Question 45 evidence tables

Question 45: What is the best antithrombotic treatment to prevent short-term vascular events and stroke after cervical artery dissection?

NB Any discrepancies between reviewers in evidence quality and comment were discussed by the topic group at the evidence review meeting to discuss the question.

VKA = vitamin k antagonist, MRI = magnetic resonance imaging, ITT = intention to treat, AC = anticoagulants, AP = antiplatelets, CAD = cervical artery disease, DWI = diffusion weighted imaging, ICB = intracranial bleed, mRS = modified Rankin Scale, eICAD = extracranial internal carotid artery dissection, MRA = magnetic resonance angiography, CTA = computed tomography angiography, DSA = digital subtraction angiography, 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
87	S. T. Engelter et al. (2021). Aspirin versus anticoagulation in cervical artery dissection (TREAT-CAD): an open-label, randomised, non-inferiority trial. *The Lancet Neurology,* 20:5 341-350	Multicentre (10 sites, in Switzerland, Denmark and Germany), randomised, open label, non inferiority trial. 194 patients >18 years with symptomatic, MRI-verified carotid artery disection within 2 weeks before enrolment were recruited	100 (52%) were assigned to the aspirin group and 94 (48%) were assigned to the vitamin K antagonist group. Per-protocol population=173, 91 (53%) aspirin group and 82 (47%) vitamin K antagonist	Primary: Clinical (stroke, major haemorrhage, or death) and MRI outcomes (new ischaemic or haemorrhagic brain lesions) in the per-protocol population, at 14 days (clinical and MRI) and 90 days (clinical only)	Primary endpoint in 21/91 (23%) patients in the aspirin group and in 12/82 (15%) patients in the vitamin K antagonist group (absolute difference 8% [95% CI –4 to 21], non-inferiority p=0·55). Aspirin was not non-inferior to vitamin K antagonist. Compared to Markus 2019, the much higher primary outcome rates were driven by MRI outcome. When only clinical outcomes were considered, the rates of clinical outcome was 4.1% in ITT and 4.6% in per-protocol i.e 7 ischaemic stroke (all in aspirin) and 1 major extracranial haemorrhage in VKA.	**++** High quality.

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87	S. T. Engelter et al. (2021). Aspirin versus anticoagulation in cervical artery dissection (TREAT-CAD): an open-label, randomised, non-inferiority trial. *The Lancet Neurology,* 20:5 341-350	Multicentre, randomised, open-label, non-inferiority trial in ten stroke centres across Switzerland, Germany, and Denmark. 194 patients randomly assigned to AC (94) and aspirin (100)	AC or AP treatment for 3 months	Follow-up, 3 months: Ischemic stroke, major bleeding or death	Per protocol analysis, 3 months, Ischemic stroke: AC 0/82 vs AP 7/91; Major bleeding AC 1/82 vs AP 0/91; Death AC 0/82 vs 0/91; Composite outcome AC 1/82 vs AP 7/91	**++** Open trial with blind assessment
88	H. Gensicke et al. (2015). New ischaemic brain lesions in cervical artery dissection stratified to antiplatelets or anticoagulants. *European Journal of Neurology,* 22(5): 859-e61	Prospective observational study included consecutive CAD patients with ischaemic or non-ischaemic symptoms within the preceding 4 weeks (n=68)	Antithrombotic treatments antiplatelets (e.g. aspirin, clopidogrel, dipyramidole, either alone or in combination) or anticoagulants (i.e. vitamin K antagonists, intravenous heparin or low molecular weight heparin)	Outcome measures were any new DWI lesions or ICBs on follow-up MRI scans	Re: PICO - The type of antithrombotic treatment had no impact either on occurrence of new DWI lesions [1.00 (0.32–3.15)] or on functional 6-month outcome [1.27 (0.41–3.94)].	**++**
88	H. Gensicke et al. (2015). New ischaemic brain lesions in cervical artery dissection stratified to antiplatelets or anticoagulants. *European Journal of Neurology,* 22(5): 859-e61	Prospective observational study included consecutive CAD patients with ischaemic or non-ischaemic symptoms within the preceding 4 weeks; AC 25 patients and AP 43 patients.	Antithrombotic treatments antiplatelets (e.g. aspirin, clopidogrel, dipyramidole, either alone or in combination) or anticoagulants (i.e. vitamin K antagonists, intravenous heparin or low molecular weight heparin)	Outcome measures were any new DWI lesions or ICBs on follow-up MRI scans	The type of antithrombotic treatment had no impact either on occurrence of new DWI lesions AC 7/25 vs AP 10/43; functional outcome (mRS 0-1) at 6-month outcome AC 19/25 (76%) vs AP 30/43 (70%).	**+**

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89	N. Hynes et al. (2021). Surgical and radiological interventions for treating symptomatic extracranial cervical artery dissection. *Cochrane Database of Systematic Reviews,* 2021(1) (no pagination):	Cochrane Review: Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) of either surgical or endovascular intervention for the management of symptomatic CeAD were eligible for inclusion. Only studies with anticoagulants or antiplatelet treatment as the control group were included.	Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) of either surgical or endovascular intervention for the management of symptomatic CeAD were eligible for inclusion. Only studies with anticoagulants or antiplatelet treatment as the control group were included.	Primary outcomes were ipsilateral stroke and disability. Secondary outcomes were death, any stroke, or transient ischaemic attack, residual stenosis (> 50%), recurrence of cervical dissection, expanding pseudoaneurysm, or major bleeding.	There are no completed RCTs or CCTs undertaken in this area of research.	**0** No new data
89	N. Hynes et al. (2021). Surgical and radiological interventions for treating symptomatic extracranial cervical artery dissection. *Cochrane Database of Systematic Reviews,* 2021(1) (no pagination):	Cochrane systematic review	Surgical and radiological interventions versus best medical treatment	No study and no data	No data	**0** Not performed as there no results
89	N. Hynes et al. (2021). Surgical and radiological interventions for treating symptomatic extracranial cervical artery dissection. *Cochrane Database of Systematic Reviews,* 2021(1) (no pagination):	Cochrane systematic review	Radiological + medical vs medical and Surgical + medical vs medical	N/A	No RCTs or controlled clinical trials found	**++** No RCTs or controlled clinical trials found

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90	S. C. Larsson et al. (2017). Prognosis of carotid dissecting aneurysms: Results from CADISS and a systematic review. *Neurology,* 88:7 646-652	SR looking at stroke risk in patients with non-surgically-treated extracranial CAD and Secondary analysis of CADISS RCT. with dissecting aneurisms.	Antiplatelets vs anticoagulation	Stroke at 12 months	There were too few events to determine whether antiplatelets or anticoagulants were more effective at preventing recurrent stroke in patients with DA: no stroke in 26 DA patients treated with antiplatelets and 1 stroke in 22 DA patients treated with anticoagulants. No association between treatment allocation and whether dissecting aneurysm at baseline persisted or whether new dissecting aneurysm developed. At 12 months there was no difference in stroke in those with and without dissecting aneurysm	+ SIGN checklist for systematic reviews
90	S. C. Larsson et al. (2017). Prognosis of carotid dissecting aneurysms: Results from CADISS and a systematic review. *Neurology,* 88:7 646-652	Secondary analysis of CADISS RCT and SR looking at dissecting aneurysms	Antiplatelets vs anticoagulation	Stroke at 12 months	No association between treatment allocation and whether dissecting aneurysm at baseline persisted or whether new dissecting aneurysm developed. At 12 months there was no difference in stroke in those with and without dissecting aneurysm	+ Secondary analysis of RCT and SR of retrospective observational studies
91	P. Lyrer & S. Engelter. (2010). Antithrombotic drugs for carotid artery dissection. *Cochrane Database Syst Rev,* :10 Cd000255	Cochrane Review: 1. To determine whether, in patients with eICAD, treatment with anticoagulants, antiplatelet agents or control was associated with a better functional outcome. 2. To compare, among patients treated with either	Randomised controlled trials, controlled clinical trials and non-randomised studies (if they reported on outcome stratified by antithrombotic	Primary outcomes were ipsilateral stroke and disability. Secondary outcomes were death, any stroke, or transient ischaemic attack, residual stenosis (> 50%), recurrence of cervical	The authors not find any completed randomised trials. Comparing antiplatelets with anticoagulants across 36 observational studies (1285 patients), there were no significant differences in the odds of death (Peto odds ratio	+ Significant number of indirect observational studies supporting best medical therapy with either agent

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		anticoagulants or antiplatelet agents, the risk of ischaemic strokes and major bleeding episodes.	treatment and included at least four patients) of anticoagulants or antiplatelet agents for the treatment of extracranial internal carotid artery dissection.	dissection, expanding pseudoaneurysm, or major bleeding.	(Peto OR) 2.02, 95% CI 0.62 to 6.60), or the occurrence of ischaemic stroke (OR 0.63, 95% CI 0.21 to 1.86) (34 studies, 1262 patients). For the outcome of death or disability, there was a nonsignificant trend in favour of anticoagulants (OR 1.77, 95% CI 0.98 to 3.22; P = 0.06) (26 studies, 463 patients). Symptomatic intracranial haemorrhages (5/627; 0.8%) and major extracranial haemorrhages (7/425; 1.6%) occurred only in the anticoagulation group; however, for both these outcomes, the authors state the estimates were imprecise and indicated no significant diHerence between the two treatment modalities.	
91	P. Lyrer & S. Engelter. (2010). Antithrombotic drugs for carotid artery dissection. *Cochrane Database Syst Rev,* :10 Cd000255	Cochrane systematic review: Included observational studies of patients with extracranial internal carotid artery dissection	AC vs AP	Primary outcomes were death (all causes) and death or disability. Secondary outcomes were ischaemic stroke, symptomatic intracrania haemorrhage, and major extracranial haemorrhage during the reported follow-up period.	No randomized controlled trial was found. Comparing AP with AC across 36 observational studies (1285 patients), there were no significant differences in the odds of death (Peto odds ratio (Peto OR) 2.02, 95% CI 0.62 to 6.60), or the occurrence of ischaemic stroke (OR 0.63, 95% CI 0.21 to 1.86) (34 studies, 1262 patients). Death or disability, there was a nonsignificant trend in favour of anticoagulants (OR 1.77, 95%	++

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					CI 0.98 to 3.22; P = 0.06) (26 studies, 463 patients). Symptomatic intracranial haemorrhages (5/627; 0.8%) and major extracranial haemorrhages (7/425; 1.6%) occurred only in the anticoagulation group; however, for both these outcomes, the estimates were imprecise and indicated no significant difference between the two treatment modalities.	
91	P. Lyrer & S. Engelter. (2010). Antithrombotic drugs for carotid artery dissection. *Cochrane Database Syst Rev,* :10 Cd000255	Cochrane systematic review	Antiplatelets, anticoagulants or control	Primary: Death, death or disability (mRS); Secondary: ischaemic stroke, sICH, major extracranial haemorrhage	No RCTs or controlled clinical trials found. 36 Non-randomised studies (n=1285), no differences in death, ischaemic stroke. Death or disability: non-significant trend in favour of anticoagulants.	**++** From a non-randomised perspective, but no RCTs or controlled clinical trials found
92	H. S. Markus et al. (2015). Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): A randomised trial. *The Lancet Neurology,* 14(4): 361-367	Multicentre (39 UK, 7 Australia), prospective, randomised, open-label, assessor blinded. 250 patients with ischaemic stroke/TIA within 7 days and extracranial carotid artery or vertebral artery dissection on MRA/CTA/DSA where enrolled.	126 patients were assigned to antiplatelet and 124 assigned to anticoagulant.	Primary endpoints were ipsilateral stroke or death within 3 months of randomisation. Secondary outcomes were ipsilateral TIA, stroke or death at 3 months; any stroke or death at 3 months, any stroke at 3 months, any TIA at 3 months; mortality at 3 months,	ITT population=250; per-protocol population=197. No stiatistically significant difference in all primary and secondary outcome using both ITT and per-protocol analysis. Only 4/250 (1.6%) patients had an ipsilateral stroke or death	**++** High quality.
92	H. S. Markus et al. (2015). Antiplatelet treatment compared with anticoagulation	Randomized, open-label international multicenter parallel design study (CADISS). Recruitment in 39 stroke and	Anticoagulants (AC) or Antiplatelets (AP) for 3 months. Evaluation	Follow-up, 3 months: Ischemic stroke, major bleeding, death or composite outcomes	Results at 3 months are included in Markus 2019. AC: 124 patients and AP 126 patients: Per-protocol	**++** Trial was open, and both patients and clinicians were

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	treatment for cervical artery dissection (CADISS): A randomised trial. *The Lancet Neurology,* 14(4): 361-367	neurology secondary care centers in the United Kingdom and 7 centers in Australia . Two hundred fifty participants with extracranial carotid (118) and vertebral dissection (132) with symptom onset within the last 7 days were recruited.	perfomred at 3 months		analysis: Follow-up, 3 months: Ischemic stroke: AC 1/96 vs AP 3/101; Major bleeding: AC 1/96 vs AP 0/101; Death: AC 0/96 vs 0/101; Composite outcome (Risk of stroke, major bleeding or death) AC 3/101 vs AP 2/96	aware of treatment allocation. However, an adjudication committee assessed all primary end points was blinded to treatment. Randomization was provided via an automated 24-hour telephone randomizat
93	H. S. Markus et al. (2019). Antiplatelet therapy vs anticoagulation therapy in cervical artery dissection: The cervical artery dissection in stroke study (cadiss) randomized clinical trial final results. *JAMA Neurology,* 76(6): 657-664	Multicentre (39 UK, 7 Australia), prospective, randomised, open-label, assessor blinded. 250 patients with ischaemic stroke/TIA within 7 days and extracranial carotid artery or vertebral artery dissection on MRA/CTA/DSA where enrolled.	126 patients were assigned to antiplatelet and 124 assigned to anticoagulant.	Primary endpoints were ipsilateral stroke or death within 3 months of randomisation. Secondary outcomes were ipsilateral stroke or death at 12 months; ipsilateral TIA, stroke or death at 3 and 12 months; any stroke or death at 3 and 12 months, any stroke	ITT population=250; per-protocol population=197. No stiatistically significant difference in all primary and secondary outcome using both ITT and per-protocol analysis. Recurrent stroke rate at 1 year was 6/250 (2.4%) on ITT analysis and 5/197 (2.5%) on PP analysis	**++** High quality.
93	H. S. Markus et al. (2019). Antiplatelet therapy vs anticoagulation therapy in cervical artery dissection: The cervical artery dissection in stroke study (cadiss) randomized clinical trial final results. *JAMA Neurology,* 76(6): 657-664	Randomized, open-label international multicenter parallel design study (CADISS). Recruitment in 39 stroke and neurology secondary care centers in the United Kingdom and 7 centers in Australia. Two hundred fifty participants with extracranial carotid (118) and vertebral dissection (132) with symptom onset within the last 7 days were recruited.	Anticoagulants (AC) or Antiplatelets (AP) for 3 months. Evaluation perfomred at 3 months and 12 months	Ischemic stroke, major bleeding, death, and composite outcome (Risk of stroke, major bleeding or death) at 3 months and 12 months	Anticoagulants (AC): 124 patients and antiplatelets (AP) 126 patients: Per-protocol analysis: Follow-up, 3 months: Ischemic stroke: AC 1/96 vs AP 3/101; Major bleeding: AC 1/96 vs AP 0/101; Death: AC 0/96 vs 0/101; Composite outcome (Risk of stroke, major bleeding or death): AC 3/101 vs AP 2/96 Follow-up, 12 months: Ischemic stroke: AC 1/96 vs AP 4/101; Major bleeding: AC 1/96 vs AP 0/101; Death: AC 0/96 vs 1/101;	**++** Trial was open, and both patients and clinicians were aware of treatment allocation. However, an adjudication committee assessed all primary end points was blinded to treatment. Randomization was provided via an automated 24-hour telephone randomizat

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					Composite outcome: AC 2/96 vs AP 4/101.	
95	T. Wein et al. (2018). Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017. *International Journal of Stroke,* 13(4): 420-443	Guideline	Antiplatelets, anticoagulants or control	Not relevant	Antithrombotic therapy for stroke prevention is recommended for individuals with a diagnosis of an extracranial carotid or vertebral artery dissection [Evidence Level B]. a. There is uncertainty about the comparative efficacy of antiplatelet therapy vs. anticoagulation with heparin/warfarin; either treatment is considered reasonable and decision should be based on individual risk/benefit analysis [Evidence Level B]. b. There is a lack of evidence regarding the optimal duration of antithrombotic therapy and the role of repeat vascular imaging in decision-making. Decisions may be based onindividual clinical factors [Evidence Level C].	**N/A** Not performed
95	T. Wein et al. (2018). Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017. *International Journal*	Guideline	Antiplatelets, anticoagulants or control	CADISS included	Antithrombotic therapy for stroke prevention is recommended for individuals with a diagnosis of an extracranial carotid or vertebral artery dissection [Evidence Level B]. a. There is uncertainty about the comparative efficacy of	**++**

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	of Stroke, 13(4): 420-443				antiplatelet therapy vs. anticoagulation with heparin/warfarin; either treatment is considered reasonable and decision should be based on individual risk/benefit analysis [Evidence Level B]. b. There is a lack of evidence regarding the optimal duration of antithrombotic therapy and the role of repeat vascular imaging in decision-making. Decisions may be based on individual clinical factors [Evidence Level C].	
691	Liu, S., et al. (2021). Antiplatelet vs. Anticoagulation in Cervical Artery Dissection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in Neurology* 12: 745106.	SRMA Two RCTs 444 patients in the IIT group and 370 patients in the PP group	Antiplatelets versus anticoagulation	TIA, intracranial haemorrhage or major extracranial haemorrhage.	In the ITT population, patients in the antiplatelet group had a higher rate of ischaemic stroke at 3 months (RR 6.73 [95% CI 1.22-37.15], I^2=0; p=0.029. There was no difference between the treatment groups for TIA, intracranial haemorrhage or major extracranial haemorrhage or the composite of these outcomes at 3 months. For the PP population, the results of the MA of outcomes were consistent with the ITT population. All cases of major bleeding occurred in the anticoagulation group.	

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691	Liu, S., et al. (2021). Antiplatelet vs. Anticoagulation in Cervical Artery Dissection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in Neurology* 12: 745106.	Systematic review and meta-analysis	Antiplatelets versus anticoagulation	TIA, ischaemic stroke, intracranial haemorrhage or major extracranial haemorrhage.	In the ITT group, thee was higher risk of IS at 3 months; there was no difference in TIA, ICH, major extracranial haemorrhage or composite of outcomes at 3 months between the two treatment groups. Similar results were observed in the per protocol population.	