Question 5 evidence tables

Question 5: Should the presence of cerebral microbleeds alter the approach to secondary prevention with antithrombotic drugs after ischaemic stroke or transient ischaemic attack?

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

DOAC = direct oral anticoagulation, OAC = oral anticoagulation, CMB = cerebral microbleeds, AF = atrial fibrillation, ASA = acetylsalicylic acid (aspirin), WMH = white matter hyperintensity, GRE = gradient echo sequences, BP = blood pressure, MACCE = major adverse cardiac and cerebrovascular events, 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
750	G. Ambler et al (2018). Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. The Lancet Neurology. 17: 6. 539-547	Observational, multicentre, prospective inception cohort study recruited adults aged 18 years or older from 79 hospitals in the UK and one in the Netherlands with atrial fibrillation and recent acute ischaemic stroke or transient ischaemic attack, treated with a vitamin K antagonist or direct oral anticoagulant, and followed up for 24 months using general practitioner and patient postal questionnaires, telephone interviews, hospital visits, and National Health Service digital data on hospital admissions or death. We excluded patients if they could not undergo MRI, had a definite contraindication to anticoagulation, or had	None.	The primary outcome was symptomatic intracranial haemorrhage occurring at any time before the final follow-up at 24 months	Between Aug 4, 2011, and July 31, 2015, we recruited 1490 participants of whom follow-up data were available for 1447 (97%), over a mean period of 850 days (SD 373; 3366 patient-years). The symptomatic intracranial haemorrhage rate in patients with cerebral microbleeds was 9·8 per 1000 patient-years (95% CI 4·0–20·3) compared with 2·6 per 1000 patient-years (95% CI 1·1–5·4) in those without cerebral microbleeds (adjusted hazard ratio 3·67, 95% CI 1·27–10·60). Compared with the HAS-BLED score alone (C-index 0·41, 95% CI 0·29–0·53), models including cerebral	++

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		previously received therapeutic anticoagulation. The log-rank test was used to compare rates of intracranial haemorrhage between those with and without cerebral microbleeds. We developed two prediction models using Cox regression: first, including all predictors associated with intracranial haemorrhage at the 20% level in univariable analysis; and second, including cerebral microbleed presence and HAS-BLED score. We then compared these with the HAS-BLED score alone.			microbleeds and HAS-BLED (0·66, 0·53–0·80) and cerebral microbleeds, diabetes, anticoagulant type, and HAS-BLED (0·74, 0·60–0·88) predicted symptomatic intracranial haemorrhage significantly better (difference in C-index 0·25,95% CI 0·07–0·43, p=0·0065; and 0·33, 0·14–0·51, p=0·00059, respectively).	
750	G. Ambler et al (2018). Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. The Lancet Neurology. 17: 6. 539-547	Observational, multicentre, prospective inception cohort study, adults aged 18 years or older from 79 hospitals in the UK and one in the Netherlands with AF and recent acute ischaemic stroke or TIA, treated with a vitamin K antagonist or DOAC, and followed up for 24 months	Treatment with vitamin K antagonists or DOAC	primary outcome was symptomatic intracranial haemorrhage in patients with and without microbleeds. The secondary outcomes were recurrent ischaemic stroke and death of any cause	1490 participants of whom follow-up data were available for 1447 (97%), The symptomatic intracranial haemorrhage rate in patients with cerebral microbleeds was 9·8 per 1000 patient-years (95% CI 4·0–20·3) compared with 2·6 per 1000 patient-years (95% CI 1·1–5·4) in those without cerebral microbleeds (adjusted hazard ratio 3·67, 95% CI 1·27–10·60)	++
508	P. Amarenco et al (2017).	Derivation in 19,100 patients with non-cardioembolic stroke in PERFORM and validation in	PERFORM (Terutroban vs aspirin) and PRoFESS (clopidogrel	ICH over 2 years	A 13-point score based on 9 items (Intracranial-B2LEED3S score). Low	+

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	The Intracranial-B2LEED3S Score and the Risk of Intracranial Hemorrhage in Ischemic Stroke Patients under Antiplatelet Treatment. Cerebrovascular Diseases. 43. 145-151.	20,332 patients with non-cardioembolic stroke or TIA in PRoFESS.	vs. aspirin + dipyridamole; telmisartan vs placebo).	Prediction score derived in PERFORM and externally validated in PRoFESS	discrimination both in PERFORM (c-statistic 0.64, 95% CI 0.61–0.68) and on external validation in PRoFESS (0.58, 95% CI 0.55–0.62).	Derivation and validation cohorts.
508	P. Amarenco et al (2017). The Intracranial-B2LEED3S Score and the Risk of Intracranial Hemorrhage in Ischemic Stroke Patients under Antiplatelet Treatment. Cerebrovascular Diseases. 43. 145-151.	Risk score developed in the PERFORM trial cohort (n = 19,100), which included patients with a noncardioembolic ischemic stroke or transient ischemic attack, and externally validated this score in one contemporary trial of very similar size and inclusion criteria, the PRoFESS trial (n = 20,332 patients).	None.	Outcome was ICH over 2 years. A Cox proportional-hazard regression analysis identified risk factors. Discrimination was quantified with c-statistics and calibration was assessed by comparing predicted and observed ICH risk in PERFORM and PRoFESS.	ICH occurred within 2 years in 263 (1.4%) patients in PERFORM trial and in 246 (1.2%) patients in PRoFESS trial. A 13-point score based on 9 items (Intracranial-B 2 LEED 3 S score – low body mass index, blood pressure, lacune, elderly, Asian ethnicity, coronary artery or cerebrovascular disease history, dual antithrombotic agent or oral anticoagulant, gender) was derived from the PERFORM trial. In PERFORM, the observed 2-year ICH risk varied from 0.75% in low-risk (score ≤ 2) to 2.44% in high-risk patients (score ≥ 5) with an acceptable calibration but a low discrimination both in PERFORM (c-statistic 0.64, 95% CI	+

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					0.61–0.68) and on external validation in PRoFESS (0.58, 95% CI 0.55–0.62).	
509	196. Charidimou et al (2017). Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology. 89: 23. 2317-2326.	Meta-analysis of cohort studies > 50 patients with IS, MRI and AF and long term anticoagulant > 6months follow up International collaboration from 8 centres	Anticoagulation	ICH and calculated OR	Baseline CMB presence (vs no CMB) was associated with ICH during follow-up (OR 2.68, 95% CI 1.19–6.01, p 5 0.017). Presence of >5 CMB was related to higher future ICH risk (OR 5.50, 95% CI 2.07–14.66, p 5 0.001). The pooled annual ICH incidence increased from 0.30% (95% CI 0.04–0.55) among CMB-negative patients to 0.81% (95% CI 0.17–1.45) in CMB-positive patients (p =0.01) and 2.48% (95% CI 1.2–6.2) in patients with >5 CMBs (p =0.001). There was no association between CMBs and recurrent ischemic stroke.	**++** Risk of bias
509	196. Charidimou et al (2017). Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology. 89: 23. 2317-2326.	Study level MA (SLMA), 8 cohort studies, 4 Asia, 3 Europe, 1 US N=1552 Included: IS AF On OAC >50pts Baseline MRI	OAC 3/8, Some NOAC 5/8, VKA Only	ICH IS	Pooled annual ICH incidence increased from 0.30% (95% CI 0.04–0.55) among CMB-negative patients to 0.81% (95% CI 0.17–1.45) in CMB-positive patients (p 0.01) and 2.48% (95% CI 1.2–6.2) in patients with >5 CMBs (p = 0.001).	

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					Baseline CMB presence (vs no CMB) was associated with ICH during follow-up (OR 2.68, [CI] 1.19–6.01, p 0.017). Presence of >5 CMB was related to higher future ICH risk (OR 5.50, 95% CI 2.07–14.66, p 0.001) Strictly lobar (OR 2.88, P=0.025, and mixed OR 2.91, p=0.052 associated with ICH There was no association between CMBs and recurrent ischemic stroke.	
510	K. K. Lau et al (2017). Long-term prognostic implications of cerebral microbleeds in Chinese patients with Ischemic Stroke. Journal of the American Heart Association. 6: 12. E00736	1,003 Hong Kong Chinese with ischaemic stroke.	Microbleeds (n=450) vs no microbleeds	ICH and ischaemic stroke	Independent of vascular risk factors, antithrombotic use, and other neuroimaging markers of small vessel disease, having ≥5 microbleeds (HR 6.08 95% CI 1.11–33.21) was an independent predictor of subsequent ICH, but neither microbleed burden nor location was predictive of recurrent ischemic stroke risk.	**+** Well analysed cohort study. Not generalisable to the UK.
511	Shoamanesh et al (2017). Microbleeds in the Secondary Prevention of Small Subcortical Strokes Trial: Stroke, mortality, and treatment interactions.	MRI substudy of SPS3 RCT ASA/placebo Guideline based SBP control 130-149 N=1278 Included: Age>30	ASA/Clopidogrel Aggressive SBP <130	All stroke	After adjusting for multiple old lacunar infarcts on MRI (>1) and WMHs, treatment group and clinical risk factors, participants with CMBs remained at	Likely selection bias, 42% had MRI

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	Annals of Neurology. 82: 2. 196-207.	Lacunar IS<6Mo No MRI contraindication Mean f/u 3.5yr			increased risk of any stroke (adjusted HR 1.9, 95%. CI 1.2–2.9). Insufficient numbers of ICH for analysis. Aggressive BP lowering significantly reduced risk of stroke recurrence in patients with CMBs (HR 0.5, 95% CI 0.3–0.9) but not patients without CMBs (HR 0.7, 95% CI 0.4–1.3); however, the difference was statistically insignificant (interaction, p 0.34). a trend suggesting that there may exist a different treatment effect on risk of recurrent stroke in those with moderate–severe disease compared to patients without CMBs (interaction, p 0.087) Risk of stroke recurrence did not differ for those assigned dual antiplatelet therapy versus aspirin alone among patients with CMBs (HR 1.2, 95% CI 0.7–2.2)	
511	196. Shoamanesh et al (2017). Microbleeds in the Secondary Prevention of Small Subcortical	SPS3 sub-study analysis Patients over 30 with MRI confirmed lacunar stroke	Aspirin& clopidogrel vs aspirin & placebo (double blind) BP control (<130 vs 13-149 mmHg)	Recurrent stroke and death	Patients with CMBs had an adjusted 2-fold increased risk of recurrent stroke (hazard ratio52.1, 95% CI51.4–3.1).	+ Selection bias not all patients had imaging data

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	Strokes Trial: Stroke, mortality, and treatment interactions. Annals of Neurology. 82: 2. 196-207.				CMBs were not a risk factor for death. There were no statistically significant interactions between CMBs and treatment assignments	only used GRE for microbleed detection
512	M. J. O'Donnell et al (2016). Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. American Heart Journal. 178. 145-150.	MRI substudy of AVERROES RCT Apixaban v ASA in NVAF f/u 1yr n=931 with paired MRI	apixaban	Clinical or MRI defined new infarction Change in CMBs from baseline to 1yr	No benefit of apixaban on new infarcts No difference in CMBs between arms Rates of IS/ICH in CMB group not reported by treatment arm	Selection bias likely
512	M. J. O'Donnell et al (2016). Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. American Heart Journal. 178. 145-150.	Substudy of the AVERROES trial (AF and ≥1 additional risk factor, not suitable for VKA, randimised to apixaban or aspirin. They performed brain MRI (T1, T2, fluid-attenuated inversion recovery, and T2* gradient echo sequences) in 1,180 at baseline and in 931 participants at follow-up. Mean interval from baseline to follow-up MRI scans was 1.0 year. The primary outcome was a composite of clinical ischemic stroke and covert embolic pattern infarction (defined as infarction N1.5 cm, cortical-based infarction, or new multiterritory infarction).	Imaging substudy – apixaban v aspirin	Composite of clinical ischemic stroke and covert embolic pattern infarction (defined as infarction N1.5 cm, cortical-based infarction, or new multiterritory infarction). Secondary outcomes included new MRI-detected brain infarcts and microbleeds and change in white matter hyperintensities.	The rate of the primary outcome was 2.0% in the apixaban group and 3.3% in the aspirin group (hazard ratio [HR] 0.55; 0.27-1.14) from baseline to follow-up MRI scan (mean duration of follow-up: 1 year). In those who completed baseline and follow-up MRI scans, the rate of new infarction detected on MRI was 2.5% in the apixaban group and 2.2% in the aspirin group (HR 1.09; 0.47-2.52), but new infarcts were smaller in the apixaban group (P = .03). There was no difference in proportion with new microbleeds on	+

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		Secondary outcomes included new MRI-detected brain infarcts and microbleeds and change in white matter hyperintensities.			follow-up MRI (HR 0.92; 0.53-1.60) between treatment groups.	
514	S. Liu; C. Li (2015). Antiplatelet Drug Use and Cerebral Microbleeds: A Meta-analysis of Published Studies. Journal of Stroke and Cerebrovascular Diseases. 24: 10. 2236-2244					
514	S. Liu; C. Li (2015). Antiplatelet Drug Use and Cerebral Microbleeds: A Meta-analysis of Published Studies. Journal of Stroke and Cerebrovascular Diseases. 24: 10. 2236-2244	Meta-analysis of 11 studies, predominantly cross-sectional, involving 10429 participants	Antiplatelet drug users vs non-users	Microbleeds	Significant association between antiplatelet therapy and cerebral microbleeds with ICH and ischaemic stroke, but not stroke-free populations (significant in Asian populations, but not Europeans).	**0** Cross-sectional. Not adjusted for confounders.
515	J. S. Lim et al (2015). Cerebral microbleeds and early recurrent stroke after transient ischemic attack: Results from the Korean Transient Ischemic Attack Expression Registry. JAMA Neurology.	Korean hospital-based, multicenter prospective cohort study. Consecutive patients with TIA were enrolled from 11 university hospitals from July 1, 2010, through December 31, 2012. Patients who were admitted within 24 hours after symptom onset and underwent	None.	Recurrent stroke within 90 days. Baseline demographics, clinical manifestations, neuroimaging findings, and use of antithrombotics or statins also were analyzed.	A total of 500 patients (mean age, 64 years; male, 291 [58.2%]; median ABCD2 score, 4) completed 90-day follow-up with guideline-based management: antiplatelets (457 [91.4%]), anticoagulants (74 [14.8%]), and statins (345	**++**

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	72: 3. 201-308	diffusion-weighted imaging were included.			[69.0%]). Recurrent stroke occurred in 25 patients (5.0%). Compared with patients without recurrent stroke, those with recurrent stroke were more likely to have crescendo TIA (20 [4.2%] vs 4 [16.0%], P = .03), white matter hyperintensities (146 [30.7%] vs 13 [52.0%], P = .03), and CMBs (36 [7.6%] vs 7 [28.0%], P = .003). On multivariable Cox proportional hazards analysis, CMBs remained as independent predictors for recurrent stroke (hazard ratio, 3.66; 95%CI, 1.47-9.09; P = .005).	
515	J. S. Lim et al (2015). Cerebral microbleeds and early recurrent stroke after transient ischemic attack: Results from the Korean Transient Ischemic Attack Expression Registry. JAMA Neurology. 72: 3. 201-308	Prospective cohort study 11 hospitals Korea Included: Hospital admitted TIA MRI done f/u to 90 days N=500 30% had DWI positive. Others not clearly IS. High rates of AP (91%), OAC (14%), statin (69%)	None	IS at 90d	Recurrent stroke occurred in 25 patients (5.0%). On multivariable Cox proportional hazards analysis, CMBs remained as independent predictors for recurrent stroke (hazard ratio, 3.66; 95%CI, 1.47-9.09; P = .005) patients with multiple CMBs had 6.5 times the risk than those without CMB (adjusted HR, 6.5; 95% CI, 2.6-16.7; P < .01.	

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513	D. N. Wang et al (2015). Quantity of Cerebral Microbleeds, Antiplatelet Therapy, and Intracerebral Hemorrhage Outcomes: A Systematic Review and Meta-analysis. Journal of Stroke and Cerebrovascular Diseases. 24: 12. 2728-2737	systematic review and meta-analysis to investigate CMB-related ICH risk in prospective cohorts reporting ICH outcomes in patients with IS or TIA with baseline CMB evaluation, 10 studies were identified	Antithrombotic therapy	ICH	pooled RR of future ICH was 7.73 (95% CI, 4.07-14.70; P < .001) in CMB versus non-CMB patients. Multiple-CMB patients were at an increased risk for future ICH (RR = 8.02; 95% CI, 3.21-20.01; P < .001), whereas single-CMB patients did not incur this risk (RR = 2.33; 95% CI, .63-8.63; P = .205). A strong association was found between CMB presence and subsequent ICH in antiplatelet users (RR = 16.56; 95% CI, 3.68-74.42; P < .001).	**+** Only reported on ICH as outcome, No IS/TIA, death or composite outcome
503	J. Wang et all (2019). The safety of antithrombotic therapy in patients with cerebral microbleeds and cardiogenic cerebral embolism due to nonvalvular atrial fibrillation. BMC Cardiovascular Disorders. 19: 1. 77	232 Chinese patients with cardio-embolic ischaemic stroke on a variety of antithrombotic therapies	Microbleeds vs no microbleeds.	ICH Death	No association with microbleeds.	**-** Retrospective, small sample size, various antithrombotic events (not stratified)
503	J. Wang et all (2019). The safety of antithrombotic therapy in patients with cerebral microbleeds and	Retrospective study in patients with stroke and NVAF and the use of antithrombotic medications in one Chinese centre between 2015 and 2018	Antithrombotic therapy	Cerebral haemorrhage and all-cause death	No significant differences were found in the event-free time, the occurrence of cerebral haemorrhage events and all-cause death.	**0** Retrospective , small numbers with high risk of bias 49% pf patients with microbleeds had

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	cardiogenic cerebral embolism due to nonvalvular atrial fibrillation. BMC Cardiovascular Disorders. 19: 1. 77					anticoagulation compared to 71% without microbleeds.
502	D. Wilson et al (2019). Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. The Lancet Neurology. 18: 7. 653-665	Pooled analysis of individual patient data from prospective cohort studies	N/A	Prespecified primary outcomes were a composite of any symptomatic intracranial haemorrhage or ischaemic stroke, symptomatic intracranial haemorrhage, and symptomatic ischaemic stroke	Irrespective of cerebral microbleed anatomical distribution or burden, the rate of ischaemic stroke exceeded that of intracranial haemorrhage (for ten or more cerebral microbleeds, 64 ischaemic strokes [95% CI 48–84] per 1000 patient-years vs 27 intracranial haemorrhages [17–41] per 1000 patient-years; and for ≥20 cerebral microbleeds, 73 ischaemic strokes [46–108] per 1000 patient-years vs 39 intracranial haemorrhages [21–67] per 1000 patient-years)	**++**
502	D. Wilson et al (2019). Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. The Lancet Neurology.	IPDMA of cohort studies of ≥50 patients with recent TIA/ischaemic stroke. 20,322 patients with a median 1.34y follow-up on any antithrombotic drug(s).		Composite of any symptomatic intracranial haemorrhage or ischaemic stroke, symptomatic intracranial haemorrhage, and symptomatic ischaemic stroke.	Relative risks of ICH greater than ischaemic stroke for patients with versus without microbleeds, but irrespective of cerebral microbleed anatomical distribution or burden, the rate of ischaemic stroke exceeded that of intracranial haemorrhage (for ten or more cerebral	**+** IPDMA Non-randomised

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	18: 7. 653-665.				microbleeds, 64 ischaemic strokes [95% CI 48–84] per 1000 patient-years vs 27 intracranial haemorrhages [17–41] per 1000 patient-years; and for ≥20 cerebral microbleeds, 73 ischaemic strokes [46–108] per 1000 patient-years vs 39 intracranial haemorrhages [21–67] per 1000 patient-years). No interaction was detected between cerebral microbleeds and antiplatelet medication (pinteraction=0·358), oral anticoagulants (pinteraction=0·717), or combined oral anticoagulants and antiplatelet medication (pinteraction=0·163) for intracranial haemorrhage risk.	
517	J. G. Best et al (2021). Development of imaging-based risk scores for prediction of intracranial haemorrhage and ischaemic stroke in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual	Aimed to develop risk scores for ICH and IS in a pooled analysis of individual-patient data from the Microbleeds International Collaborative Network, which comprises 38 hospital-based prospective cohort 167 studies from 18 countries. All studies recruited participants with previous IS or TIA, acquired 168 baseline MRI allowing quantification of CMBs. Included those with IS or TIA of any mechanism including AF.	None.	Ischaemic stroke and ICH.	The included studies recruited participants between 28th August 2001 and 4th 177 February 2018. 15,766 participants had follow-up for ICH, and 15,784 for IS. Over a median 178 follow-up of two years, 184 ICH and 1,048 IS occurred. The risk models we developed 179 included CMB burden and simple clinical variables. Optimism-adjusted c-indices were 0·73 180 (95% CI 0·69-0·77) for ICH and 0·63 for IS (95% CI 0·62-0·65);	++

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	patient data from cohort studies. The Lancet Neurology. 20: 4. 294-303.				calibration slopes were 0·94 181 (95% CI 0·81-1·06) and 0·97 (95% CI 0·87-1·07) respectively, indicating good calibration.	
493	H. K. Park et al (2021). Cilostazol versus aspirin in ischemic stroke with cerebral microbleeds versus prior intracerebral hemorrhage. International Journal of Stroke. 16: 9. 1019-1030	Post hoc analysis of PICASSO study, we divided patients into the cerebral microbleeds and prior intracerebral hemorrhage subgroups.	Cilostazol v aspirin.	The primary safety end point was the first occurrence of cerebral haemorrhage. The primary efficacy end point was the composite of stroke, myocardial infarction, or vascular death.	Of 1512 patients, 903 (59.7%) had multiple cerebral microbleeds and 609 (40.3%) had prior intracerebral hemorrhage. The cerebral hemorrhage risk was lower with cilostazol versus aspirin (0.12%/year vs. 1.49%/year; hazard ratio, 0.08 [95% confidence interval 0.01–0.60]; p¼0.015) in the cerebral microbleeds subgroup, but was not different (1.26%/year vs. 0.79%/year; hazards ratio 1.60 [0.52–4.90]; p¼0.408) in the prior intracerebral hemorrhage subgroup. The interaction of treatment-by-subgroup was significant (pinteraction 0.011). For the composite of major vascular events, there was a trend toward a lower risk with cilostazol versus aspirin (3.56%/year vs. 5.53%/year; hazards ratio 0.64 [0.41–1.01]; p=0.056) in the cerebral microbleeds subgroup, but was comparable (5.21%/year vs. 5.05%/year; hazards ratio 1.03 [0.63–1.67]; p=0.913) in	

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					the prior intracerebral haemorrhage subgroup without a significant treatment-by-subgroup interaction (pinteraction=0.165).	
493	H. K. Park et al (2021). Cilostazol versus aspirin in ischemic stroke with cerebral microbleeds versus prior intracerebral hemorrhage. International Journal of Stroke. 16: 9. 1019-1030	Post hoc analysis of the PICASSO study	Cilostazol vs Aspirin in patient with CMB or prior ICH	Primary safety end point was the first occurrence of cerebral haemorrhage. The primary efficacy end point was the composite of stroke, myocardial infarction, or vascular death.	The cerebral haemorrhage risk was lower with cilostazol versus aspirin (0.12%/year vs. 1.49%/year; hazard ratio, 0.08 [95% confidence interval 0.01-0.60]; p = 0.015) in the cerebral microbleeds subgroup, but was not different (1.26%/year vs. 0.79%/year; hazards ratio 1.60 [0.52-4.90]; p = 0.408) in the prior intracerebral haemorrhage subgroup	Post hoc analysis Will need RCTs to confirm efficacy of Cilostazol vs Aspirin
494	K. Sakuta et al (2021). Cerebral Microbleeds Load and Long-Term Outcomes in Minor Ischemic Stroke. Journal of Stroke and Cerebrovascular Diseases. 30: 9. 105973.	Retrospective case control study Japan Included: IS, nonsevere (NIHSS <4), noncardioembolic On AP	None	90d poor functional outcome (MRS 3-6)	CMB burden associated with poor outcome (aOR 1.07 1.02-1.12, p 0.003) No specific data on recurrent IS or ICH provided	Selection bias
494	K. Sakuta et al (2021). Cerebral Microbleeds Load and Long-Term Outcomes in Minor Ischemic Stroke.	Retrospective cohort study in non-cardiogenic minor IS patients admitted within 48 hours and treated with antiplatelets therapy	Antiplatelet therapy	Clinical outcome as defined by MRS (poor outcome 3-6)	A higher burden of CMBs was linearly correlated with the incidence of poor outcomes (4% in the absent group, 8% in the 1	**0** High selection bias Retrospective cohort study in once centre with a small sample size

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	Journal of Stroke and Cerebrovascular Diseases. 30: 9. 105973.				CMB group, 13% in the 2_4 CMB group, and 20% in the > 4 CMB group, P = 0.002)	
495	N. Meng et al (2020). Antiplatelet therapy may be safe in ischemic stroke patients with cerebral microbleed. Journal of International Medical Research. 48: 8.	retrospective cohort study 1 hospital China Included: IS – selected On AP tx MRI done f/u 1-4y n 184	None	ICH IS All cause death	No association of CMB with ICH (0 ICH events) or IS/death	
495	N. Meng et al (2020). Antiplatelet therapy may be safe in ischemic stroke patients with cerebral microbleed. Journal of International Medical Research. 48: 8.	Hospital based retrospective study included ischaemic stroke patients admitted to a single hospital from 2015 to 2018. Baseline information was extracted from the computerized database.	None	Symptomatic cerebral hemorrhage, recurrent cerebral infarction, and death, were collected by phone.	184 ischemic stroke patients were examined, including 106 with and 78 without cerebral microbleed. No patient experienced symptomatic cerebral hemorrhage after discharge. Patients with cerebral microbleed had a higher prevalence of hypertension (92% vs 74%) and suffered from more serious leukoaraiosis (3.0 1.7 vs 1.3 1.4 points on the Fazekas scale). Leukoaraiosis scores were correlated with the number of cerebral microbleeds (r¼0.42).	-
496	Y. Cheng et al (2021). Use of anticoagulant therapy and cerebral	Systematic review of 47 observational studies comparing prevalence and incidence of	Anticoagulant users versus non-users.	Microbleeds	Anticoagulant use associated with CMB prevalence in stroke-free, TIA/ischaemic	- Observational studies

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	microbleeds: a systematic review and meta-analysis. Journal of Neurology. 268: 5. 1666-1679.	microbleeds in anticoagulant users versus non-users (n=25,245).			stroke and ICH populations. Anticoagulant use associated with strictly lobar microbleeds. Warfarin, but not NOAC associated with microbleed prevalence. Anticoagulant use associated with microbleed incidence.	Cross-sectional and cohort associations only.
497	J. Aoki et at (2021). Microbleeds and clinical outcome in acute mild stroke patients treated with antiplatelet therapy: ADS post-hoc analysis. Journal of Clinical Neuroscience. 89. 216-222.	Post hoc analysis using acute dual study database (multicenter, prospective, randomized, open-label trial that compared the safety and efficacy of acute aspirin plus cilostazol dual therapy for acute mild stroke within 48 h of the symptom onset), examining the impact of cerebral microbleeds (MBs) after mild non-cardioembolic stroke on clinical outcome	Aspirin and cilostazol vs aspirin	neurological deterioration and stroke recurrence within 14 days. Safety outcomes included ICH and/or SAH as well as extracranial haemorrhages.	The number of MBs was not associated with the neurological deterioration and/or stroke recurrence (p = 0.934), ICH and/or SAH (p = 0.743), and extracranial haemorrhage (p = 0.205). Combined cilostazol and aspirin therapy did not alter any rates of efficacy and safety outcomes among the no MBs, MBs 1–4, MBs 5–9, and MBs _ 10 groups compared to aspirin alone (all p > 0.05)	+ Retrospective post hoc analysis of registry data, Mild stroke, Asian population
498	A. Shoamanesh et al (2021). Microbleeds and the Effect of Anticoagulation in Patients with Embolic Stroke of Undetermined Source: An Exploratory Analysis of the NAVIGATE ESUS Randomized Clinical Trial.	An Exploratory Analysis of the NAVIGATE ESUS Randomized Clinical Trial (double-blind, randomized, event-driven phase 3 clinical trial)	Rivaroxaban 15 mg vs Aspirin in ESUS patients	The primary outcome was recurrent stroke. Secondary outcomes were ischemic stroke, intracerebral haemorrhage, and all-cause mortality	The presence of microbleeds was associated with a 1.5-fold increased risk of recurrent stroke (hazard ratio [HR], 1.5; 95%CI, 1.0-2.3), a 4-fold risk of intracerebral hemorrhage (HR, 4.2; 95%CI, 1.3-13.9), a 2-fold risk of all-cause mortality (HR, 2.1; 95%CI, 1.1-4.3), and strictly lobar	++ Retrospective exploratory analysis, Selection bias

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	JAMA Neurology. 78: 1. Nov-20.				microbleeds with an approximately 2.5-fold risk of ischemic stroke (HR, 2.3; 95%CI, 1.3-4.3). There were no interactions between microbleeds and treatment assignments for recurrent stroke, ischemic stroke, or all-cause mortality.	
	A. Shoamanesh et al (2021). Microbleeds and the Effect of Anticoagulation in Patients with Embolic Stroke of Undetermined Source: An Exploratory Analysis of the NAVIGATE ESUS Randomized Clinical Trial. JAMA Neurology. 78: 1. Nov-20.	Sub-group analysis of 3,699 of 7,213 in NAVIGATE ESUS RCT. Patients aged 50 years or older who had neuroimaging-confirmed ESUS between 7 days and 6 months before screening, without prior ICH.	Rivaroxaban 15mg of versus aspirin 100mg od	Recurrent stroke	Microbleeds were associated with an increase in risk of recurrent stroke, ischaemic stroke, and ICH. There were no interactions between microbleeds and treatment assignments for recurrent stroke, ischemic stroke, or all-cause mortality.	+ RCT Sub-group analysis
499	K. Sakuta et al (2020). The Impact of Cerebral Microbleeds Presence on Outcome Following Minor Stroke Treated With Antiplatelet Therapy. Frontiers in Neurology. 11. 552.	Retrospective Japanese hospital cohort study of consecutive patients with a non-cardiogenic minor ischemic stroke (NIHSS <4 on admission) who underwent initial brain magnetic resonance imaging within the first 48 h following symptom onset	None	mRS score in the 3–6 range measured 90 days after symptom onset.	240 patients (187 men, median age 66 years old) were enrolled in our study. There was a non-significant trend toward a worsening shift of 3-month mRS score distribution in the CMB group compared with the no-CMB group. Multivariate analysis	-

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					revealed that the presence of CMBs was independently predictive of poor outcome (OR, 3.44; 95% CI, 1.08–10.93; P = 0.036).	
500	K. H. Choi et al (2020). Microbleeds and Outcome in Patients with Acute Ischemic Stroke and Atrial Fibrillation Taking Anticoagulants. Stroke. 3514-3522.	Single-center Korean cohort study used data from the prospective acute stroke registry for patients with AIS over the age of 18 years, who were admitted to our government-initiated comprehensive stroke center.	None.	Primary composite outcome was the occurrence of MACCE (a composite of stroke, acute myocardial infarction, or vascular death) over a 2-year period according to CMB status.	CMB presence was significantly associated with the risk of future MACCE (hazard ratio, 1.89 [95% CI, 1.23–2.88]; P=0.003) after adjustment for confounders in patients with acute ischemic stroke and atrial fibrillation taking OACs. Patients with exactly 1 CMB had a similar rate of MACCE compared with those without CMBs (P=0.461). However, patients with multiple CMBs (≥2), particularly high burden CMBs (≥5), had a significantly higher proportion of MACCE. Both CMB-positive groups with lobar and deep CMB had more frequent MACCE than the CMB-negative group, and the rate of MACCE was not different according to CMB location. In patients treated with warfarin, CMB was significantly associated with a risk of MACCE (P=0.002), but not in patients treated with direct OACs (P=0.517).	+

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
500	K. H. Choi et al (2020). Microbleeds and Outcome in Patients with Acute Ischemic Stroke and Atrial Fibrillation Taking Anticoagulants. Stroke. 3514-3522.	Prospective cohort study 1 hospital Korea Included: Hospital admitted IS MRI done AF OAC, selected. 31% DOAC, 69% VKA f/u to 2yr N=1742	No	MACCE IS ICH Vascular death AMI	CMB presence was significantly associated with the risk of future MACCE (hazard ratio, 1.89 [95% CI, 1.23–2.88];P=0.003) after adjustment for confounders. patients with multiple CMBs (≥2), particularly high burden CMBs (≥5), had a significantly higher proportion of MACCE. Both CMB-positive groups with lobar and deep CMB had more frequent MACCE than the CMB-negative group, and the rate of MACCE was not different according to CMB location. Presence and burden of CMB associated with MACCE, IS, ICH. strictly lobar CMB associated with ICH, MACCE, not IS.	
501	B. J. Kim et al (2020). Cilostazol versus aspirin in ischemic stroke patients with high-risk cerebral hemorrhage subgroup analysis of the PICASSO trial. Stroke. 931-937	Substudy analyzed interactions between treatment and subgroups of the PICASSO trial (Prevention of Cardiovascular Events in Asian Ischemic Stroke Patients With High Risk of Cerebral Hemorrhage).	Ischemic stroke patients with a previous intracerebral hemorrhage or multiple microbleeds were randomized to treatment with cilostazol or aspirin and followed up for a mean 1.8 years.	Efficacy, defined as the composite of any stroke, myocardial infarction, and vascular death, and safety, defined as the incidence of hemorrhagic stroke.	Among all 1534 patients enrolled, a significant interaction between treatment group and index of high risk for cerebral hemorrhage on hemorrhagic stroke (P for interaction, 0.03) was observed. Hemorrhagic stroke was less frequent in the cilostazol than in the aspirin group in patients with	Support hypothesis that cilostazol might be safer in patients with IS and multiple CMBs. No impact on the guideline.

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					multiple microbleeds (1 versus 13 events; hazard ratio, 0.08 [95% CI, 0.01–0.61]; P=0.01). A marginal interaction between treatment group and white matter change on any stroke (P for interaction, 0.08) was observed. Cilostazol reduced any stroke significantly in patients with mild (5 versus 16 events; hazard ratio, 0.36 [95% CI, 0.13–0.97]; P=0.04)-to-moderate (16 versus 32 events; hazard ratio, 0.50 [95% CI, 0.29–0.92]; P=0.03) white matter changes. Heart rate and HDL (high-density lipoprotein) cholesterol level were significantly higher in the cilostazol group than in the aspirin group at follow-up.	
504	B. J. Kim et al (2018). Prevention of cardiovascular events in Asian patients with ischaemic stroke at high risk of cerebral haemorrhage (PICASSO): a multicentre, randomised controlled trial. The Lancet Neurology. 17: 6.	1,534 Asian patients with ischaemic stroke and past ICH or microbleeds.	Cilostazol (100 mg twice a day) versus aspirin (100 mg once a day).	MACE (efficacy) ICH (Safety)	Cilostazol was non-inferior (but not superior) to aspirin for the prevention of MACCE but did not reduce the risk of haemorrhagic stroke.	+ Double-blind RCT

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	509-518.					
505	J. Qiu et al (2018). Antiplatelet Therapy, Cerebral Microbleeds, and Intracerebral Hemorrhage: A Meta-Analysis. Stroke. 49: 7. 1751-1754.	Meta-analysis of different effects of antiplatelet therapy on lobar and deep MBs	Antiplatelets therapy	Pooled OR for CMB incidence and distribution (strictly lobar, deep/infratentorial) in antiplatelet users versus non antiplatelet users and calculated the OR for the incidence of intracerebral haemorrhage in antiplatelet users with CMBs versus those without	CMBs were more frequent in antiplatelet users than those in Non antiplatelet users (pooled OR, 1.21; 95% CI, 1.07–1.36; P=0.002). There was a significant association of antiplatelet therapy with strictly lobar MBs (OR, 1.45; 95% CI, 1.15–1.84; P=0.002) rather than deep/ infratentorial MBs (OR, 1.37; 95% CI, 0.98–1.90; P=0.062). Intracerebral haemorrhage incidence was higher in participants with CMBs than those without CMBs (OR, 3.40; 95% CI, 2.00–5.78; P=0.000) in antiplatelet users.	+ Inherent bias Risk of omission of other studies Heterogeneity
505	J. Qiu et al (2018). Antiplatelet Therapy, Cerebral Microbleeds, and Intracerebral Hemorrhage: A Meta-Analysis. Stroke. 49: 7. 1751-1754.	Study level MA (SLMA), 37 studies N=20998 Included: IS, ICH, or stroke free Baseline MRI AP status known	None	ICH	CMBs were more frequent in antiplatelet users than those in non-antiplatelet users (pooled OR, 1.21; 95% ci 1.07–1.36; P=0.002) Intracerebral hemorrhage incidence was higher in participants with CMBs than those without CMBs (OR, 3.40; 95% CI, 2.00–5.78; P=0.000) in antiplatelet users	

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
506	K. K. Lau et al (2018). Antiplatelet treatment after transient ischemic attack and ischemic stroke in patients with cerebral microbleeds in 2 large cohorts and an updated systematic review. Stroke. 49: 6 1434-1442.	2 pooled prospective cohorts, OXVASC, Hong Kong (HKU). Also SLMA N=2083 Included: IS/TIA, consecutive Baseline MRI Follow up available Mean follow up 3.5 years	None	ICH Extracranial bleeds IS ACS Death	After adjusting for age, sex, and vascular risk factors, a high microbleed burden was an independent predictor of recurrent ischemic stroke, ICH, all cause mortality, and nonvascular death (all Ptrend<0.05) In patients with microbleeds, the 5-year absolute risks of a nondisabling ischemic stroke exceeded that of a nondisabling ICH (9.4% versus 1.2%; P<0.0001), even among those with ≥5 microbleeds (9.8% versus 2.1%; P=0.008) in patients with ≥5 microbleeds, risks of a disabling/fatal ICH increased substantially, such that the 5-year absolute risks of a disabling/fatal ischemic stroke and ICH were similar (9.0% versus 9.4%; P=0.81) in years 1 to 5, the risks of ICH increased steeply such that the risks of ICH matched that of ischemic stroke (11.2% versus 12.0%)	
506	K. K. Lau et al (2018). Antiplatelet treatment after transient	Two cohort studies (OXVASC and Hong Kong) of 2,083 patients with ischaemic stroke (Hong	Microbleeds vs no microbleeds. Microbleed burden	ICH, major extracranial haemorrhage, ischaemic stroke, coronary events	Major extracranial bleeds unrelated to microbleed burden. 5-year risk of ICH	+ Non-randomised

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	ischemic attack and ischemic stroke in patients with cerebral microbleeds in 2 large cohorts and an updated systematic review. Stroke. 49: 6 1434-1442.	Kong) or ischaemic stroke or TIA (OXVASC); these analyses are of the 1,811 on any antiplatelet drugs.			steeply related to microbleed burden. Relative risk of ischaemic stroke also increased with microbleed burden, such that the absolute risk of ischaemic stroke and coronary events exceeded ICH and major extracranial bleeds during the first year, even among patients with ≥5 microbleeds (11.6% versus 3.9%). Absolute risk of haemorrhage (11.2%) matched that of ischaemic events (12.0%) after 1 year.	Two cohorts and study-level meta-analysis
751	Chabriat H, et al (2013). Results of the perform magnetic resonance imaging study. Journal of Neurology. 260. 3071–3076.	748 patients PERFORM MRI sub-study (of 1,056 patients randomised in the main trial). PERFORM was stopped early for futility. mean age of the population was 67.7 ± 8 years (range 55–98 years), 65 % patients were male, 87.4 % of qualifying events were ischemic stroke (69 % atherothrombotic or likely atherothrombotic stroke, 26 % lacunar stroke), 12 % were TIAs, and 0.6 % were arterial retinal ischemic events. According to the modified Rankin Scale scores, 87 % the patients had no or slight disability.	Terutroban vs aspirin	Microbleeds and various other SVD MRI features at 1m and 24m after randomisation	In the PERFORM study, the progression of FLAIR lesions, of cerebral or hippocampal atrophy and of microbleeds did not differ between patients treated by terutroban and those treated by aspirin.	**+**
751	Chabriat H, et al (2013).	MRI substudy of PERFORM RCT ASA N=748	Terutroban, specific thromboxane receptor inhibitor	Change in MRI hypointense, hyperintense lesions on	No significant difference in any parameter between 2 groups.	**++/+** High

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	Results of the perform magnetic resonance imaging study. Journal of Neurology. 260. 3071–3076.	Included: Age>55 IS/TIA<3Mo (8d for TIA) No MRI contraindication		FLAIR, volumes of brain and hippocampi, New CMBs, from M1-m24	CMBs (new) in 10.7% (ASA) and 16.3% (terutroban)	
516	Martí-Fàbregas J et al (2019). MRI predicts intracranial hemorrhage in patients who receive long-term oral anticoagulation. Neurology. 92. 2432-2443.	Multicenter and prospective observational study in Spain. Age older than 64 years, recent cardioembolic ischemic stroke, and were new users of oral anticoagulants.	None.	Primary endpoint was ICH that occurred during follow-up.	937 patients (aged 77.6 ± 6.5 years; 47.9% were men). Microbleeds were detected in 207 patients (22.5%), moderate/severe white matter hyperintensities in 419 (45.1%), and superficial siderosis in 28 patients (3%). After a mean follow-up of 23.1 ± 6.8 months, 18 patients (1.9%) experienced an ICH. In multivariable analysis, microbleeds (hazard ratio 2.7, 95% confidence interval [CI] 1.1–7, p = 0.034) and moderate/severe white matter hyperintensities (hazard ratio 5.7, 95% CI 1.6–20, p = 0.006) were associated with ICH (C index 0.76, 95% CI 0.66–0.85). Rate of ICH was highest in patients with both microbleed and moderate/severe WMH (3.76 per 100 patient-years, 95% CI 1.62–7.4).	++