Question 8 evidence tables

Question 8: What is the optimal management for secondary stroke prevention after intracranial haemorrhage in cerebral amyloid angiopathy?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

CAA = cerebral amyloid angiopathy, LAA = Left Atrial Appendage Closure, LAAC = Left Atrial Appendage Closure, LAAO = Left Atrial Appendage Occlusion, CT = computed tomography, MRI = magnetic resonance imaging, mRS = modified rankin scale, CGI-C = Clinical Global Impression of Change, T2/FLAIR = T2-weighted-Fluid-Attenuated Inversion Recovery, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I^2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
291	R. Al-Shahi Salman et al. (2019). Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. *The Lancet Neurology,* 18:7 643-652	Prospective, randomised, open-label, blinded-endpoint, parallel-group trial at 122 hospitals in the UK that assessed whether starting antiplatelet therapy might reduce the risk of recurrent symptomatic intracerebral haemorrhage compared with avoiding antiplatelet therapy. For this prespecified subgroup analysis, consultant neuroradiologists masked to treatment allocation reviewed brain CT or MRI scans performed before randomisation to confirm participant eligibility and rate features of the intracerebral haemorrhage and surrounding brain.	Starting antiplatelet therapy vs avoid	Primary (recurrent symptomatic intracerebral haemorrhage) and secondary (ischaemic stroke) outcomes for up to 5 years	537 participants were enrolled, of whom 525 (98%) had intracerebral haemorrhage: 507 (97%) were diagnosed on CT (252 assigned to start antiplatelet therapy and 255 assigned to avoid antiplatelet therapy, of whom one withdrew and was not analysed) and 254 (48%) underwent the required brain MRI protocol (122 in the start antiplatelet therapy group and 132 in the avoid antiplatelet therapy group). There were no clinically or statistically significant hazards of antiplatelet therapy on recurrent intracerebral	++ Open label is one weakness, as is limited sample size (particularly the small number of participants with evidence of CAA: n=29 in the CT study and n=47 in the MRI substudy)

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					haemorrhage in primary subgroup analyses of cerebral microbleed presence (2 or more) versus absence (0 or 1) (adjusted hazard ratio [HR] 0 30 [95% CI 0 08–1 13] vs 0 77 [0 13–4 61]; pinteraction=0 41), cerebral microbleed number 0–1 versus 2–4 versus 5 or more (HR 0 77 [0 13–4 62] vs 0 32 [0 03–3 66] vs 0 33 [0 07–1 60]; pinteraction=0 75), or cerebral microbleed strictly lobar versus other location (HR 0 52 [0 004–6 79] vs 0 37 [0 09–1 28]; pinteraction=0 85). There was no evidence of heterogeneity in the effects of antiplatelet therapy in any exploratory subgroup analyses (all pinteraction>0 05).	
292	H. Arima et al. (2010). Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. *Stroke,* 41:2 394-6	RCT 6105 Patients IS 71% ICH 11% Unknown stroke 4.5% TIA 22%	Perindopril +/- indapamide	Recurrent ICH 16 CAA-ICH 51 HT-ICH 44 unclassified ICH	Active treatment: 77% reduction CAA ICH (19-93%) 46% reduction HT-ICH (4-69) 43% reduction unclassified ICH (-5 -69)	++
293	A. Biffi et al. (2015). Association Between Blood Pressure Control and Risk of Recurrent	Single site, tertiary centre observational study of 1145 of 2197 patient with ICH survived at least 90 days	Observational, BP readings obtained at 3,6,9, 12 months and every 6 months	Recurrent ICH and location within the brain (lobar vs non lobar)	In patients with lobar ICH and inadequate BP control there were 84 events per 1000 person years vs 49 events per	+ Acceptable

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	Intracerebral Hemorrhage. *Jama,* 314:9 904-12	(from 1994 to 2013), median follow up 36.8 months			1000 in patient with adequate control. in non-lobar ICH there were 52 events per 1000 person with inadequate BP control vs 27 per 1000 with adequate BP control. Inadequate BP control was associated with higher rate of recurrence of both lobar ICH (HR 3.53 (1.65-7.54) and non-lobar ICH HR 4.23 (1.02-17.52	
293	A. Biffi et al. (2015). Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. *Jama,* 314:9 904-12	Setting: One hospital Design: Cohort study Patients: 1,145 90-day ICH survivors	Intervention: Inadequate BP control Comparator: Adequate BP control (ie, systolic BP <140mmHg and diastolic BP <90mmHg if no evidence of diabetes; systolic BP <130mmHg and diastolic BP <80 mm Hg for individuals with diabetes)	Outcome: Recurrent ICH Timepoint: median 3 years	For patients with lobar ICH, the HR was 3.53 [95%CI, 1.65-7.54] for the association between inadequate BP control and recurrent ICH. Systolic BP during follow-up was associated with increased risk of lobar ICH recurrence (HR, 1.33 per 10-mm Hg increase)	**+** Comment: Incomplete data. Not prospectively planned
294	A. Biffi et al. (2017). Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. *Ann Neurol,* 82:5 755-765	Observational cohort study including individual patient data (OAC related ICH survivors) from: (1) the multicenter RETRACE study (n = 542), (2) a U.S.-based single-center ICH study (n = 261), and (3) the Ethnic/Racial Variations of Intracerebral Hemorrhage study (n = 209).	Resumption of oral anticoagulant therapy.	(1) mortality, (2) favourable functional outcome (modified Rankin Scale = 0–3), and (3) stroke incidence.	1,012 OAC-related ICH survivors (633 nonlobar and 379 lobar). Among nonlobar ICH survivors, 178/633 (28%) resumed OAC, whereas 86/379 (23%) lobar ICH survivors did. In multivariate analyses, OAC resumption after nonlobar ICH was associated with decreased mortality (hazard ratio [HR] = 0.25, 95% confidence interval	**+/-** likely subject to bias and confounding by indication and physician factors

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					[CI] = 0.14–0.44, p < 0.0001) and improved functional outcome (HR = 4.22, 95% CI = 2.57–6.94, p < 0.0001). OAC resumption after lobar ICH was also associated with decreased mortality (HR = 0.29, 95% CI = 0.17–0.45, p < 0.0001) and favorable functional outcome (HR = 4.08, 95% CI = 2.48–6.72, p < 0.0001). Furthermore, OAT resumption was associated with decreased all-cause stroke incidence in both lobar and nonlobar ICH (both p < 0.01). Results for CAA A total of 190/379 lobar ICH survivors (50%) had available MRI data to formulate a diagnosis of possible (n = 136) or probable (n = 54) CAA. None of the patients' characteristics listed in Table 1 was associated with MRI data availability (all p > 0.20). OATCresumption was associated with decreased mortality and favorable outcome in both possible and probable CAA (Table 5). Presence of multiple (≥2) cerebral microbleeds or of cortical superficial siderosis did not modify the associations between OAC resumption and mortality/favorable outcome	

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					after lobar ICH (all interaction p values > 0.20). Due to the limited number of strokes occurring in this subset of lobar ICH patients (11 recurrent ICH cases and 12 ischemic strokes), we opted not to perform analyses investigating the association of OAC resumption with stroke incidence.	
295	A. Charidimou et al. (2017). Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. *Neurology,* 89:8 820-829	SR/MA 10 prospective cohorts N 1306 with CAA or non- CAA ICH 325 CAA ICH Risk of recurrent ICH stratified by CMBs	None	Recurrent ICH	7.4% V 1.1% Annual rates over 1-3 years (CAA VS non CAA) OR: 3.1 (if 2-4 CMB) 4.3 (If 5-10 CMB) 3.4 (if >10 CMB) REFERENT 0 CMB On meta regression, AP/ OAC had no influence on outcomes	**++**
296	J. C. Hemphill et al. (2015). Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. *Stroke,* 46:7 2032-2060	AHA/ASA guideline	Summary	Multiple	Multiple	**N/A**

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296	J. C. Hemphill et al. (2015). Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. *Stroke,* 46:7 2032-2060	Setting: USA Design: Clinical guideline Patients: None	Intervention: n/a Comparator: n/a	Outcome: n/a Timepoint: n/a	N/A	**++** Comment: There is nothing relevant to CAA in this guideline.
297	I. C. Hostettler et al. (2019). Intracerebral hemorrhage: an update on diagnosis and treatment. *Expert Review of Neurotherapeutics,* 19:7 679-694	SR/IPD 13 cohorts Mix prospective/retrospective 190 pts with possible/ probable CAA (mod Boston) Mean age 74.5, 45% female	None	Recurrent ICH cSAH IS Death	Per patient year: ICH 13.2% cSAH 11.1% IS 5.1% Death 8.3% Data on starting or restarting antithrombotics in 90%. Neither associated with outcomes	**++**
297	I. C. Hostettler et al. (2019). Intracerebral hemorrhage: an update on diagnosis and treatment. *Expert Review of Neurotherapeutics,* 19:7 679-694	Setting: Multicentre (13) Design: IPDMA of cohort studies Patients: n=190 with cSAH associated with Boston possible or probable biomarkers of CAA	Intervention: cSAH Comparator: No cSAH	Outcome: intracerebral haemorrhage (ICH), recurrent convexity subarachnoid haemorrhage (cSAH), and ischemic stroke Timepoint: median 1.4y	The risks of each outcome (per patient-year) were: ICH 13.2% (95% CI 9.9–17.4); recurrent cSAH 11.1% (95% CI 7.9–15.2); combined ICH, cSAH, or both 21.4% (95% CI 16.7–26.9), ischemic stroke 5.1% (95% CI 3.1–8) and death 8.3% (95% CI 5.6–11.8). Patients with probable CAA (compared to possible CAA) had a higher risk of ICH (HR 8.45, 95% CI 1.13–75.5, p = 0.02) and cSAH (HR 3.66, 95% CI 0.84–15.9, p = 0.08) but not ischaemic stroke	**+** Comment: Included studies were small and potentially subject to selection / small study bias.

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					(HR 0.56, 95% CI 0.17–1.82, p = 0.33) or death (HR 0.54, 95% CI 0.16–1.78, p = 0.31).	
298	C. Leurent et al. (2019). Immunotherapy with ponezumab for probable cerebral amyloid angiopathy. *Annals of Clinical and Translational Neurology,* 6:4 795-806	Setting: Multicentre Design: RCT Patients: n=36 with probable CAA (not necessarily lobar ICH)	Intervention: Ponezumab Comparator: Placebo	Outcome: Cerebrovascular reactivity (CVR) on BOLD fMRI Timepoint: text	No significant difference in CVR, microbleeds,	**+** Comment: Small sample size precluding meaningful conclusions
298	C. Leurent et al. (2019). Immunotherapy with ponezumab for probable cerebral amyloid angiopathy. *Annals of Clinical and Translational Neurology,* 6:4 795-806	Phase 2, randomized, double–blind, parallel group, placebo–controlled trial in patients (55-80 years) with probable CAA in 5 countries (USA, Canada, UK, Netherlands, France)	Ponezumab (Monoclonal antibody) vs placebo	The primary efficacy endpoint was change from baseline to Day 2 or Day 90 in cerebrovascular reactivity measured by (BOLD) fMRI in response tovisual stimulation. Safety, tolerability, and pharmacokinetics of ponezumab	Reduced CVR in Ponezumab group at day 90. Treatment effect was opposite to the hypothesized direction. Therefore, prespecified efficacy criteria were not met.	**SIGN –** Potential selection bias, higher load of CMB and SVD in Ponezumab arm
299	E. Rodriguez et al. (2020). Corticosteroids lead to short-term improvement in cerebral amyloid angiopathy-related inflammation. *Journal of Neuroimmunology,* 348: 577377	Retrospective chart review 13 pts with CAA-RI 8/13 with ICH	11/13 treated with po/ IV steroids acutely	Early (non standardised) MRS Clinical Global Impression – Change score FLAIR volume	MRS change 2.6 to 1.6 Improved CGI-C Improved T2/FLAIR No data on secondary prevention	**SIGN -**
299	E. Rodriguez et al. (2020). Corticosteroids lead to short-term	Setting: One hospital Design: Retrospective cohort study	Intervention: corticosteroids	Outcome: mRS, T2/FLAIR lesion volume, global clinical impression	Corticosteroid-treatment led to short-term	**SIGN –**

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	improvement in cerebral amyloid angiopathy-related inflammation. *Journal of Neuroimmunology,* 348: 577377	Patients: 13 with CAAri of 152 CAA cases identified by ICD-10 code. CAA-ri criteria of diagnostic certainty (definite: biopsy-proven; probable: age ≥ 40 years with presence of a) ≥ 1 clinical features [headache, decrease in consciousness / behavioral changes, seizures, focal-neurological signs], b) ≥ 1 hemorrhagic lesion and c) unifocal or multifocal asymmetric white matter lesions extending to the immediate subcortical white matter not directly attributable to an alternate cause)	Comparator: no corticosteroids	Timepoint: text	reduction in modified Rankin Scale scores (2.6 1.4 vs. 1.6 1.5; p = 0.01) and T2/FLAIR lesion volume (78.1 52.2 cm3 vs. 30 30.9 cm3, p < 0.01) as well as short-term improvement in post-treatment Clinical Global Impression - Global Change scores compared to pre-treatment scores (clinical: 6 1 vs. 2.6 1.3, p = 0.03; radiological: 4.6 1.9 vs. 1.2 0.4, p = 0.03).	Comment: Single centre retrospective case series. Not analysed appropriately.
300	M. Schrag et al. (2021). Left Atrial Appendage Closure for Patients with Cerebral Amyloid Angiopathy and Atrial Fibrillation: the LAA-CAA Cohort. *Translational Stroke Research,* 12:2 259-265	Multicentre, observational cohort study of patients with severe CAA (with or without ICH) and AF who were treated with LAA closure	LAAC (device or surgical) + antiplatelets or OAC for 6-12 months post procedure, No comparator group	Safety (complications), tolerability, stroke , and haemorrhage, new arrhythmia, death	26 patients were treated, 13 with a history of symptomatic lobar haemorrhage and 13 without. no documented ischemic strokes or symptomatic ICH during the 30 days after device implantation. Patients were followed for an average of 25 months. One patient who underwent Lariat LAAC had an ischemic stroke in follow-up	**0** Unacceptable Observational cohort study, small sample size with high risk of selection bias
300	M. Schrag et al. (2021). Left Atrial Appendage Closure for Patients with Cerebral Amyloid Angiopathy and Atrial	Observational cohort study of participants with evidence of CAA ("severe CAA") treated with LAAO. Twenty-six patients with a mean CHA2DS2-VASc score of 4.6	LAAO (non-randomised; no control group). Patients with symptomatic ICH and	Ischaemic stroke, intracerebral haemorrhage, death	There was one ischaemic stroke, one ICH and one death (of status epilepticus)	**+**

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	Fibrillation: the LAA-CAA Cohort. *Translational Stroke Research,* 12:2 259-265	were treated, 13 with a history of symptomatic lobar haemorrhage and 13 without.	those naive to anticoagulation were placed on clopidogrel and/or aspirin for 6 weeks after the procedure; patients who previously tolerated anticoagulation remained on warfarin or a DOAC for 6 weeks post-procedure. All anticoagulation therapy was discontinued after confirmation of LAAO.			