Question 18 evidence tables

Question 18: Should antiplatelet therapy be used for vascular prevention after ICH?

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

ATT = antithrombotic trialist collaboration, CAA = cerebral amyloid angiopathy, OAC = oral anticoagulation, DOAC = direct oral anticoagulant, DVT = deep vein thrombosis, APT = antiplatelet therapy, SE = secondary event, MRI = magnetic resonance imaging, AF = atrial fibrillation, 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, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
42	R. Al-Shahi Salman et al. (2019). Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *The Lancet,* 393:10191 2613-2623	Multicentre - UK, prospective, randomised, openlabel, blinded endpoint, parallel-group, adults ≥ 18 taking antithrombotics and developed ICH and survived 24 hours	Restart antithrombotic or avoid (1:1)	Recurrent ICH, secondary outcome a composite of all major haemorrhages and composite of all occlusive events	562 participants recruited, 268 to start antiplatelets, 269 no antiplatelets, 4% had recurrent ICH vs 9%, No difference secondary outcome (major haemorrhage and occlusive vascular events) apart from events defined by the ATT collaboration.	**++** High quality
42	R. Al-Shahi Salman et al. (2019). Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *The Lancet,* 393:10191 2613-2623	Multicentre - UK, prospective, randomised, openlabel, blinded endpoint, parallel-group, adults ≥ 18 taking antithrombotics and developed ICH and survived 24 hours	Restart antithrombotic or avoid (1:1)	Recurrent ICH, secondary outcome a composite of all major haemorrhages and composite of all occlusive events	537 participants were recruited a median of 76 days (IQR 29–146) after ICH symptom onset: 268 were assigned to start and 269 (one withdrew) to avoid antiplatelet therapy. Followed for a median of 2·0 years (IQR [1·0– 3·0]; completeness 99·3%). 12 (4%) of 268 participants allocated to antiplatelet therapy had recurrence of intracerebral haemorrhage compared with	Not sure how to calculate a score. But this is a high quality study. The main concerns are lack of power (under-recruited) and being open label. There are also few participants with probable CAA (diagnosed by CT or MRI) so the results may not fully generalise to those at highest risk of recurrent ICH.

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					23 (9%) of 268 participants allocated to avoid antiplatelet therapy (adjusted hazard ratio 0·51 [95% CI 0·25–1·03]; p=0·060). 18 (7%) participants allocated to antiplatelet therapy experienced major haemorrhagic events compared with 25 (9%) participants allocated to avoid antiplatelet therapy (0·71 [0·39–1·30]; p=0·27), and 39 [15%] participants allocated to antiplatelet therapy had major occlusive vascular events compared with 38 [14%] allocated to avoid antiplatelet therapy (1·02 [0·65–1·60]; p=0·92).	
43	R. Al-Shahi Salman et al. (2021). Effects of Antiplatelet Therapy After Stroke Caused by Intracerebral Hemorrhage: Extended Follow-up of the RESTART Randomized Clinical Trial. *JAMA Neurology,* 78:10 1179-1186	Multicentre - UK, prospective, randomised, openlabel, blinded endpoint, parallel-group, adults ≥ 18 taking antithrombotics and developed ICH and survived 24 hours	Restart antithrombotic or avoid (1:1)	Recurrent ICH, secondary outcome a composite of all major haemorrhages and composite of all occlusive events	562 participants recruited, 268 to start antiplatelets, 269 no antiplatelets, 4% had recurrent ICH vs 9%, No difference secondary outcome (major haemorrhage and occlusive vascular events) apart from events defined by the ATT collaboration.	**++** High quality
43	R. Al-Shahi Salman et al. (2021). Effects of Antiplatelet Therapy After Stroke Caused by Intracerebral Hemorrhage: Extended	Multicentre - UK, prospective, randomised, openlabel, blinded endpoint, parallel-group, adults ≥ 18 taking antithrombotics and developed ICH and survived 24 hours	Restart antithrombotic or avoid (1:1)	Longer term - Recurrent ICH, secondary outcome a composite of all major haemorrhages and composite of all occlusive events	No evidence of an effect of restarting antiplatelet therapy on recurrent ICH or all vascular events. Did not confirm the original fnding	see RESTART main paper

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	Follow-up of the RESTART Randomized Clinical Trial. *JAMA Neurology,* 78:10 1179-1186				that ICH mgiht be reduced. The primary outcome of recurrent ICH affected 22 of 268 participants (8.2%) allocated to antiplatelet therapy compared with 25 of 268 participants (9.3%) allocated to avoid antiplatelet therapy (adjusted hazard ratio, 0.87; 95%CI, 0.49-1.55; P = .64). A major vascular event affected 72 participants (26.8%) allocated to antiplatelet therapy compared with 87 participants (32.5%) allocated to avoid antiplatelet therapy (hazard ratio, 0.79; 95%CI, 0.58-1.08; P = .14).	
47	X. Ding et al. (2018). Resumption of antiplatelet therapy in patients with primary intracranial hemorrhage-benefits and risks: A meta-analysis of cohort studies. *J Neurol Sci,* 384: 133-138	Systematic review and meta-analysis of studies examining association of resumption of APT after intracranial haemorrhage on APT and recurrent thromboembolic ischaemic events. Included: 1. RCTs or cohort studies; (2) intracranial haemorrhage at baseline (3	Resumption of APT	Recurrent ICH or haematoma expansiion. Ischaemic or thromboembolic events	825 APT resumption. 1091 non-APT resumption. 1202 resumed other anti thrombotic agents. APT resumption not associated with increased risk of recurrent ICH/haematoma expansion (pooled RR 0.84, CI 0.47-1.51, I squared 71%) vs no APT resumption. APT resumption associated with reduced risk of Ischaemic or TE events HR 0.61 (CI 0.48-0.79, I squared 20%)	
44	L. Li et al. (2021). Risks of recurrent stroke and all serious vascular events after	Pooled population based cohort studies, Oxfordshire and Lothian UK, n=674 with spontaneous ICH. Also meta analysis of hospital	None	Rates of recurrent ICH, recurrent IS, serious vascular events (broadly defined)	Event rates/100 person years, recurrent ICH: All ICH (pooled): 3.2; Lobar ICH: 5.1; Non-lobar ICH 1.8; AF present:	

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	spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *The Lancet Neurology,* 20:6 437-447	and population based cohort studies , 5 additional studies all hospital based			3.3; AF absent: 3.2 Event rates/100 person years, recurrent IS: All ICH (pooled): 1.7; Lobar ICH: 3.2; Non-lobar ICH 1.6; AF present: 6.3; AF absent: 0.7	
44	L. Li et al. (2021). Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *The Lancet Neurology,* 20:6 437-447	Pooled population-based cohort studies, Oxfordshire and Lothian UK, n=674 with spontaneous ICH. Also meta analysis of hospital and population based cohort studies .	none	Recurrent ICH, recurrent IS, serious vascular events	The rates of ischaemic stroke and recurrent ICH support the generalisability of the event rates observed in RESTART. Highest Ich riks oin lobar ICH, highest IS risk in those with AF.	**++** High quality population-based studies.
45	L. A. Perry et al. (2017). Antithrombotic treatment after stroke due to intracerebral haemorrhage. *The Cochrane database of systematic reviews,* 5:5 CD012144-CD012144	2 RCTs with a total of 121 participants. Both RCTs were of short-term parenteral anticoagulation early after ICH	parenteral anticoagulation	Death, major bleeding, ICH, ischaemic events, DVT	No difference in death, ischaemic stroke, DVT or bleeding outcomes	
46	L. Poli et al. (2018). Anticoagulants Resumption after Warfarin-Related Intracerebral Haemorrhage: The Multicenter Study on Cerebral Hemorrhage	Multicentre in Italy, observational, registry, retrospective, non randomised, patiemt admitted with ICH and on OAC and survived intitial admission	Restart OAC (warfarin/DOAC) vs Antithrombotic vs no treatement	Primary end point composit of Stroke, systemic embolism and all cause mortality, secondary outcome ischaemic stroke/Se, all cause mortality, recurrent	3492 subjects included in strudy, 432 subjects were receiving OAC, only 244 included in final analysis, follow up for 7,054 person months, OAC resumed in 32.4%, antiplatlets in 21.3% and no treatment in 46.3%,	**+** Acceptable,Observational study and prone for selection bias and multiple confounders, the numbers included in the study are small, issues with ICH

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	in Italy (MUCH-Italy). *Thromb Haemost,* 118:3 572-580			ICH amd major extracranial hamorrhage	26.2% of patients reached the combined end-point, 36 (56.2%) were receiving no antithrombotic treatment, 9 (14.1%) were under OACs treatment, and 19 (29.7%) were receiving antiplatelet medications. OAC resumption after ICHwas associated (likelihood ratio test, p < 0.001) with reduction of the longterm risk of all-cause mortality and ischemic stroke/SE in comparison with no antithrombotic therapy . All-cause mortality was recorded in 38 (15.6%) patients: 24 (63.2%) not under antithrombotic treatment, 5 (13.1%) receiving OACs (weighted HR, 0.17; 95% CI, 0.06–0.45), and 9 (23.7%) receiving antiplatelet agents (weighted HR, 0.67; 95% CI, 0.30–1.49). Of the 34 (13.9%) patients who experienced ischemic stroke/SE, 19 (55.9%) were receiving no antithrombotic drugs, 4 (11.8%) were on OAC treatment (weighted HR, 0.19; 95% CI, 0.06–0.60), and 11 (32.3%) on antiplatelets (weighted HR, 0.88, 95% CI, 0.40–1.94). (3.3%) patients experienced major bleeding (four recurrent ICH and four major extracranial bleeding). Antithrombotic treatment	characterisation and the lack of use of advanced imaging (MRI)

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					(either with antiplatelets or OACs) did not turn out to significantly increase the risk of bleeding in comparison with no-antithrombotic therapy.	
46	L. Poli et al. (2018). Anticoagulants Resumption after Warfarin-Related Intracerebral Haemorrhage: The Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy). *Thromb Haemost,* 118:3 572-580	Prospective cohort study, hospital-based, multi-centre, Italy, longitudinal follow-up (median 18 months, maximum approx. 10 years). Included spontaneous ICH, 2002-2014, associated with OAC use, in survivors >4 weeks, with available follow up. Studied asso	Resumption of OAC or APT	Primary outcome - stroke/SE/All cause death. Secondary - stroke/SE alone, All cause death alone, Major bleeding.	Indications: 61% AF/flutter, 12% VTE, 27% other (mainly valve heart disease). In all patients, 32% resumed OAC, 21% APT, 47% no antithrombotic therapy. For primary analysis, adjusted HR 0.21 (0.09-0.45) for OAC resumption, HR 0.87 (0.48-1.59) for APT. Similar benefit for all-cause death (aHR 0.17, CI 0.06-0.45) and stroke/SE (aHR 0.19, CI 0.06-0.60). In NVAF subgroup only, results were similar.	
48	K.-C. Teo et al. (2017). Antiplatelet Resumption after Antiplatelet-Related Intracerebral Hemorrhage: A Retrospective Hospital-Based Study. *World Neurosurgery,* 106: 85-91	Hospital based, Observational, antiplatelet associated ICH survivors (n=109)	none	cardiovascular outcomes, ICH	The median duration of follow-up was 3.5y. More ischaemic events than ICH (6.8 v 2.6 per 100 pt-years). Antiplatelet use not associated with increased ICH, HR 1.11 (0.27-4.62). CAA predicted ICH (HR 24.34, 2.8-211.47)	- Poor, risk of selection bias, confounding by indication, low statistical power and precision.