1   **Title:** Small vessel disease and ischemic stroke risk during anticoagulation for atrial

2   fibrillation after cerebral ischemia

3

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54   **ABSTRACT**

55   **Background and purpose:** The causes of recurrent ischemic stroke despite

56   anticoagulation for atrial fibrillation (AF) are uncertain, but might include small

57   vessel occlusion. We investigated whether magnetic resonance imaging (MRI)

58   markers of cerebral small vessel disease (SVD) are associated with ischemic stroke

59   risk during follow-up in patients anticoagulated for AF after recent ischemic stroke or

60   transient ischemic attack (TIA).

61   **Methods:** We analyzed data from a prospective multicenter inception cohort study of

62   ischemic stroke or TIA anticoagulated for atrial fibrillation (CROMIS-2). We rated

63   markers of SVD on baseline brain MRI: basal ganglia perivascular spaces (BGPVS,

64   number ≥ 11); cerebral microbleeds (CMBs, number ≥ 1); lacunes (number ≥ 1); and

65   white matter hyperintensities (WMH, periventricular Fazekas grade 3 or deep white

66   matter Fazekas grade ≥ 2). We investigated the associations of SVD presence (defined

67   as presence of ≥ 1 SVD marker) and severity (composite SVD score) with the risk of

68   ischemic stroke during follow-up using a Cox proportional hazards model adjusted for

69   CHA_2DS_2-VASc (congestive heart failure, hypertension, age >75, diabetes, stroke,

70   vascular disease, age 65-74, female) score.

71   **Results:**   We included 1419 patients (mean age: 75.8 years [SD 10.4]; 42.1%

72   female). The ischemic stroke rate during follow-up in patients with any SVD was 2.20

73   per 100-patient years (95% CI 1.60-3.02), compared with 0.98 per 100 patient-years

74   (95% CI 0.59-1.62) in those without SVD (p = 0.008). After adjusting for

75   CHA_2DS_2-VASc score, SVD presence remained significantly associated with

76   ischemic stroke during follow-up (hazard ratio [HR] 1.89, 95% CI 1.01-3.53, p =

77   0.046); the risk of recurrent ischemic stroke increased with SVD score (HR per point

78   increase 1.33 95% CI 1.04-1.70, p = 0.023).

79   **Conclusions:** In patients anticoagulated for AF after ischemic stroke or TIA, MRI

80   markers of SVD are associated with an increased risk of ischemic stroke during

81   follow-up; improved stroke prevention treatments are required in this population.

82

83   **Clinical Trial Registration**—URL: https://www.clinicaltrials.gov. Unique identifier:

84   NCT02513316.

85

Non-standard Abbreviations and Acronyms

AF: atrial fibrillation; BGPVS: basal ganglia perivascular spaces; CHA_2DS_2-VASc:

congestive heart failure, hypertension, age >75, diabetes, stroke, vascular disease, age

65-74, female; CMBs: cerebral microbleeds; CROMIS-2: Clinical Relevance of

Microbleeds In Stroke Study; CSOPVS: centrum semiovale perivascular spaces;

DOAC: direct oral anticoagulant; FLAIR: fluid attenuation inversion recovery;

GRE: gradient recalled echo; HR: hazard ratio; MRI: magnetic resonance

imaging; OAC:oral anticoagulation; SVD: small vessel disease; TIA: transient

ischemic attack; TTR: therapeutic time in range; VKA: Vitamin K antagonist;

WMH: white matter hyperintensities;

INTRODUCTION

Although oral anticoagulation (OAC) is highly effective for secondary prevention

after ischemic stroke or transient ischemic attack (TIA) associated with atrial

fibrillation (AF), some studies indicate a substantial risk (4.7%-7.7%/year)[1-2] of

recurrent cerebrovascular events despite OAC. Recurrent ischemic stroke despite

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102   anticoagulation for AF may reflect either inadequate anticoagulation, or alternative

103   stroke mechanisms, since AF is commonly present concurrently with other relevant

104   pathologies, including large artery atherosclerosis or cerebral small vessel disease

105   (SVD). A recent case-control study reported a prevalence of 32.7% of other stroke

106   etiologies than cardioembolism in patients with AF on anticoagulant therapy for

107   stroke prevention, with SVD contributing 10.4%.[3] Cerebral SVD - associated with

108   age, hypertension,[4,5] and a major contributor to stroke and cognitive dysfunction[4]- can

109   be detected and quantified by magnetic resonance imaging (MRI) biomarkers

110   including perivascular spaces, cerebral microbleeds (CMBs), lacunes, and white

111   matter hyperintensities (WMH).[6] Previous studies in unselected ischemic stroke

112   populations demonstrated basal ganglia perivascular spaces (BGPVS), CMB burden,

113   severe WMH, and multiple lacunes to be associated with recurrent ischemic stroke.[7-8]

114   Conversely, in patients with intracranial arterial stenosis, SVD was not associated

115   with ischemic stroke risk. [5]

116   Our aim was to examine the association between SVD presence and the risk of

117   ischemic stroke during follow-up in a prospective multicenter observational inception

118   cohort of patients anticoagulated for AF after ischemic stroke or TIA; we

119   hypothesized that the risk of ischemic stroke during follow-up despite OAC is

120   associated with baseline SVD presence and severity.

121

122   **METHODS**

123   **Data availability statement**

124   Data of this study are available from UCL Institute of Neurology on reasonable

125   request and after consideration by the CROMIS-2 Steering Committee. Persons

126   interested in obtaining access to the data should contact the corresponding author at:

127   d.werring@ucl.ac.uk.

128

129   **Clinical data:** We included participants recruited to the Clinical Relevance of

130   Microbleeds In Stroke Study (CROMIS-2) study, a multicenter prospective inception

131   cohort study of patients anticoagulated for AF after ischemic stroke or TIA, between

132   August 3, 2011, and July 31, 2015. The details of study design, inclusion and

133   exclusion criteria have previously been published.[9,10] We followed all adult patients

5

134   (i.e., ≥18 years of age) using standard structured postal questionnaires or telephone

135   interviews to patients and their general practitioners or hospital visit at 6,12, and 24

136   months following their index ischemic event. We defined ischemic stroke during

137   follow-up as a new clinical event with neurologic deficit consistent with ischemic

138   stroke.[11] Clinicians at different participating centers assessed the recurrent event

139   subtype using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)

140   classification. We excluded patients without appropriate brain MRI at baseline or

141   follow-up data.

142

143   **Imaging analysis:**   We included standardized parameters for the MRI sequences,

144   including axial T2-weighted, T2-weighted gradient-recalled echo (T2*-GRE), coronal

145   T1-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted

146   imaging (DWI) at each site.[9,10] All structural markers of SVD were rated in

147   accordance with consensus criteria.[6] BGPVS and centrum semiovale perivascular

148   spaces (CSOPVS) were defined and rated by two raters (GB, HD) on T2 and FLAIR

149   sequences using a validated 4-point visual rating scale on a single predefined slice. [6,12]

6

150   CMBs were evaluated by two raters (DW, GB) using T2*-GRE sequences and the

151   validated Microbleed Anatomical Rating Scale.[6,10] Lacunes of presumed vascular

152   origin were rated by two raters (GB, HD) as ovoid or round, subcortical, CSF-signal

153   like cavities between 3-15 mm in diameter on T2 and FLAIR sequences. [6] WMH

154   were rated by a single rater (DW) on T2 and FLAIR sequences using the Fazekas

155   scale.[6,13] All raters were well trained as documented previously.[10,12] We quantified

156   intra-rater and inter-rater reliability for structural markers of SVD using Cohen's κ

157   coefficient. SVD presence was defined as any presence of the following: $\geq$11 BGPVS,

158    $\geq$1 CMBs, $\geq$1 lacunes, or moderate to severe WMH (Fazekas grade 3 in

159   periventricular or grade 2 to 3 in deep) [4-5] as defined in a composite SVD scale.[4] We

160   also calculated the total SVD score, which allocates 1 point for the presence of each

161   of the following: $\geq$11 BGPVS, $\geq$1 CMBs, $\geq$1 lacunes, or moderate to severe WMH.[4]

162

163   **Standard protocol approvals, registrations, and patient consents:** CROMIS-2

164   was approved by the National Institute for Health Clinical Research Network (NIHR,

7

165   Research Ethics Committee reference: 10/H0716/64), and registered with

166   ClinicalTrails.gov (No.NCT02513316). [9-10]

167

168   **Statistics:** Continuous data were summarized as mean values with standard

169   deviations (if normally distributed) or median value with interquartile range (if not

170   normally distributed), and categorical data as counts with proportions. We calculated

171   absolute event rates per 100 patient-years for ischemic stroke during follow-up. We

172   compared the univariate Kaplan-Meier probabilities of ischemic stroke during

173   follow-up for patients with and without SVD presence and individual SVD markers.

174   We developed two Cox proportional hazards models to evaluate the unadjusted and

175   adjusted risks of ischemic stroke during follow-up in patients with the presence and

176   absence of SVD and individual SVD markers: first including $CHA_2DS_2\text{-}VAS_C$ as a

177   single confounder; and second, including variables which were associated with

178   recurrent ischemic stroke in univariable analysis ($p < 0.1$). The risk of ischemic stroke

179   during follow-up with increasing SVD score was also investigated using Cox

180   proportional hazards models. We used the Fisher's exact test to compare the baseline

8

181   SVD presence among different recurrent mechanisms. All the statistical analyses were

182   done using SPSS 25.0 (IBM) (SPSS Inc, Chicago, IL).

183

184   **RESULTS**

185   We included 1419 eligible patients (75.8 years [SD 10.4]; 42.1% female) in the final

186   analysis (**Fig 1**). The 43 patients without follow-up were similar to those with

187   follow-up in age (73.8 years [SD 11.4] Vs 75.8 years [10.3]; p = 0.173), sex (female

188   46.5% Vs 42.1%; p = 0.561), hypertension (57.1% Vs 63.4%; p = 0.411), and SVD

189   presence (46.5% Vs 54.1%, p = 0.324). The median follow-up duration was 2.3 years

190   [SD 1.0], providing 3265 patient-years of follow-up data. Of 1419 participants, 53

191   patients had ischemic stroke during follow-up, an event rate of 1.62 per 100-patient

192   years (95% CI 1.24-2.12).

193

194   SVD was present in 768 (54.1%) patients. The prevalence of individual SVD markers

195   were as follows: ≥11 BGPVS presence 375 (26.4%) patients; ≥11 CSOPVS presence

196   681 (48.0%) patients; CMBs presence 298 (21.0%) patients (strictly lobar in 109

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197 patients, strictly deep in 117 patients, and mixed in 72 patients); lacunes 295 (20.8%)

198 patients; and moderate to severe WMH 283 (19.9%) patients. Among those with ≥11

199 BGPVS, 261(18.4%) patients had 11-20 BGPVS and 114 (8.0%) patients had >20

200 BGPVS. Intra-rater and inter-rater reliability were as follows: for the presence of

201 BGPVS 0.86 (95% CI 0.69-1.00) and 0.82 (95% CI 0.60-0.96); for the presence of

202 CSOPVS 0.90 (95% CI 0.78-1.00) and 0.80 (95% CI 0.66-0.95), for presence of

203 CMBs 0.93 (95% CI 0.86-1.00) and 0.85 (95% CI 0.74-0.96); and for presence of

204 lacunes 0.87 (95% CI 0.70-1.00) and 0.81 (95% CI 0.63-1.00).

205

206 The baseline characteristics of clinical and MRI factors with and without ischemic

207 stroke during follow-up are shown in **Table 1**. Patients with ischemic stroke during

208 follow-up had a higher median $CHA_2DS_2-VAS_C$ score of 6 [IQR 5-7] vs 5 [4-6]. Age

209 (unadjusted HR 1.04 95% CI 1.01-1.07), female sex (unadjusted HR 2.01 95% CI

210 1.17-3.48), diabetes (unadjusted HR 2.11 95% CI 1.16-3.84), and vascular disease

211 (unadjusted HR 2.24 95%CI 1.26-3.99) were associated with ischemic stroke during

212 follow-up. Of the individual baseline SVD radiological features, ≥11 BGPVS

10

213 (unadjusted HR 2.44 95%CI 1.42-4.19) were associated with ischemic stroke during

214 follow-up. We found weak evidence of an association between CMBs presence

215 (unadjusted HR 1.62 95%CI 0.90-2.91), moderate to severe WMH presence

216 (unadjusted HR 1.72 95% CI 0.95-3.12) and ischemic stroke during follow-up.

217

218 The ischemic stroke event rate during follow-up in patients with SVD presence was

219 2.20 per 100-patient years (95% CI 1.60-3.02), compared with 0.98 per 100

220 patient-years (95% CI 0.59-1.62) in those without SVD presence. The absolute rate

221 increase associated with SVD presence was 1.22 per 100 patient-years (95% CI

222 1.01-1.40). In Kaplan-Meier analysis, the ischemic stroke event during follow-up was

223 more frequent in patients with SVD presence compared to those without SVD

224 presence (log-rank test, p = 0.008, **Fig 2A**). In univariate Cox regression analysis,

225 patients with SVD had a 2.2-times higher risk of ischemic stroke during follow-up (95%

226 CI 1.21-4.01, p = 0.009). We found an association between higher SVD score with

227 increasing risk of ischemic stroke during follow-up (HR per point increase: 1.45

228 95%CI 1.14-1.83, p = 0.002). After adjusting for $CHA_2DS_2-VAS_C$, patients with SVD

229 presence still had a 1.9-times higher risk of ischemic stroke during follow-up (95% CI

230 1.01-3.53, p = 0.046); the risk of ischemic stroke during follow-up remained

231 significantly increased with increasing SVD score (HR per point increase: 1.33 95%

232 CI 1.04-1.07, p = 0.023). To better appreciate the effects of the different components

233   in the $CHA_2DS_2-VAS_C$ score, we adjusted for age, sex, diabetes and vascular disease

234   in another multivariate model. The adjusted HRs for the presence of SVD, SVD per

235   point increase and individual SVD markers were very similar to those adjusted for

236      $CHA_2DS_2-VAS_C$ as a single confounder. (**Table 2**).

237

238   We performed three sensitivity analyses to investigate whether the associations of

239   SVD presence and SVD score with ischemic stroke during follow-up were robust to

240   other potential confounders; (1) adjusted for therapeutic time in range (TTR) in

241   Vitamin K antagonist (VKA)-treated patients (available in 861 patients); (2) adjusted

242   for carotid-artery stenosis (available in 682 patients, of which 581 were <50%

243   stenosis, 60 were 50-70% stenosis, 41 were >70% stenosis); and (3) adjusted for

244   antihypertensive and statin treatment (data available in 1383 patients) (**Table 3**).

245

246   The ischemic stroke event rate during follow-up in patients with ≥11 BGPVS was

247   2.98 per 100-patient years (95% CI 1.99-4.44), compared with 1.18 per 100

248   patient-years (95% CI 0.82-1.70) in those with 0-10 BGPVS. In Kaplan-Meier

249   analysis, ischemic stroke during follow-up was more frequent in patients with

250   ≥11BGPVS compared with those with 0-10 BGPVS (log-rank test, *p* = 0.001, **Fig2B**).

251   We found weak evidence that the rate of ischemic stroke during follow-up was higher

252   with the presence of moderate to severe WMH (log-rank test, p = 0.073), CMBs

253   (log-rank test, p = 0.104), but not with the presence of CSOPVS (log-rank test, p =

254 0.196), and lacunes (log-rank test, p = 0.494). However, after adjusting for

255 $CHA_2DS_2-VAS_C$ as a single confounder in the multivariate Cox regression analysis,

256 only ≥11 BGPVS [adjusted HR 2.11, 95% CI 1.21-3.67, p = 0.008] remained

257 statistically significant. The presence of moderate to severe WMH (adjusted HR 1.33

258 95% CI 0.72-2.45 p = 0.366) and CMBs (adjusted HR 1.47 95% CI 0.81-2.65 p =

259 0.206) were not significantly associated with ischemic stroke during follow-up.

260

261 Data on the likely mechanism of recurrent ischemic stroke is shown **in Table 4**. There

262 were no significant differences in baseline SVD presence among different recurrent

263 mechanisms. However, the absolute rate of recurrent small artery occlusion in patients

264 with baseline SVD was higher than those without SVD (7.9% vs 0%).

265

266 **DISCUSSION**

267 In our prospective multicenter inception cohort study of patients anticoagulated for

268 AF after ischemic stroke or TIA, MRI-defined SVD is independently associated with

269 an increased risk of ischemic stroke during follow-up; moreover, a higher composite

270 SVD score is associated with increasing risk. Thus, these findings suggest that the risk

271 of ischemic stroke during follow-up despite OAC in some patients might be related to

13

272   SVD presence and severity (and, in some cases, due to small vessel occlusion),

273   suggesting a need for better stroke prevention strategies in this patient group.

274

275   Having AF does not necessarily mean that this is the exclusive cause of an index or

276   recurrent stroke[3, 14]，since AF commonly coexists with other etiologies, including

277   SVD. In line with our findings, data from the OXVASC study also showed that

278   patients with cardioembolic stroke who had increasing SVD score were at increasing

279   risk of ischemic stroke recurrence (unadjusted HR 1.34, 95%CI 1.00-1.78) [7].

280   Therefore, preventing recurrent ischemic stroke in stroke or TIA patients with AF and

281   SVD requires better management options. Previous randomized controlled trials

282   (ORBIT-AF [The Outcomes Registry for Better Informed Treatment of Atrial

283   Fibrillation],[15] ARISTOTLE [Apixaban for Reduction in Stroke and Other

284   Thromboembolic Events in Atrial Fibrillation],[16] and ROCKET-AF [Rivaroxaban

285   Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism

286   for Prevention of Stroke and Embolism Trial in Atrial Fibrillation][17]) do not support

287   combining antiplatelet and standard dose anticoagulation therapy for stroke

14

288   prevention in patients with AF. Findings of recent studies (COMPASS

289   [Cardiovascular Outcomes for People Using Anticoagulation Strategies][18] and

290   PIONEER AF-PCI [An Open-Label, Randomized, Controlled, Multicenter Study

291   Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral

292   Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who

293   Undergo Percutaneous Coronary Intervention][19]) suggested that low dose rivaroxaban

294   2.5mg twice daily plus single antiplatelet therapy might be a reasonable treatment

295   option for patients with AF and atherosclerotic (including carotid) cardiovascular

296   disease. However, these trials did not measure SVD or include participants known to

297   have SVD.

298

299   The use of antiplatelet or anticoagulant medication might usefully be guided by stroke

300   subtype and mechanism. For example, a prospective intervention study showed the

301   recurrent stroke event rate in warfarin-treated patients with AF and lacunar stroke was

302   similar to that in those treated with aspirin alone (8.8% [3.1%-14.6%] vs 8.9%

303   [1.8%-16.1%]).[14] This finding raises the uncertainty whether antiplatelet therapy (for

304   example using cilostazol, which is a promising agent in SVD; ClinicalTrials.gov

305   Identifier: NCT03451591) might be an alternative approach to anticoagulation for

306   secondary prevention in mild stroke or TIA patients with AF and SVD.

307   Nonpharmacological approaches, such as left atrial appendage closure (LAAO) also

308   reduce stroke occurrence in patients with AF.[20] Whether long-term antiplatelet therapy

309   following LAAO might improve secondary prevention for patients with AF and

310   coexistent SVD has not been investigated.

311

312   Complementary treatments targeting common risk factors for SVD and non-valvular

313   AF, in addition to anticoagulation, also need to be considered. A previous study

314   showed higher statin adherence predicted reduced recurrent ischemic stroke risk in

315   patients with stroke due to AF after controlling for warfarin TTR (HR 0.61, 95% CI

316   0.41–0.90, p = 0.012).[21] A subgroup analysis of the SPS3 (Secondary Prevention of

317   Small Subcortical Strokes) study showed aggressive blood pressure lowering was

318   significantly associated with reduced risk of stroke recurrence in patients who have

319   SVD with CMBs (HR 0.5, 95% CI 0.3-0.9).[22]   In our cohort, neither

320   antihypertensives (HR 1.63, 95%CI 0.69-3.89) nor statin treatment (HR 0.91, 95%CI

321   0.48-1.92) were associated with an increased ischemic stroke risk during follow-up

322   after adjusting for $CHA_2DS_2-VAS_C$. However, our protocol did not measure statin

323   adherence or strict blood pressure control.

324

325   Our data did not demonstrate that baseline SVD is associated with the subtype of

326   recurrent ischemic stroke. However, the absolute rate of recurrent small artery

327   occlusion in patients with baseline SVD was higher than in those without SVD. Our

328   findings were in line with a prospective study that showed stroke patients with large

329   artery atherosclerosis and baseline SVD had higher risk of recurrent stroke regardless

330   of its recurrence mechanism. [23] One possible explanation is that SVD is associated

331   with risk factors for atherosclerosis, which are known predictors of stroke recurrence.

332   It is always challenging to identify the exact etiology of a stroke if there are two or

333   more potential causes. The proportion of recurrent small vessel occlusion in our

334   cohort is much lower than those in previous studies,[14,24] but might be underestimated.

335   First, only a minority of patients underwent MRI for their recurrent stroke, reducing

336   our ability to accurately classify small vessel occlusions. Second, in patients with

337   known AF clinicians are more likely to regard the recurrent event as cardioembolic,

338   reflecting the TOAST criteria.[25]

339

340   Another important finding of our study is that ≥11 BGPVS are independently

341   associated with the risk of ischemic stroke during follow-up in patients anticoagulated

342   for AF. BGPVS are defined as cerebrospinal fluid-filled spaces surrounding

343   penetrating arteries in basal ganglia,[6] and are recognized as a marker of hypertensive

344   arteriopathy due to their association with age and hypertension.[7,26] Previous studies

345   demonstrated an independent association between BGPVS and severity of intracranial

346   and extracranial atherosclerosis.[26-28] Possible mechanisms for this link include chronic

347   cerebral hypoperfusion[28] and increased arterial stiffness.[29]

348

349   We acknowledge limitations: first, there is inevitable selection bias at baseline since

350   we only recruited patients able to undergo MR imaging. Second, despite

351   standardization, minor local variations in the MR sequences are inevitable. Third, we

352 did not adjust for the time between index stroke/TIA events to receiving

353 anticoagulation treatment; this is because clinicians decided on timing of OAC based

354 on best clinical judgment. However, we found no evidence that OAC timing affected

355 a composite of endpoint of stroke, TIA or death at 90 days follow-up[30]; the optimal

356 timing of OAC after stroke due to AF remains uncertain.[31-32]

357

358 Our study has important strengths. We prospectively studied a large prospective

359 inception cohort of patients at multiple hospital stroke units using standardized MRI

360 sequences, rated for imaging markers of small vessel disease using validated scales by

361 trained observers. Our follow-up rate was 97%, and experienced observers

362 adjudicated all primary events blinded to baseline neuroimaging findings. We

363 undertook survival analysis to take into account baseline confounding factors.

364

365 **Summary:** Our findings suggest that oral anticoagulation is not as effective in

366 patients with AF who have small vessel disease as it is in those without; this patient

367 group should be a focus for trials of new prevention strategies.

19

385

Disclosures

406

407 **Supplemental Materials**

408 Appendix I：Author affliation and contribution

409

410 **Appendix**

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Table 1. Clinical and radiological characteristics at baseline (n=1419) for patients with and without ischemic stroke during follow-up

	Recurrence (n =53)	No recurrence (n= 1366)	HR (95% CI)	p value
Age yr, mean±SD	79.3±9.77	75.7±10.4	1.04[1.01-1.07]	0.006
Female, n (%)	31(58.5%)	566(41.4%)	2.01[1.17-3.48]	0.012
Hypertension, n (%)	39(73.6%)	846(62.9%)	1.66[0.90-3.05]	0.106
Hyperlipidemia, n (%)	21(39.6%)	601(44.7%)	0.84[0.48-1.45]	0.529
Diabetes mellitus, n (%)	15(28.8%)	222(16.3%)	2.11[1.16-3.84]	0.015
Chronic heart failure, n (%)	4(7.5%)	55(4.0%)	1.94[0.70-5.38]	0.203
Vascular disease, n (%)	17(32.1%)	248(18.2%)	2.24[1.26-3.99]	0.006
Previous ischemic stroke, n (%)	8(15.7%)	127(9.4%)	1.81[0.85-3.86]	0.122

Previous TIA, n (%)	7(14.0%)	142(10.7%)	1.34[0.60-2.98]	0.471
Previous ICH, n (%)	1(1.9%)	7(0.5%)	3.56[0.49-25.82]	0.209
Ischemic heart disease, n (%)	7(13.2%)	226(16.5%)	0.79[0.36-1.76]	0.566
Paroxysmal AF, n (%)	6(11.5%)	148(11.2%)	1.06[0.45-2.48]	0.895
AF prior to stroke, n (%)	18(35.3%)	430(31.9%)	1.19[0.67-2.12]	0.552
CHA_2DS_2-VASc score (IQR)	6(5-7)	5(4-6)	1.53[1.25-1.89]	<0.001
Ever smoker, n (%)	21(41.2%)	678(50.7%)	0.69[0.40-1.21]	0.194
Ever alcohol user, n (%)	32(61.5%)	936(71.5%)	0.63[0.36-1.10]	0.105
Anticoagulation started, n (%)	51(96.2%)	1322(96.8%)	0.67[0.16-2.74]	0.573

Anticoagulation treatment				0.722
VKA, n (%)	35 (68.6%)	826 (62.5%)	1 (Ref)	
DOAC, n (%)	16 (31.4%)	496 (37.5%)	0.90 [0.49 -1.63]	
Good TTR, n (%)	30/35（85.7%）	702/826（85.0%）	0.83[0.32-2.15]	0.699
（available in 861 patients on VKA）				
SVD presence, n (%)	38 (71.7%)	730(53.4%)	2.21[1.21-4.01]	0.009
≥11 BGPVS presence, n (%)	24(45.3%)	351(25.7%)	2.44[1.42-4.19]	0.001
≥11 CSOPVS presence, n (%)	30(56.6%)	651(47.7%)	1.43[0.83-2.47]	0.193
CMBs presence, n (%)	16(30.2%)	282(20.6%)	1.62[0.90-2.91]	0.108

CMBs absence	37(69.8%)	1084(79.4%)	1(Ref)	0.285
CMBs strictly lobar, n (%)	4(7.5%)	105(7.7%)	1.16[0.41-3.25]	
CMBs strictly deep, n (%)	8(15.1%)	109(8.0%)	2.05[0.95-4.40]	
CMBs mixed, n (%)	4(7.5%)	68(5.0%)	1.58[0.56-4.44]	
Moderate to severe WMH presence, n (%)	15(28.3%)	258(18.9%)	1.72[0.95-3.12]	0.076
Lacunes presence, n (%)	13(24.5%)	282(20.6%)	1.24[0.67-2.33]	0.495
Lacunes absence, n (%)	40(75.5%)	1084(79.4%)	1(Ref)	0.645
Single lacune presence, n (%)	7(13.2%)	177(13.0%)	1.08[0.49-2.42]	
Multiple lacunes presence, n (%)	6(11.3%)	105(7.7%)	1.51[0.64-3.55]	

Abbreviations: HR = hazard ratio; CI = confidence interval; SD = standard deviations; TIA = transient ischemic attack; ICH = intracranial hemorrhage; AF = atrial fibrillation;

IQR = interquartile range; VKA = vitamin K antagonist; DOAC: direct oral anticoagulant; TTR = therapeutic time in range; SVD = small vessel disease; BGPVS = basal ganglia perivascular spaces; CSOPVS = centrum semiovale perivascular spaces; CMBs = cerebral microbleeds; WMH = white matter hyperintensities;

p value is derived from univariate COX hazards proportional model;

Table 2. Association of SVD presence, SVD score or individual SVD markers and ischemic stroke during follow-up

	Unadjusted		Adjusted for CHA$_2$DS$_2$-VAS$_c$		Adjuested for age, sex, diabetes and VD	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Any SVD presence	2.21[1.21-4.01]	0.009	1.89[1.01-3.53]	0.046	1.96[1.04-3.70]	0.038
SVD score per point increase	1.45[1.14-1.83]	0.002	1.33[1.04-1.70]	0.023	1.33[1.04-1.70]	0.023
≥11 BGPVS	2.44[1.42-4.19]	0.001	2.11[1.21-3.67]	0.008	2.20[1.25-3.88]	0.006
≥11 CSOPVS	1.43[0.83-2.47]	0.193	1.63[0.94-2.83]	0.083	1.69[0.97-2.93]	0.065
Moderate to severe WMH	1.72[0.95-3.12]	0.076	1.33[0.72-2.45]	0.366	1.29[0.69-2.41]	0.420
≥1 CMBs	1.62[0.90-2.91]	0.108	1.47[0.81-2.65]	0.206	1.45[0.80-2.64]	0.223
CMBs absence	1(Ref)	0.285	1(Ref)	0.502	1(Ref)	0.527

CMBs strictly lobar	1.16[0.41-3.25]		1.15[0.41-3.24]		1.20[0.43-3.38]	
CMBs strictly deep	2.05[0.95-4.40]		1.80[0.83-3.90]		1.79[0.83-3.90]	
CMB mixed	1.58[0.56-4.44]		1.34[0.48-3.79]		1.24[0.44-3.53]	
≥1 lacunes	1.24[0.67-2.33]	0.495	1.13[0.61-2.14]	0.689	1.16[0.62-2.18]	0.643
lacunes absence	1(Ref)	0.645	1(Ref)	0.826	1(Ref)	0.795
Single lacune	1.08[0.49-2.42]		1.02[0.47-2.29]		1.04[0.46-2.33]	
Multiple lacunes	1.51[0.64-3.55]		1.31[0.55-3.11]		1.35[0.57-3.19]	

Abbreviations: HR = hazard ratio; CI = confidence interval; SVD = small vessel disease; BGPVS = basal ganglia perivascular spaces; CSOPVS = centrum semiovale perivascular spaces; WMH = white matter hyperintensities; CMBs = cerebral microbleeds; VD = vascular disease

Table 3. Association of SVD presence, SVD score and ischemic stroke during follow-up adjusted for confounders in addition to CHA$_2$DS$_2$-VAS$_C$ as sensitivity analyses

Variable	Confouder	Adjusted HR with 95%CI	Variable	Confouder	Adjusted HR with 95%CI
	TTR	2.38 95%CI 1.06-5.33		TTR	1.39 95%CI 1.01-1.89
SVD presence	Carotid artery stenosis	2.55 95%CI 1.09-5.93	SVD per point increase	Carotid artery stenosis	1.41 95%CI 1.05-1.89
	Statins and AHT	1.86 95%CI 1.00-3.49		Statins and AHT	1.31 95%CI 1.03-1.68

Abbreviations: TTR = therapeutic time in range; SVD = small vessel disease; AHT = antihypertension therapy; HR = hazard ratio; CI = confidence interval;

Table 4. Baseline small vessel disease between different mechanisms of recurrent stroke

	LAA (n=4)	CE (n=31)	SAO (n=3)	Undetermined (n=15)	p value
With SVD (n=38)	3(7.9%)	21(55.3%)	3(7.9%)	11(28.9%)	0.690
Without SVD (n=15)	1(6.7%)	10(66.7%)	0(0.0%)	4(26.7%)	

Abbreviations: LAA = large artery atherosclerosis; CE = cardioembolic embolism; SAO = small artery occlusion;

Title and Figure legends

Figure 1 title: Flow chart of patient selection

Figure 2 title: Cumulative probability of being free of recurrent ischemic stroke stratified by SVD (A) and ≥11 BGPVS (B)

Figure 2 legend: SVD = small vessel disease; BGPVS = basal ganglia perivascular spaces