotensive without treatment. Second, the prevalence of different brain lesions was unexpectedly high, and a relevant part of these brain lesions were clinically silent. Third, BP and hypertension were linearly associated with moderate to severe white matter disease and its volume. Fourth, whereas SBP was positively associated with SNCIs, BP and hypertension were not associated with LNCCIs. Fifth, uncontrolled hypertension was associated with the presence of microbleeds in this population of

**Table 2. Prevalence and Volume of Brain Lesions Stratified by Blood Pressure Categories**

| | n (%) | Prevalence Fazekas ≥2 | Volume WML mm³ | Prevalence LNCCI | Volume LNCCI, mm³ | Prevalence SNCI | Volume SNCI, mm³ | Prevalence MB* | Number MB |
|---|---|---|---|---|---|---|---|---|---|
| Overall | | 933 (53.7) | 3918 (1455–9795) | 390 (22.4) | 1640 (258–7326) | 372 (21.4) | 63 (30–166) | 373 (22.2) | 1 (1–2) |
| **Systolic blood pressure** | | | | | | | | | |
| <120 mm Hg | 355 (20.4) | 165 (46.5) | 2921 (1168–7166) | 79 (22.3) | 2121 (369–7481) | 65 (18.3) | 57 (30–169) | 70 (19.7) | 1 (1–2) |
| 120–140 mm Hg | 740 (42.6) | 375 (50.7) | 3516 (1395–9204) | 162 (21.9) | 1572 (257–7185) | 141 (19.1) | 78 (33–216) | 149 (20.1) | 1 (1–2) |
| 140–160 mm Hg | 469 (27.0) | 270 (57.6) | 4725 (1534–11'900) | 103 (22.0) | 1056 (195–6498) | 112 (23.9) | 66 (32–166) | 100 (21.3) | 1 (1–2) |
| ≥160 mm Hg | 174 (10.0) | 123 (70.7) | 5516 (2806–16'426) | 46 (26.4) | 2025 (568–7212) | 54 (31.0) | 47 (22;110) | 54 (31.0) | 1 (1–2) |
| P value | | <0.001 | <0.001 | 0.62 | 0.65 | 0.001 | 0.12 | 0.02 | 0.91 |
| **Diastolic blood pressure** | | | | | | | | | |
| <70 mm Hg | 392 (22.6) | 224 (57.1) | 4303 (1828–10'612) | 99 (25.3) | 1617 (270–7371) | 96 (24.5) | 77 (39–155) | 87 (22.2) | 1 (1–2) |
| 70–80 mm Hg | 555 (31.9) | 302 (54.4) | 3726 (1422–9204) | 121 (21.8) | 2151 (342–8730) | 115 (20.7) | 69 (31–198) | 125 (22.5) | 1 (1–2) |
| 80–90 mm Hg | 502 (28.9) | 253 (50.4) | 3714 (1384–9527) | 99 (25.3) | 1035 (183–5220) | 106 (21.1) | 57 (30–162) | 100 (19.9) | 1 (1–2) |
| ≥90 mm Hg | 289 (16.6) | 154 (53.3) | 4226 (1392–10'569) | 71 (24.6) | 1884 (434–6432) | 55 (19.0) | 51 (21–156) | 61 (21.1) | 1 (1–2) |
| P value | | 0.23 | 0.28 | 0.19 | 0.12 | 0.34 | 0.31 | 0.68 | 0.63 |

Data are n (%) or median (interquartile range). LNCCI indicates large noncortical or cortical infarcts; MB, microbleeds; SNCI, small noncortical infarcts; and WML, white matter lesions.

*n=55 with missing information on microbleeds.

mostly anticoagulated AF patients. Our results suggest that BP and hypertension have an impact on microvascular disease in patients with AF, but not on lesions of presumed embolic origin such as LNCCIs. Finally, SBP and DBP were not associated with neurocognitive function, when using different neurocognitive tests.

From a prognostic standpoint, WMLs are important because patients with WMLs face an increased risk of stroke,[27] cognitive impairment, and vascular dementia.[11,28,29] For example, different types of brain lesions have been found to be associated with cognitive decline in a general population[29] and large infarcts and WML have been shown to be associated with lower cognitive function in our cohort of patients with AF.[11] Moderate to severe WMLs (defined as Fazekas ≥2), present in over half of our study population, are known to be common in elderly populations[30] and their extent by volume in our study is high. Our findings are in line with studies in patients without AF showing an association of BP or hypertension with WMLs.[13] One study in patients of similar age compared to our cohort (65–75 years) but with poorly controlled hypertension, also showed a significantly higher risk of severe WMLs compared to normotensive patients.[12] Even in young adults in the Framingham Heart Study (mean age, 39 years), an association between SBP and white matter integrity was
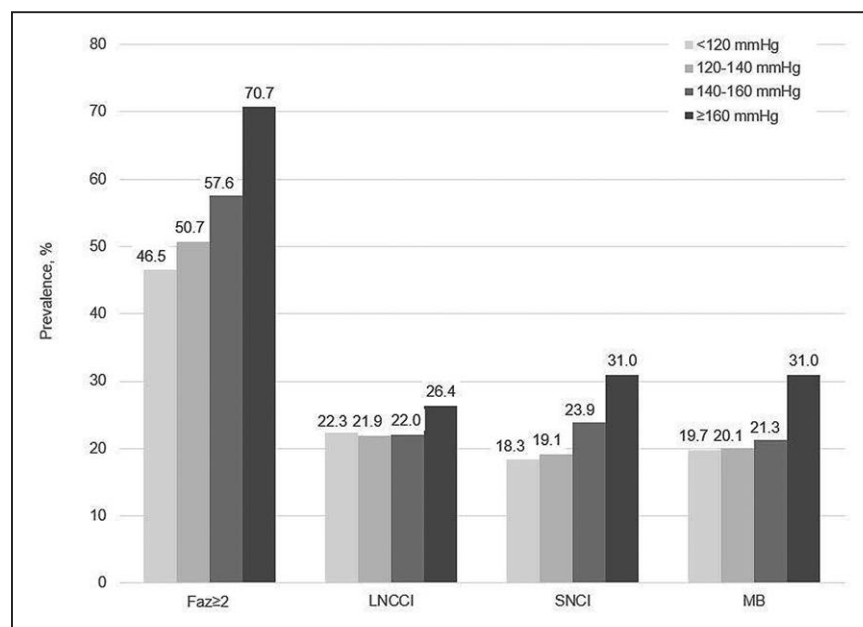


**Figure 2. Prevalence of brain lesions stratified by systolic blood pressure categories.**
Faz indicates Fazekas; LNCCI, large noncortical or cortical infarcts; MB, microbleeds; and SNCI, small noncortical infarcts.

**Table 3. Association Between Blood Pressure and WML**

| | Presence of Fazekas ≥ 2 | | Volume WML | |
| --- | --- | --- | --- | --- |
| | OR (95% CI) model 1 | OR (95% CI) model 2 | β-coefficient (95% CI) model 1 | β-coefficient (95% CI) model 2 |
| Systolic blood pressure | | | | |
| <120 mm Hg | Reference | Reference | Reference | Reference |
| 120–140 mm Hg | 1.18 (0.89 to 1.55) | 1.25 (0.94 to 1.66) | 0.16 (0.01 to 0.31) | 0.16 (0.01 to 0.32) |
| 140–160 mm Hg | 1.30 (0.96 to 1.77) | 1.41 (1.03 to 1.93) | 0.23 (0.06 to 0.39) | 0.23 (0.06 to 0.40) |
| ≥160 mm Hg | 2.22 (1.46 to 3.40) | 2.54 (1.65 to 3.95) | 0.48 (0.26 to 0.70) | 0.48 (0.25 to 0.70) |
| P for linear trend | <0.001 | <0.001 | <0.001 | <0.001 |
| Continuous, per 5 mm Hg | 1.05 (1.02 to 1.08), $P$<0.001 | 1.07 (1.03 to 1.10), $P$<0.001 | 0.03 (0.02 to 0.05), $P$<0.001 | 0.04 (0.02 to 0.05), $P$<0.001 |
| Diastolic blood pressure | | | | |
| <70 mm Hg | Reference | Reference | Reference | Reference |
| 70–80 mm Hg | 1.23 (0.92 to 1.64) | 1.28 (0.96 to 1.72) | 0.06 (−0.10 to 0.22) | 0.08 (−0.08 to 0.24) |
| 80–90 mm Hg | 1.09 (0.81 to 1.46) | 1.21 (0.90 to 1.64) | 0.10 (−0.06 to 0.27) | 0.14 (−0.02 to 0.30) |
| ≥90 mm Hg | 1.35 (0.97 to 1.90) | 1.51 (1.07 to 2.15) | 0.18 (−0.01 to 0.37) | 0.21 (0.02 to 0.39) |
| P for linear trend | 0.14 | 0.03 | 0.048 | 0.02 |
| Continuous, per 5 mm Hg | 1.05 (1.00 to 1.09), $P$=0.04 | 1.07 (1.02 to 1.12), $P$=0.005 | 0.03 (0.01 to 0.06), $P$=0.01 | 0.04 (0.01; 0.06), $P$=0.004 |

Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for educational status, body mass index, smoking status, previous stroke, diabetes, heart failure, coronary heart disease, atrial fibrillation type, oral anticoagulation, antithrombotic treatment, and antihypertensive treatment. Missing values in the multivariable-adjusted model: n=7. OR indicates odds ratio; and WML, white matter lesions.

found, emphasizing the importance of BP control early in life.[31] WMLs are thought to be microangiopathic in origin and located mainly in the periventricular and deep white brain region. WMLs in patients with AF in our cohort most likely represent BP-induced end-organ damage and reflect the hypertensive burden as a composite of severity of hypertension, quality of BP control, and time since diagnosis. However, whether the presence or absence of AF modifies the extent of WML cannot be answered due to the lack of a control group. Nevertheless, an additional impact of AF on the association between hypertension and brain lesions is conceivable for example due to the large beat-to-beat cycle length variations in patients with AF, which result in BP peaks followed by very low BP

values. A hypothesis could be that the extreme BP variations increase the risk of different types of brain lesions, mainly those of microvascular origin. If so, this could constitute further evidence supporting rhythm control in patients with AF.

LNCCI and SNCI were present in >20% in this population of patients with AF. LNCCIs are thought to represent an event of cardioembolic or arterioembolic origin. These mechanisms are considered the main underlying mechanisms of cerebral infarcts in patients with AF. In our study, the volume affected by LNCCIs is markedly higher compared to the volume of SNCIs, but much less than that of WMLs. Neither BP nor hypertension were associated with LNCCIs. This could be explained by
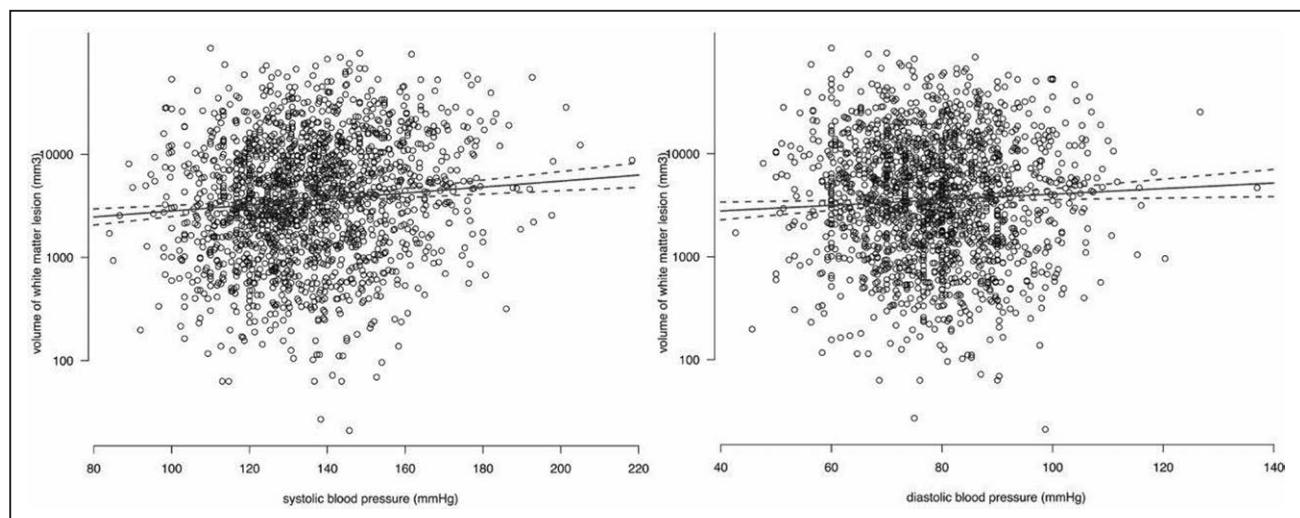


**Figure 3. Scatterplot of the age and sex-adjusted association of blood pressure with volume of white matter lesions.**
The solid line represents the model-based predicted values, and the dotted lines represent the 95% pointwise CI.

potential competing mechanisms involved in the pathogenesis of LNCCIs as well as the protective effect of the oral anticoagulation, which is commonly prescribed in patients with AF based on risk stratification schemes such as the $CHA_2DS_2$-VASc score encompassing cardiovascular comorbidities (eg, hypertension).[32] In contrast, SNCIs are, at least to some extent, caused by cerebral small vessel disease and this assumption is supported by the association between SBP and the presence of SNCI found in this analysis.

Patients with microbleeds face an increased risk of intracerebral hemorrhage. In this cohort, ≈20% of patients had at least one microbleeds, which is in line with previous studies in elderly subjects.[9,33] Hypertension has been shown to be strongly associated with the presence of microbleeds in healthy adults, in hypertensive adults, and also in patients with cerebrovascular diseases (including ischemic stroke and intracerebral hemorrhage).[15,33,34] This association was partly confirmed in our population of mostly anticoagulated AF patients. Different pathophysiological mechanisms may explain the occurrence of microbleeds in patients with hypertension, including ruptured arteriosclerotic microvessels,[35] lipohyalinosis, and amyloid deposits in cerebral amyloid angiopathy, which may increase the vessel permeability and result in leakage of blood into the brain parenchyma.[36]

The question whether more aggressive BP control in patients with AF and bMRI-detected lesions (WML, LNCCIs, SNCIs, or microbleeds) is associated with better outcomes or whether these lesions can be prevented cannot be answered with our study. The SPRINT-MIND study (Systolic Blood Pressure Intervention Trial-Memory and Cognition in Decreased Hypertension) showed slower WML progression but a greater decrease in total brain volume in patients with intensive antihypertensive treatment compared to patients with a standard antihypertensive treatment.[37] Whether the decrease in WML with more intensive BP lowering is beneficial in light of the more pronounced brain atrophy currently remains unclear.[38] Optimal BP treatment is always a trade-off between achieving the beneficial effect of antihypertensive treatment and avoiding potential side-effects, including hypotension, syncope, or electrolyte abnormalities.[39]

Whether BP is independently associated with cognitive decline or dementia is controversially discussed, as stated in the scientific statement from the American Heart Association.[40] Based on data of an observational study from the general population, higher systolic BP and lower diastolic BP seem to be associated with a faster cognitive decline in global cognition over 8 years.[41] Another study found no significant associations of having ideal BP values and different neurocognitive functions.[42] In the randomized SPRINT-MIND study, the authors found a lower risk of mild cognitive impairment in patients of the intensive treatment group (systolic BP goal of <120 mm Hg) compared with patients in the standard treatment group (systolic BP goal of <140 mm Hg).[38] However, there was no association of BP treatment with probable dementia, which might be explained with the early termination of the SPRINT study. In this cross-sectional study, BP was not associated with neurocognitive function after multivariable adjustment, suggesting that this association is affected by multiple other factors, including age, sex, or educational status. However, we found potential indication for Fazekas≥2 to be an effect modifier of the association between hypertension and the MoCA score, with an inverse association of hypertension and neurocognitive function in patients with a Fazekas ≥2 but no association in patients with a Fazekas <2.

## Strengths and Limitations

A main strength of this analysis is the large sample of well-characterized patients with AF. All patients had a standardized bMRI, which was centrally analyzed according to a standardized protocol. However, some limitations should be considered when interpreting the results. First, most patients in our study were of European origin, and the generalizability of our results to other populations is not clear. Second, as Swiss-AF is an observational study, residual confounding might be possible, although we adjusted our models for a comprehensive set of potential confounders. Potential unmeasured confounders, including the time since diagnosis of hypertension, AF burden, arterial stiffness, brain perfusion, and genetic determinants might have an impact on the results. Third, no information on brain perfusion is available based on the performed brain MRI scans. It is assumed that cerebral hypoperfusion could be a plausible mechanism for cognitive impairment. Therefore, advanced brain MRI might be of added value. Finally, office BP was measured 3× at one time point, making it possible for white coat hypertension to be present or masked hypertension to be missed.

## Perspective

BP and hypertension in patients with AF are strongly associated with WML and to a lesser extent with SNCIs, but not with LNCCIs. Our data suggest that the presence and extent of WMLs are altered by the burden of hypertension. Further studies are needed to assess the effect of more aggressive BP control on brain lesions in patients with AF.

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## APPENDIX

### List of all Swiss-AF investigators according to participating center:

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