National Institute for Health and Care Excellence

Guideline version (Consultation)

Subarachnoid haemorrhage

[Q] Evidence reviews for long-term medicines for reducing the risk of subsequent SAH

NICE guideline <number>

Evidence review underpinning

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Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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ISBN
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Contents

1 Long-term medicines for reducing the risk of subsequent subarachnoid haemorrhage

Evidence review underpinning recommendations 1.4.7 to 1.4.10 and research recommendations in the NICE guideline.

1.1 Review question: What is the clinical and cost effectiveness of long-term medicines for reducing the risk of subsequent subarachnoid haemorrhage, such as antihypertensive medicines, in adults with confirmed subarachnoid haemorrhage?

1.2 Introduction

Pharmacological interventions that might reduce the risk of recurrent subarachnoid haemorrhage (aSAH) are of considerable interest to people with confirmed subarachnoid haemorrhage and to clinicians involved in their care.

Currently, standard blood pressure management guidelines are followed in the management of aSAH patients with systemic hypertension, but it has been suggested that tighter control of blood pressure might be beneficial.

In current practice antithrombotic therapy is only offered to people with another indication (e.g. established atrial fibrillation, venous thromboembolism), but there is interest in whether use of antithrombotic therapy might reduce the risk of subsequent SAH.

This review focuses on the evidence for the clinical and cost-effectiveness of different blood pressure control strategies and for antithrombotic medication in reducing the risk of subsequent aneurysmal subarachnoid haemorrhage.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm.
Intervention(s)	• Antihypertensive medical management (Target BP control) ○ Tight control of blood pressure ○ Standard blood pressure control (>140/90 mmHg) • Antithrombotic medication (e.g. warfarin)
Comparison(s)	Comparators: • To each other ○ Tight control of BP compared to standard management ○ Use of antithrombotic medication compared to restriction of antithrombotic medication • To no treatment
Outcomes	• Mortality • Health and social-related quality of life (any validated measure)

	• Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) • Subsequent subarachnoid haemorrhage Outcomes will be grouped at <30 days, 30days-6 months, 6-12 months, and at yearly time-points thereafter.
Study design	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.

1.4 Clinical evidence

1.4.1 Included studies

Three studies were included in the review,[13, 30, 38] these are summarised in Table 2 below. Given the paucity of evidence and no common outcomes between varying modalities of intervention (e.g. antithrombotic medication), the committee agreed to review each modality separately. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). No evidence was identified for this review on blood pressure control.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix F:.

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

1.4.3 1 Summary of clinical studies included in the evidence review

2 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Darkwah Oppong 2019[13]	**Intervention: Aspirin +/- Clopidogrel** Aspirin was administered in a daily dose of 100mg for at least 3 weeks. If a stent was additionally applied, the antiplatelet therapy was extended using Clopidogrel 75mg daily for at least 6 weeks (n=43) and aspirin use was extended to lifelong (n=329) **Control: No antiplatelet therapy** No antiplatelet therapy was given to patients within this group (n=251)	Patients with aneurysmal subarachnoid haemorrhage who underwent endovascular treatment Mean age (SD): Aspirin: 55 (13) No Aspirin: 54 (14) Germany Cohort study	• In hospital mortality • mRS <3 at 6 months	Confounding factors: groups matched for age
Nagahama 2018[30]	**Intervention: Tirofiban + Aspirin + Clopidogrel** Patients treated with a stent or flow diverter were given tirofiban infusion at the maintenance dosage without bolus doses immediately after device deployment and continued for 2 hours after the procedure. These patients also received 600mg of crushed clopidogrel and 325mg of aspirin via an orogastric tube at the end of the procedure and	Patients selected for this study were those who suffered from aSAH secondary to rupture of a saccular cerebral aneurysm, Hunt & Hess I – III or showed improvement of their neurological status to Hunt and Hess I – III post ventriculostomy. Mean age (SD): DAPT: 56.1 (12.3)	• DCI • Vasospasm	Confounding factors: outcome data was adjustment for potential confounders, such as age, sex, aneurysm location, Hunt and Hess grade, and Fisher grade. Only adjusted data used from the study.

Study	Intervention and comparison	Population	Outcomes	Comments
	continued to receive both medications daily (length of intervention not specified) (n=85). **Control: No antiplatelet therapy** Those patients who underwent coil embolization alone without the use of a stent or flow diverter and therefore received neither clopidogrel nor aspirin made up the control group (n=76).	Control: 51.5 (11.5) USA Cohort study		
Shaw 1985[38]	**Intervention: Dipyridamole** Dipyridamole of 100mg/day orally or 10mg/day intravenously. Medication was continued for 3 months postoperatively (n=336) **Control: Placebo** Placebo medication (orally or IV) continued for 3 months to match active medication arm of study (n=341)	Patients presenting to hospital with SAH Mean age: Dipyridamole: 45 years Placebo: 45.8 years UK Randomized controlled trial	• Glasgow outcome scale (3 months)	

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2 See Appendix D:for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Dipyridamole vs Placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Dipyridamole (95% CI)
GOS 1 (Glasgow outcome scale, 1 -death)	348 (1 study) 3 months	⨁⨁⊖⊖ LOW1 due to imprecision	RR 1.06 (0.60 to 1.89)	114 per 1000	7 more per 1000 (from 46 fewer to 102 more)
GOS 2 (Glasgow outcome scale, 2 - persistent vegetative state)		⨁⨁⊖⊖ LOW1 due to imprecision	Peto OR 7.52 (0.47 to 120.69)	0 per 1000	10 more per 1000 (from 10 fewer to 30 fewer)
GOS 3 (Glasgow outcome scale, 3 - severe disability)		⨁⨁⨁⊖ MODERATE1 due to imprecision	RR 0.56 (0.27 to 1.13)	114 per 1000	50 fewer per 1000 (from 83 fewer to 15 more)
GOS 4 (Glasgow outcome scale, 4 -moderate disability)		⨁⨁⨁⊖ MODERATE1 due to imprecision	RR 1.40 (0.80 to 2.48)	103 per 1000	41 more per 1000 (from 21 fewer to 152 more)
GOS 5 (Glasgow outcome scale, 5 - Low disability)		⨁⨁⨁⨁ HIGH	RR 0.97 (0.82 to 1.16)	600 per 1000	18 fewer per 1000 (from 108 fewer to 96 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 4: Clinical evidence summary: Aspirin +/- Clopidogrel vs Control: No antiplatelet therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aspirin (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aspirin (95% CI)
mRS <3 Scale 0-6; high score represents poor outcome	580 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias and imprecision	RR 1.18 (1.05 to 1.32)	626 per 1000	113 more per 1000 (from 31 more to 200 more)
Bleeding events	580 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias and imprecision	RR 2.21 (1.10 to 4.45)	40 per 1000	48 more per 1000 (from 4 more to 137 more)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

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2 **Table 5: Clinical evidence summary: Dual Antiplatelet Therapy (Tirofiban, Clopidogrel and Aspirin) vs Control: No Antiplatelet**
3 **Therapy**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Dual Antiplatelet Therapy	Risk difference with DAPT (95% CI)
DCI	161 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	Adjusted OR 0.06 (0.01 to 0.31)	Not reported	-
Vasospasm	161 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	Adjusted OR 0.24 (0.10 to 0.61)	Not reported	-
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

4 See Appendix F: for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 6: UK costs of drugs

Drug	Daily dose	Cost per unit	Cost per day
Dipyridamole			
Dipyridamole 50mg/5ml oral suspension	100mg	£1.42	£2.83
Dipyridamole 100mg tablet	100mg	£0.07	£0.07
Clopidogrel			
Clopidogrel 75mg tablet	75mg	£0.06	£0.06
Clopidogrel 300mg tablet	600mg	£4.75	£9.50
Aspirin			
Aspirin 75mg dispersible tablet	75mg	£0.04	£0.04

Source: NHS Drug Tariff, August 2020[34]

1.6 Evidence statements

1.6.1 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes for this question were mortality, health and social related quality of life, degree of disability and subsequent subarachnoid haemorrhage. The number of people achieving target blood pressure, return to daily activity, need for retreatment and complications of interventions were considered important outcomes for decision making.

Evidence was found for health and social quality of life and complications.

1.7.1.2 The quality of the evidence

The evidence for use of anti-thrombotic medication ranged from high to very low quality. Most of the evidence was low or very low quality as it was from observational or non-randomised studies and because of imprecision. Evidence from observational studies is automatically reduced to a lower quality due to inherent risk of selection bias from a lack of randomisation. There was a high risk of uncertainty around a number of outcomes due to significant statistical imprecision around the summary effect estimates. This was indicated by wide-ranging confidence intervals crossing the thresholds which demonstrate clinical significance, with which the committee would typically judge if an intervention shows benefit or harm. The committee noted that the small size of studies and the low event rate of outcomes likely contributed towards this imprecision and reduced the overall quality of outcome data.

The small amount of low quality evidence available prevented the committee from making any strong recommendation for the use of long-term medicines to reduce the risk of subsequent aSAH. The committee agreed however that it would be useful to make consensus recommendations for the use of antiplatelets or anticoagulants for other reasons in people who have had SAH.

No evidence was found for treating people who have had SAH to tighter levels of blood pressure control.

1.7.1.3 Benefits and harms

The use of anti-platelets or anti-coagulants may be of benefit if they reduce subsequent SAH or may cause harm if additional bleeding occurs. The committee were clear that a distinction has to be made between the different causes of intracranial bleeding and that treatment of SAH differs from treatment of stroke where the role of anti-platelet therapy is established. If a culprit aneurysm is secured the risk of subsequent SAH is low so the theoretical benefit of antiplatelet therapy is less clear.

The evidence available did not indicate convincing benefit from use of antiplatelets or anticoagulants when an aneurysm has been secured using current methods of coiling and clipping. One randomised controlled trial showed no difference between dipyridamole and placebo following an aSAH in degree of disability at 3 months.

There were 2 cohort studies comparing aspirin alone or a combination of aspirin, clopidogrel and tirofiban to no antiplatelet therapy. The indication for antiplatelet therapy in these studies was to reduce the risk of thrombosis in a stent or flow diverter used to secure the aneurysm.

There was a clinically significant increase in the number of participants with lower level of disability (mRS <3) but a slight increase (although not clinically significant) in the number of bleeding events with aspirin and clopidogrel administration. Although the data did not show the origin of this excess bleeding, the committee considered that this was likely to be due to bleeding such as GI bleeding, rather than intracranial bleeding.

The comparison of antiplatelet therapy with tirofiban, clopidogrel and aspirin versus no additional antiplatelet therapy showed a clinically significant benefit of reduced likelihood of experiencing DCI or vasospasm with intervention. However, the committee noted that patients receiving antiplatelet therapy were also treated with stents or flow-diverters, and any observed benefits may have been due to this combined intervention rather than purely due to antiplatelet therapy.

The available evidence did not suggest harm from use of antiplatelets and anti-coagulants. The committee agreed that the evidence available was of insufficient quality and quantity to, on its own, allow the committee to make any recommendation for the use of long-term medicines to reduce the risk of subsequent aSAH. The committee agreed that it would be

useful to make consensus recommendations for the use of antiplatelets or anticoagulants for other reasons in people who have had SAH. As such, the committee made a consensus recommendation to balance the risks and benefits of treatment with an antiplatelet or anticoagulant, taking into account specialist assessment of the risk of a future subarachnoid haemorrhage. The committee also recommended through consensus that treatment with antiplatelets or anticoagulants should not be withheld solely on the basis of an aneurysmal subarachnoid aneurysm as long as the culprit aneurysm has been secured by coiling or clipping.

The committee considered it important to stress that these medications should not be withheld solely on the basis of a person having had a subarachnoid haemorrhage if their use is warranted for another reason such as prevention of systemic thromboembolism. In their experience these treatments are safe for people with a secured aneurysm considered to be at low risk of a subsequent SAH and it was important that people received appropriate treatment for other conditions.

The committee were aware that some patients (for example with large non-culprit aneurysms) are judged to be at increased risk of another SAH. Antithrombotic treatment is not thought to increase the risk of SAH in these patients, but if haemorrhage occurs it is likely to be severe. The committee agreed that clinicians should individualise the balance of risks and benefits in these patients and that the decision about management should involve specialist advice from the neurosurgical centre.

There was no evidence identified for the clinical efficacy of antihypertensive medical management. The committee highlighted that systemic hypertension can be a risk factor for subarachnoid haemorrhage and agreed that it would be beneficial to control hypertension in a person who has had a SAH to prevent subsequent SAH. The committee added that there is no known reason to treat people with aSAH and hypertension differently to a person who presents with primary hypertension and no history of SAH. As such, a consensus recommendation was made to manage blood pressure in people who have had an aneurysmal subarachnoid haemorrhage in line with the NICE guideline on hypertension in adults. The committee agreed that this remained an important question and developed a research recommendation on the effectiveness of a lower blood pressure target relative to standard blood pressure control for people with aSAH.

1.7.2 Cost effectiveness and resource use

No published economic literature was identified for this review. Due to the lack of clinical evidence, the cost effectiveness of long-term medicines for reducing the risk of subarachnoid haemorrhage could not be assessed in this population. However, the committee considered that the management of hypertension should be the same in people with a history of subarachnoid haemorrhage as those without, and so cross referred to the hypertension guideline in which cost effectiveness will have been taken into consideration. This recommendation is therefore not expected to have significant resource impact.

The committee considered that people with a successfully secured aneurysm will generally be at low risk of subsequent SAH and anti-thrombotic medication for other indications (such as VTE prophylaxis or prevention of systemic thromboembolism) is likely to be cost effective in people who have an indication for anti-thrombotic therapy (in line with NICE guidance on anti-coagulants and anti-platelets). However, there is much more uncertainty about the cost effectiveness of anti-thrombotic medication in people who have had a SAH and are at high risk of subsequent SAH, and in these patients the risk of thromboembolic events will need to be balanced against the risk of recurrent subarachnoid haemorrhage.

The committee were aware that some practitioners are currently reluctant to prescribe anti-thrombotic medication to people with a history of aSAH without first checking with a specialist, sometimes leading to a delay in the initiation of anti-thrombotic treatment. The

committee made a recommendation not to withhold treatment in those with a low risk of subsequent subarachnoid haemorrhage and a good indication for antithrombotic treatment. Given the small size of the population, this recommendation is not expected to have a substantial resource impact.

1.7.3 Other factors the committee took into account

The committee acknowledged that smoking can be a risk factor for initial SAH. Medication for smoking cessation may therefore be beneficial to general health but may also reduce the risk for subsequent SAH. The committee decided to cross refer to the NICE guideline NG92 Stop smoking interventions and services.

References

1. Al-Shahi Salman R, Law ZK, Bath PM, Steiner T, Sprigg N. Haemostatic therapies for acute spontaneous intracerebral haemorrhage. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD005951. DOI: https://dx.doi.org/10.1002/14651858.CD005951.pub4.

2. Asano T, Takakura K, Sano K, Kikuchi H, Nagai H, Saito I et al. Effects of a hydroxyl radical scavenger on delayed ischemic neurological deficits following aneurysmal subarachnoid hemorrhage: results of a multicenter, placebo-controlled double-blind trial. Journal of Neurosurgery. 1996; 84(5):792-803

3. Baharoglu M, Germans M, Rinkel G, Algra A, Vermeulen M, van Gijn J et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD001245. DOI: 10.1002/14651858.CD001245.pub2.

4. Behrouz R, Sadat-Hosseiny Z. Pharmacological agents in aneurysmal subarachnoid hemorrhage: successes and failures. Clinical Neuropharmacology. 2015; 38(3):104-108

5. Bruder M, Won SY, Kashefiolasl S, Wagner M, Brawanski N, Dinc N et al. Effect of heparin on secondary brain injury in patients with subarachnoid hemorrhage: an additional 'H' therapy in vasospasm treatment. Journal of Neurointerventional Surgery. 2017; 9(7):659-663

6. Buchner H, Hacke W, Kugel I. Antifibrinolytic therapy following an aneurysmal subarachnoid hemorrhage. Intensivmedizin. 1985; 22(6):424-427

7. Cagnazzo F, Derraz I, Lefevre PH, Gascou G, Dargazanli C, Riquelme C et al. Antiplatelet therapy in patients with aneurysmal SAH: impact on delayed cerebral ischemia and clinical outcome. A meta-analysis. American Journal of Neuroradiology. 2019; 40(7):1201-1206

8. Cagnazzo F, Di Carlo DT, Petrella G, Perrini P. Ventriculostomy-related hemorrhage in patients on antiplatelet therapy for endovascular treatment of acutely ruptured intracranial aneurysms. A meta-analysis. Neurosurgical Review. 2020; 43:397-406

9. Cagnazzo F, Perrini P, Lefevre PH, Gascou G, Dargazanli C, Riquelme C et al. Comparison of prasugrel and clopidogrel used as antiplatelet medication for endovascular treatment of unruptured intracranial aneurysms: a meta-analysis. American Journal of Neuroradiology. 2019; 40(4):681-686

10. Chalmers J, Wang X, Arima H, Heeley E, Delcourt C, Hirakawa Y. Association between magnitude of blood pressure reduction and clinical outcomes after acute intracerebral hemorrhge: the INTERACT2 trial. Hypertension. 2014; 63(6):e150

11. Cho WS, Lee J, Ha EJ, Kim KH, Lee J, Cho YD et al. Low-dose prasugrel vs clopidogrel-based tailored premedication for endovascular treatment of cerebral aneurysms. Neurosurgery. 2019; 85(1):E52-E59

12. Curran MP, Robinson DM, Keating GM. Intravenous nicardipine: its use in the short-term treatment of hypertension and various other indications. Drugs. 2006; 66(13):1755-1782

13. Darkwah Oppong M, Gembruch O, Pierscianek D, Kohrmann M, Kleinschnitz C, Deuschl C et al. Post-treatment antiplatelet therapy reduces risk for delayed cerebral ischemia due to aneurysmal subarachnoid hemorrhage. Neurosurgery. 2019; 85(6):827-833

14. Dorhout Mees SM, group M-Is. Magnesium in aneurysmal subarachnoid hemorrhage (MASH II) phase III clinical trial MASH-II study group. International Journal of Stroke. 2008; 3(1):63-65

15. Dorhout Mees SM, Van Den Bergh WM, Algra A, Rinkel GJE. Antiplatelet therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD006184. DOI: http://dx.doi.org/10.1002/14651858.CD006184.pub2.

16. Dorhout Mees SM, Van Den Bergh WM, Algra A, Rinkel GJE. Antiplatelet therapy for subarachnoid haemorrhage. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006184. DOI: http://dx.doi.org/10.1002/14651858.CD006184.

17. Guo XJ, Ding WL, Zhu HH. Clinical efficacy and prognosis of aspirin combined with clopidogrel in patients with cerebral hemorrhage after operation. European Review for Medical and Pharmacological Sciences. 2020; 24(4):2087-2094

18. Haley EC, Jr., Kassell NF, Apperson-Hansen C, Maile MH, Alves WM. A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. Journal of Neurosurgery. 1997; 86(3):467-474

19. Harrigan MR. Hypertension may be the most important component of hyperdynamic therapy in cerebral vasospasm. Critical Care. 2010; 14:151

20. Hasan DM, Mahaney KB, Brown RD, Jr., Meissner I, Piepgras DG, Huston J et al. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke. 2011; 42(11):3156-3162

21. Heeley E, Delcourt C, Stapf C, Huang Y, Wang J, Lindley R. Comparison of patient characteristics in the INTEnsive blood pressure reduction in acute cerebral haemorrhage (INTERACT) trials. International Journal of Stroke. 2010; 5:24

22. Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. Journal of Neurosurgery. 2002; 97(4):771-778

23. Hop JW, Rinkel GJ, Algra A, Berkelbach van der Sprenkel JW, van Gijn J. Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. Neurology. 2000; 54(4):872-878

24. Juvela S. Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery. 1995; 82(6):945-952

25. Kassell NF, Haley EC, Jr., Apperson-Hansen C, Alves WM. Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand. Journal of Neurosurgery. 1996; 84(2):221-228

26. Keir SL, Wardlaw JM, Sandercock PA, Chen Z. Antithrombotic therapy in patients with any form of intracranial haemorrhage: a systematic review of the available controlled studies. Cerebrovascular Diseases. 2002; 14(3-4):197-206

27. Khattar NK, Bak E, White AC, James RF. Heparin treatment in aneurysmal subarachnoid hemorrhage: a review of human studies. 'In:' Martin R, Boling W, Chen G, Zhang J, editors. Subarachnoid Hemorrhage Acta Neurochirurgica Supplement. 127. Cham: Springer. 2020. p. 15-19.

28. Lanzino G, Kassell NF. Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part II. A cooperative study in North America. Journal of Neurosurgery. 1999; 90(6):1018-1024

29. Mendelow AD, Stockdill G, Steers AJW, Hayes J, Gillingham FJ. Double-blind trial of aspirin in patients receiving tranexamic acid for subarachnoid haemorrhage. Acta Neurochirurgica. 1982; 62(3-4):195-202

30. Nagahama Y, Allan L, Nakagawa D, Zanaty M, Starke RM, Chalouhi N et al. Dual antiplatelet therapy in aneurysmal subarachnoid hemorrhage: association with reduced risk of clinical vasospasm and delayed cerebral ischemia. Journal of Neurosurgery. 2018; 129(3):702-710

31. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

32. Neil-Dwyer G, Walter P, Cruickshank J, Stratton G. Beta-blockade in subarachnoid haemorrhage. Drugs. 1983; 25(Suppl. 2):273-277

33. Neil-Dwyer G, Walter P, Cruickshank JM. Beta-blockade benefits patients following a subarachnoid haemorrhage. European Journal of Clinical Pharmacology. 1985; 28(Suppl):25-29

34. NHS Business Services Authority. NHS electronic drug tariff (August 2020). Available from: http://www.nhsbsa.nhs.uk/PrescriptionServices/4940.aspx Last accessed: 05/08/2020.

35. Ono H, Mizukami M, Kitamura K, Kikuchi H. Ticlopidine: quo vadis? Subarachnoid hemorrhage. Agents and Actions Supplements. 1984; 15:259-272

36. Roos Y. Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial. STAR Study Group. Neurology. 2000; 54(1):77-82

37. Sedat J, Chau Y, Gaudart J, Sachet M, Beuil S, Lonjon M. Prasugrel versus clopidogrel in stent-assisted coil embolization of unruptured intracranial aneurysms. Interventional Neuroradiology. 2017; 23(1):52-59

38. Shaw MDM, Foy PM, Conway M. Dipyridamole and postoperative ischemic deficits in aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery. 1985; 63(5):699-703

39. Siironen J, Juvela S, Varis J, Porras M, Poussa K, Ilveskero S et al. No effect of enoxaparin on outcome of aneurysmal subarachnoid hemorrhage: a randomized, double-blind, placebo-controlled clinical trial. Journal of Neurosurgery. 2003; 99(6):953-959

40. Simard JM, Aldrich EF, Schreibman D, James RF, Polifka A, Beaty N. Low-dose intravenous heparin infusion in patients with aneurysmal subarachnoid hemorrhage: a preliminary assessment. Journal of Neurosurgery. 2013; 119(6):1611-1619

41. Toussaint LG, 3rd, Friedman JA, Wijdicks EF, Piepgras DG, Pichelmann MA, McIver JI et al. Influence of aspirin on outcome following aneurysmal subarachnoid hemorrhage. Journal of Neurosurgery. 2004; 101(6):921-925

42. van den Bergh WM, Algra A, Rinkel GJE. Magnesium and aspirin treatment in patients with subarachnoid haemorrhage: comparison of effects after endovascular and neurosurgical aneurysm occlusion. Journal of Neurology. 2009; 256(2):213-216

43. van den Bergh WM, Group MS, Algra A, Dorhout Mees SM, van Kooten F, Dirven CM et al. Randomized controlled trial of acetylsalicylic acid in aneurysmal subarachnoid hemorrhage: the MASH Study. Stroke. 2006; 37(9):2326-2330

44. van den Bergh WM, Kerr RS, Algra A, Rinkel GJ, Molyneux AJ, International Subarachnoid Aneurysm Trial Collaborative Group. Effect of antiplatelet therapy for endovascular coiling in aneurysmal subarachnoid hemorrhage. Stroke. 2009; 40(6):1969-1972

45. Vergouwen MDI, Etminan N, Ilodigwe D, MacDonald RL. Lower incidence of cerebral infarction correlates with improved functional outcome after aneurysmal subarachnoid hemorrhage. Journal of Cerebral Blood Flow and Metabolism. 2011; 31(7):1545-1553

46. Vermeulen M, Lindsay KW, Murray GD, Cheah F, Hijdra A, Muizelaar JP et al. Antifibrinolytic treatment in subarachnoid hemorrhage. New England Journal of Medicine. 1984; 311(7):432-437

47. Wurm G, Holl B, Tomancok B, Lungenschmid K, Adelwohrer C, Heissler H. Prevention of vasospasm in patients with spontaneous subarachnoid haemorrhage: a double-blind randomized comparison of enoxaparin versus placebo. Thrombosis and Haemostasis. 1999; (Suppl S):1279

48. Young AM, Karri SK, Ogilvy CS. Non-steroidal anti-inflammatory drugs used as a treatment modality in subarachnoid hemorrhage. Current Drug Safety. 2012; 7(3):197-201

Appendices

Appendix A: Review protocols

Table 7: Review protocol: long-term medicines for reducing the risk of subsequent subarachnoid haemorrhage

Field	Content
PROSPERO registration number	CRD42019153687
Review title	What is the clinical and cost effectiveness of long-term medicines for reducing the risk of subsequent subarachnoid haemorrhage, such as antihypertensive medicines, in adults with confirmed subarachnoid haemorrhage?
Review question	What is the clinical and cost effectiveness of long-term medicines, such as antihypertensive or antithrombotic medicines, for reducing the risk of subsequent subarachnoid haemorrhage in adults with confirmed subarachnoid haemorrhage?
Objective	To determine which intervention to manage the long-term risk of subsequent subarachnoid haemorrhage is the most clinically and cost-effective.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
Intervention	• Antihypertensive medical management (Target BP control) o Tight control of blood pressure o Standard blood pressure control (>140/90 mmHg) • Antithrombotic medication (e.g. warfarin)
Comparator/Reference standard/Confounding factors	Comparators: • To each other

	○ Tight control of BP compared to standard management ○ Use of antithrombotic medication compared to restriction of antithrombotic medication • To no treatment
Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
Other exclusion criteria	Exclusions: • Non- English language studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	Review aims to address the long-term management of people with aSAH following discharge.
Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) • Subsequent subarachnoid haemorrhage Outcomes will be grouped at <30 days, 30days-6 months, 6-12 months, and at yearly time-points thereafter.
Secondary outcomes (important outcomes)	• Number achieving target BP • Return to daily activity (e.g. driving) • Need for retreatment • Complications of intervention (such as headache, dizziness, nausea and vomiting, tiredness) Outcomes will be grouped at <30 days, 30days-6 months, 6-12 months, and at yearly time-points thereafter.
Data extraction (selection and coding)	• EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. • EviBASE will be used for data extraction.
Risk of bias (quality) assessment	• Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • For Intervention reviews ○ Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) ○ Randomised Controlled Trial: Cochrane RoB (2.0) ○ Non randomised study, including cohort studies: Cochrane ROBINS-I • 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: ○ papers were included /excluded appropriately ○ a sample of the data extractions

<table>
<tr><td></td><td colspan="2">

correct methods are used to synthesise data
a sample of the risk of bias assessments

• Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
</td></tr>
<tr><td>Strategy for data synthesis</td><td colspan="2">
• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).
• GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome.
• The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group http://www.gradeworkinggroup.org/
• Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.
• Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.
</td></tr>
<tr><td>Analysis of sub-groups</td><td colspan="2">
Strata:
• n/a
Subgroups (if heterogeneity):
• Primary treatment of haemorrhage:
○ clipping
○ coiling
○ conservative management
• Method of antihypertensive therapy:
○ Mono-therapy
○ Combination therapy
</td></tr>
<tr><td rowspan="7">Type and method of review</td><td>☒</td><td>Intervention</td></tr>
<tr><td>☐</td><td>Diagnostic</td></tr>
<tr><td>☐</td><td>Prognostic</td></tr>
<tr><td>☐</td><td>Qualitative</td></tr>
<tr><td>☐</td><td>Epidemiologic</td></tr>
<tr><td>☐</td><td>Service Delivery</td></tr>
<tr><td>☐</td><td>Other (please specify)</td></tr>
<tr><td>Language</td><td colspan="2">English</td></tr>
<tr><td>Country</td><td colspan="2">England</td></tr>
<tr><td>Anticipated or actual start date</td><td colspan="2"></td></tr>
</table>

<table>
<tr><td>Anticipated completion date</td><td colspan="3">3 February 2021</td></tr>
<tr><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
<tr><td>Data extraction</td><td>☑</td><td>☑</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☑</td><td>☑</td></tr>
<tr><td>Data analysis</td><td>☑</td><td>☑</td></tr>
<tr><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

5b Named contact e-mail
SAH@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</td></tr>
<tr><td>Review team members</td><td colspan="3">From the National Guideline Centre:
• Ms Gill Ritchie
• Mr Ben Mayer
• Mr Audrius Stonkus
• Mr Vimal Bedia
• Ms Emma Cowles
• Ms Jill Cobb
• Ms Amelia Unsworth</td></tr>
<tr><td>Funding sources/sponsor</td><td colspan="3">This systematic review is being completed by the National Guideline Centre which receives funding from NICE.</td></tr>
<tr><td>Conflicts of interest</td><td colspan="3">All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.</td></tr>
<tr><td>Collaborators</td><td colspan="3">Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with</td></tr>
</table>

	section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
Other registration details		
Reference/URL for published protocol		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Subarachnoid haemorrhage; medicines; reduce risk of subsequent	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information		
Details of final publication	www.nice.org.uk	

1

2 **Table 8: Health economic review protocol**

Review question	All questions where health economic evidence applicable
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.

Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[31]

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will decide based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.
- Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B: Literature search strategies

This literature search strategy was used for the following review;

- What is the clinical and cost effectiveness of long-term medicines, such as antihypertensive or blood thinning medicines, for reducing the risk of subsequent subarachnoid haemorrhage in adults with confirmed subarachnoid haemorrhage?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[31]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 –24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/

13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	25 not 26
28.	limit 27 to English language
29.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol).ti,ab.
30.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
31.	exp Adrenergic beta-Antagonists/
32.	Nitrates/
33.	(nitrate* or glyceryl trinitrate or isosorbide or Nitroglycerin* or trinitroglycerin or TNG or GTN or trinitroxypropane or nitroprusside).ti,ab.
34.	Nitroglycerin/
35.	Nitroprusside/
36.	exp Calcium Channel Blockers/
37.	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
38.	(amlodipine or clevidipine or diltiazem or felodipine or lacidipine or lercanidipine or nicardipine or nifedipine or verapamil).ti,ab.
39.	((hypertens* or blood pressure or BP) adj3 (manage* or managing or control* or reduc* or limit* or lower*)).ti,ab.
40.	((anti-hypertens* or antihypertens*) adj3 (drug* or agent*)).ti,ab.
41.	Antihypertensive Agents/
42.	exp Anticoagulants/
43.	exp Coumarins/
44.	(anticoagulant* or anti coagulant* or antithrombotic*).ti,ab.
45.	(apixaban or Abciximab or Acenocoumarol or Ancrod or antivitamin K or Becaplermin or beta 2-Glycoprotein or beta2glycoprotein or bivalirudin or citric acid or dabigatran or Dalteparin or Dermatan or Dextrans or Dicumarol or edoxaban or Edetic Acid or Ethylenediaminetetraacetic acid or Enoxaparin or Ethyl Biscoumacetate or fondaparinux or Gabexate or heparin* or Nadroparin or Pentosan Sulfuric Polyester or pentosan polysulfate or polysulphate or Phenindione or Phenprocoumon or Protein C or Protein S or Sodium Citrate or rivaroxaban or Tinzaparin or warfarin or enoxaparin or ximelagatran or coumarin* or 4 hydrox?coumarin* or vitamin K antagonist* or VKA*).ti,ab.
46.	(blood adj2 thin*).ti,ab.
47.	(clot* adj2 inhibit*).ti,ab.
48.	(fibrin* adj2 (degradation or split*)).ti,ab.

49.	or/29-48
50.	28 and 49
51.	Meta-Analysis/
52.	exp Meta-Analysis as Topic/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.
58.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	randomized controlled trial.pt.
63.	controlled clinical trial.pt.
64.	randomi#ed.ti,ab.
65.	placebo.ab.
66.	randomly.ti,ab.
67.	Clinical Trials as topic.sh.
68.	trial.ti.
69.	or/62-68
70.	Epidemiologic studies/
71.	Observational study/
72.	exp Cohort studies/
73.	(cohort adj (study or studies or analys* or data)).ti,ab.
74.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
75.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
76.	Controlled Before-After Studies/
77.	Historically Controlled Study/
78.	Interrupted Time Series Analysis/
79.	(before adj2 after adj2 (study or studies or data)).ti,ab.
80.	exp case control study/
81.	case control*.ti,ab.
82.	Cross-sectional studies/
83.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
84.	or/70-83
85.	50 and (61 or 69 or 84)

1 **Embase (Ovid) search terms**

1.	*subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.

3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol).ti,ab.
26.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
27.	exp beta adrenergic receptor blocking agent/
28.	nitrate/
29.	(nitrate* or glyceryl trinitrate or isosorbide or Nitroglycerin* or trinitroglycerin or TNG or GTN or trinitroxypropane or nitroprusside).ti,ab.
30.	glyceryl trinitrate/
31.	nitroprusside sodium/
32.	exp calcium channel blocking agent/
33.	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
34.	(amlodipine or clevidipine or diltiazem or felodipine or lacidipine or lercanidipine or nicardipine or nifedipine or verapamil).ti,ab.
35.	((hypertens* or blood pressure or BP) adj3 (manage* or managing or control* or reduc* or limit* or lower*)).ti,ab.
36.	((anti-hypertens* or antihypertens*) adj3 (drug* or agent*)).ti,ab.
37.	exp antihypertensive agent/
38.	exp anticoagulant agent/
39.	(anticoagulant* or anti coagulant* or antithrombotic*).ti,ab.
40.	(apixaban or Abciximab or Acenocoumarol or Ancrod or antivitamin K or Becaplermin or beta 2-Glycoprotein or beta2glycoprotein or bivalirudin or citric acid or dabigatran or Dalteparin or Dermatan or Dextrans or Dicumarol or edoxaban or Edetic Acid or Ethylenediaminetetraacetic acid or Enoxaparin or Ethyl Biscoumacetate or fondaparinux or Gabexate or heparin* or Nadroparin or Pentosan Sulfuric Polyester or

	pentosan polysulfate or polysulphate or Phenindione or Phenprocoumon or Protein C or Protein S or Sodium Citrate or rivaroxaban or Tinzaparin or warfarin or enoxaparin or ximelagatran or coumarin* or 4 hydrox?coumarin* or vitamin K antagonist* or VKA*).ti,ab.
41.	(blood adj2 thin*).ti,ab.
42.	(clot* adj2 inhibit*).ti,ab.
43.	(fibrin* adj2 (degradation or split*)).ti,ab.
44.	or/38-43
45.	24 and 44
46.	random*.ti,ab.
47.	factorial*.ti,ab.
48.	(crossover* or cross over*).ti,ab.
49.	((doubl* or singl*) adj blind*).ti,ab.
50.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
51.	crossover procedure/
52.	single blind procedure/
53.	randomized controlled trial/
54.	double blind procedure/
55.	or/46-54
56.	systematic review/
57.	meta-analysis/
58.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
59.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
60.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
61.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
62.	(search* adj4 literature).ab.
63.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
64.	cochrane.jw.
65.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
66.	or/56-65
67.	Clinical study/
68.	Observational study/
69.	family study/
70.	longitudinal study/
71.	retrospective study/
72.	prospective study/
73.	cohort analysis/
74.	follow-up/
75.	cohort*.ti,ab.
76.	74 and 75
77.	(cohort adj (study or studies or analys* or data)).ti,ab.
78.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

79.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
80.	(before adj2 after adj2 (study or studies or data)).ti,ab.
81.	exp case control study/
82.	case control*.ti,ab.
83.	cross-sectional study/
84.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
85.	or/67-73,76-84
86.	45 and (55 or 66 or 85)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) near/3 (hemorrhag* or haemorrhag* or bleed* or blood*)):ti,ab
#3.	(SAH or aSAH):ti,ab
#4.	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) near/3 (aneurysm* or aneurism* or hematoma* or haematoma*)):ti,ab
#6.	(or #1-#5)
#7.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol):ti,ab
#8.	((beta or b) near/3 (block* or antagonist*)):ti,ab
#9.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#10.	MeSH descriptor: [Nitrates] this term only
#11.	(nitrate* or glyceryl trinitrate or isosorbide or Nitroglycerin* or trinitroglycerin or TNG or GTN or trinitroxypropane or nitroprusside):ti,ab
#12.	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#13.	(calcium near/3 (block* or inhibit* or antagonist*)):ti,ab
#14.	(amlodipine or clevidipine or diltiazem or felodipine or lacidipine or lercanidipine or nicardipine or nifedipine or verapamil):ti,ab
#15.	((hypertens* or blood pressure or BP) near/3 (management or control* or reduc* or limit* or lower*)):ti,ab
#16.	((anti-hypertens* or antihypertens*) near/3 (drug* or agent*)):ti,ab
#17.	MeSH descriptor: [Antihypertensive Agents] this term only
#18.	MeSH descriptor: [Anticoagulants] explode all trees
#19.	MeSH descriptor: [Coumarins] explode all trees
#20.	(anticoagulant* or anti coagulant* or antithrombotic*).ti,ab.
#21.	(apixaban or Abciximab or Acenocoumarol or Ancrod or antivitamin K or Becaplermin or beta 2 Glycoprotein or beta2glycoprotein or bivalirudin or citric acid or dabigatran or Dalteparin or Dermatan or Dextrans or Dicumarol or edoxaban or Edetic Acid or Ethylenediaminetetraacetic acid or Enoxaparin or Ethyl Biscoumacetate or fondaparinux or Gabexate or heparin* or Nadroparin or Pentosan Sulfuric Polyester or pentosan polysulfate or polysulphate or Phenindione or Phenprocoumon or Protein C or Protein S or Sodium Citrate or rivaroxaban or Tinzaparin or warfarin or enoxaparin or ximelagatran or coumarin* or 4 hydrox?coumarin* or vitamin K antagonist* or VKA*):ti,ab
#22.	(blood next/2 thin*):ti,ab
#23.	(clot* next/2 inhibit*):ti,ab
#24.	(fibrin* next/2 (degradation or split*)):ti,ab

#25.	(or #7-#24)
#26.	#6 and #25

B.21 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to subarachnoid haemorrhage population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003 – 23 June 2020	Exclusions Health economics studies
Embase	2003 – 23 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 23 June 2020 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/

22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/

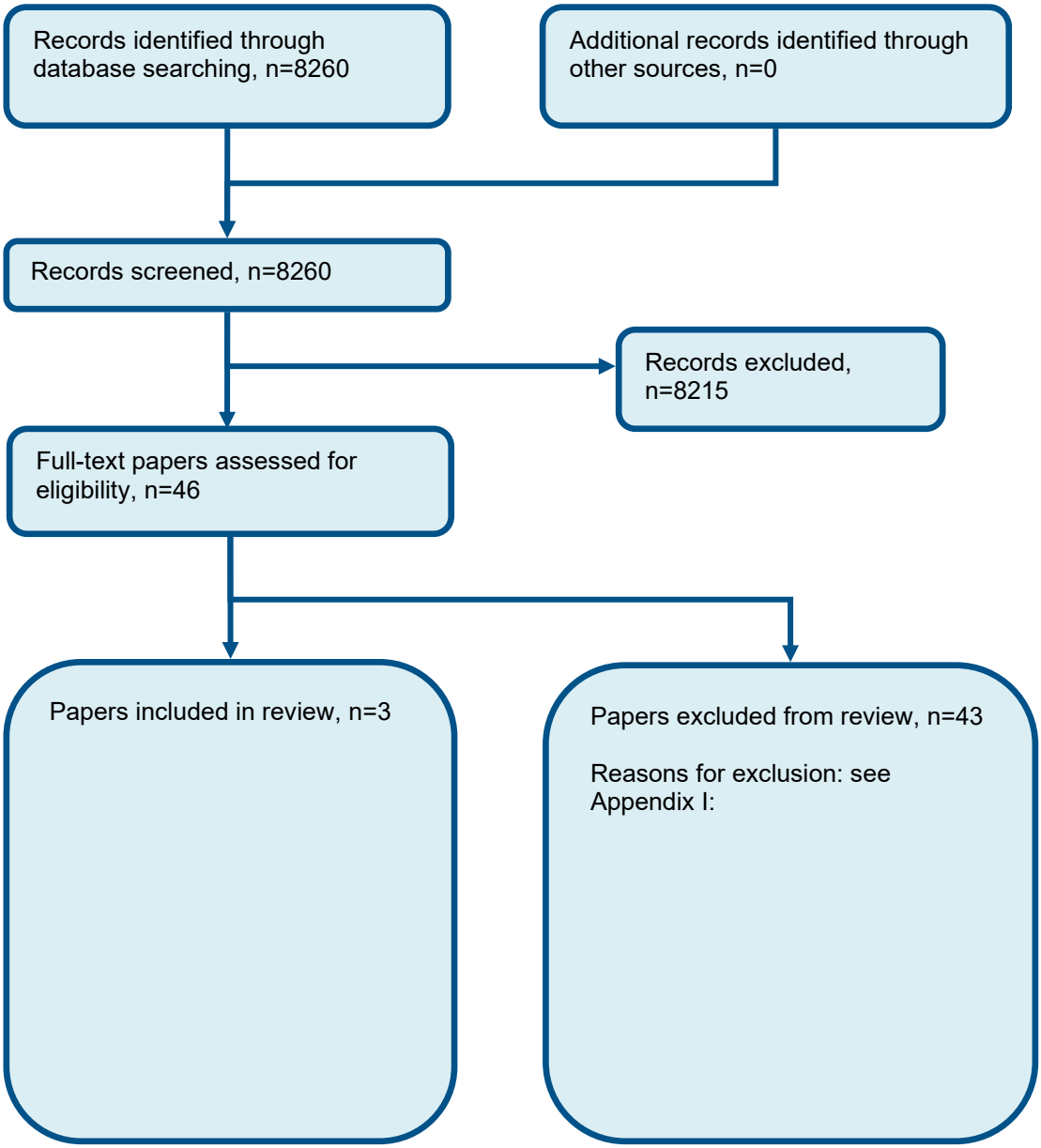
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

1 NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Subarachnoid Hemorrhage EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#3.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)))
#4.	((SAH or aSAH))
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Aneurysm EXPLODE ALL TREES
#7.	((aneurysm* or hematoma* or haematoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Intracranial Aneurysm EXPLODE ALL TREES
#10.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (aneurysm* or hematoma* or haematoma*)))
#11.	#9 OR #10
#12.	MeSH DESCRIPTOR Aneurysm, ruptured
#13.	(((ruptur* or weak* or brain or trauma*) adj3 (aneurysm* or hematoma* or haematoma*)))
#14.	#12 OR #13
#15.	(#5 or #8 or #11 or #14)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of long-term medicines for reducing the risk of subsequent subarachnoid haemorrhage



Appendix D: Clinical evidence tables

Study	Darkwah Oppong 2019[13]
Study type	Cohort study
Number of studies (number of participants)	(n=580)
Countries and setting	Conducted in Germany; Setting: Neurosurgical Centre, Germany
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients with aneurysmal subarachnoid haemorrhage admitted between January 2003 and June 2016 who underwent endovascular treatment.
Exclusion criteria	Not specified
Recruitment/selection of patients	patients with aneurysmal subarachnoid haemorrhage who underwent endovascular treatment.
Age, gender and ethnicity	Age - Mean (SD): Aspirin: 55 (13); No aspirin: 54 (14). Gender (M:F): 189/391.
Further population details	1. Primary treatment of haemorrhage: Coiling (Endovascular coiling for all patients +/- stenting).
Indirectness of population	No indirectness
Interventions	(n=329) Intervention 1: Antithrombotic medication . Aspirin was administered in a daily dose of 100mg for at least 3 weeks. If a stent was additionally applied, the antiplatelet therapy was extended by the use of Clopidogrel 75mg daily for at least 6 weeks and aspirin was extended to life long. . Duration 3 weeks to life long . Concurrent medication/care: Nimodipine was administered for 21 days after SAH. . Indirectness: No indirectness Further details: 1. Method of antihypertensive therapy: (n=251) Intervention 2: No treatment. No antiplatelet or dual antiplatelet therapy was given to patients within

	this group. Duration post endovascular intervention. Concurrent medication/care: Nimodipine was administered for 21 days after SAH. . Indirectness: No indirectness Further details: 1. Method of antihypertensive therapy:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN +/- CLOPIDOGREL versus NO TREATMENT

Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) at Define
- Actual outcome: mRS < 3 at 6 months; Group 1: 242/329, Group 2: 157/251; Comments: p value 0.006
Risk of bias: All domain - Very high, Selection - High, Confounding – High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Need for retreatment at Define
- Actual outcome: Bleeding events (minor or major) at Not specified ; Group 1: 29/329, Group 2: 10/251; Comments: p value 0.03
Risk of bias: All domain - Very high, Selection - High, Confounding – High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Mortality: Health and social quality of life; Subsequent subarachnoid haemorrhage; Number achieving target BP; Return to daily activity (e.g. work); Complications of intervention (such as headache, dizziness, nausea and vomiting, tiredness)

Study	Nagahama 2018[30]
Study type	Cohort study
Number of studies (number of participants)	(n=161)
Countries and setting	Conducted in USA; Setting: Neurosurgical medical centre, USA
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients selected for this study were those who suffered aSAH secondary to rupture of a saccular cerebral aneurysm, presented with Hunt and Hess grade I - III or showed improvement of their neurological status to Hunt and Hess grade I - III after ventriculostomy within 24 hours of their initial presentation (with grade IV or V with clinical and imaging evidence of hydrocephalus), and had a CT perfusion study done on admission.
Exclusion criteria	SAH secondary to rupture of an aneurysm associated with an arteriovenous malformation or a mycotic aneurysm; microsurgical clipping of the aneurysm; coiling of the aneurysm with unintended protrusion of a portion of coil into the parent vessel requiring aspirin therapy; Hunt and Hess Grade IV or V; presence of intraparenchymal haemorrhage; aSAH induced cardiomyopathy; death due to pulmonary embolism, myocardial infarction, sepsis, and or medical complications; no clinical follow ups.
Recruitment/selection of patients	Patients who suffered aSAH secondary to rupture of a saccular cerebral aneurysm
Age, gender and ethnicity	Age - Mean (SD): DAPT: 56.1 (12.3); Control: 51.5 (11.5). Gender (M:F): 110/51.
Further population details	1. Primary treatment of haemorrhage: Coiling
Indirectness of population	No indirectness
Interventions	(n=85) Intervention 1: Antithrombotic medication . If a stent or flow diverter was used, tirofiban infusion was started at the maintenance dosage without bolus doses immediately after deployment of the stent or flow diverter and was continued for 2 hours after the procedure. These patients also received 600mg of crushed clopidogrel and 325mg of aspirin via an orogastric tube at the end of the procedure and continued to receive both clopidogrel and aspirin daily. Duration Not specified. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Method of antihypertensive therapy:

	(n=76) Intervention 2: No treatment. The patients who underwent coil embolization alone without use of a stent or flow diverter and therefore received neither aspirin or clopidogrel made up the control group. . Duration Not specified . Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Method of antihypertensive therapy:
Funding	Academic or government funding (Supported by a grant from the National Institutes of Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN + CLOPIDOGREL versus NO TREATMENT Protocol outcome 1: Complications of intervention (such as headache, dizziness, nausea and vomiting, tiredness) at Define - Actual outcome: Delayed cerebral ischemia at not specified ; OR; (DCI - DAPT: OR 0.056 (0.01 - 0.318) p value 0.001), Comments: adjusted for age, sex, aneurysm location, Hunt and Hess grade, and fisher grade); Risk of bias: All domain – Very High, Selection - High, Confounding – Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Vasospasm at not specified ; OR; (Vasospasm - DAPT: OR 0.244 (0.097 - 0.615) p value 0.003), Comments: adjusted for age, sex, aneurysm location, Hunt and Hess grade, and fisher grade); Risk of bias: All domain – Very High, Selection - High, Confounding – Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Subsequent subarachnoid haemorrhage; Number achieving target BP; Return to daily activity (e.g. work); Need for retreatment

Study	Shaw 1985[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=677)
Countries and setting	Conducted in United Kingdom; Setting: Surgical centres, Mersey Region, UK
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with SAH who went to surgery
Exclusion criteria	Patients who were randomized but didn't undergo surgery
Recruitment/selection of patients	Patients with SAH
Age, gender and ethnicity	Age - Other: Mean age: Dipyridamole: 45.8; Placebo: 45.8. Gender (M:F): not specified .
Further population details	1. Primary treatment of haemorrhage: Not stated / Unclear (Clipping).
Indirectness of population	No indirectness
Interventions	(n=336) Intervention 1: Antithrombotic medication. Dipyridamole in a standard dose of 100mg/day orally or 10mg/day IV. Duration 3 months postoperatively. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Method of antihypertensive therapy: (n=341) Intervention 2: No treatment - Placebo. Placebo with the same regimen as intervention. Duration 3 months. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Method of antihypertensive therapy:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIPYRIDAMOLE versus PLACEBO

Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) at Define

- Actual outcome: GOS 1 at 3 months ; Group 1: 21/173, Group 2: 20/175 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 163, Reason: no aneurysm, death, poor neurological state, other; Group 2 Number missing: 166, Reason: no aneurysm, death, poor neurological state, other - Actual outcome: GOS 2 at 3 months ; Group 1: 2/173, Group 2: 0/175 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 163, Reason: no aneurysm, death, poor neurological state, other; Group 2 Number missing: 166, Reason: no aneurysm, death, poor neurological state, other - Actual outcome: GOS 3 at 3 months ; Group 1: 11/173, Group 2: 20/175 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 163, Reason: no aneurysm, death, poor neurological state, other; Group 2 Number missing: 166, Reason: no aneurysm, death, poor neurological state, other - Actual outcome: GOS 4 at 3 months ; Group 1: 25/173, Group 2: 18/175 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 163, Reason: no aneurysm, death, poor neurological state, other; Group 2 Number missing: 166, Reason: no aneurysm, death, poor neurological state, other - Actual outcome: GOS 5 at 3 months ; Group 1: 101/173, Group 2: 105/175 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 163, Reason: no aneurysm, death, poor neurological state, other; Group 2 Number missing: 166, Reason: no aneurysm, death, poor neurological state, other	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Subsequent subarachnoid haemorrhage; Number achieving target BP; Return to daily activity (e.g. work); Need for re-treatment; Complications of intervention (such as headache, dizziness, nausea and vomiting, tiredness)

1

2

1 Appendix E: Forest plots

E.1 2 Dipyridamole vs Placebo

Figure 2: GOS 1 - death (Glasgow outcome scale 1-5) - better indicated by lower score)

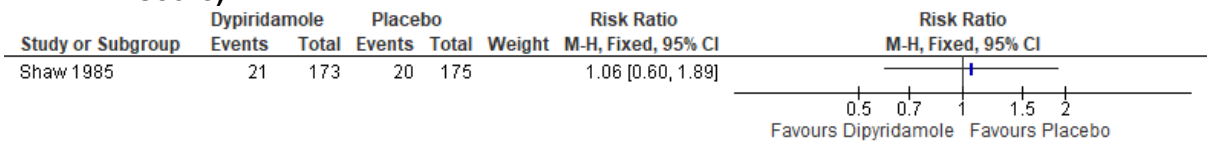
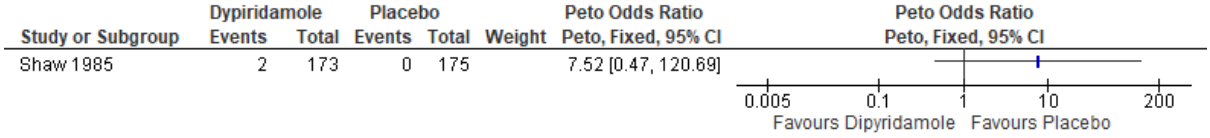
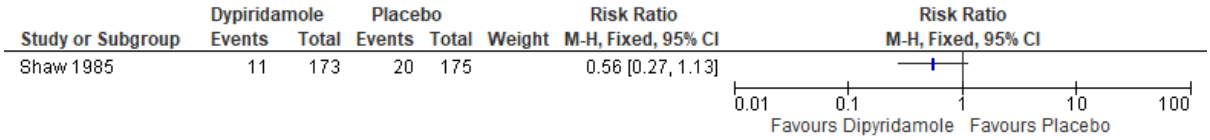


Figure 3: GOS 2 - persistent vegetative state (Glasgow outcome scale 1-5) - better indicated by lower score



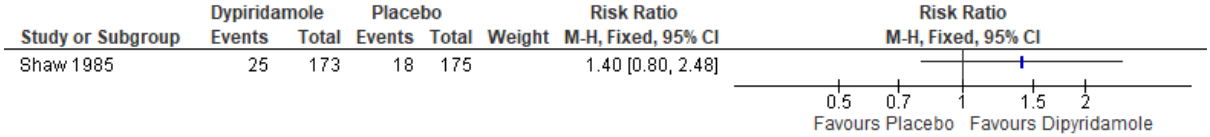
3

Figure 4: GOS 3 - severe disability (Glasgow outcome scale 1-5) - better indicated by lower score



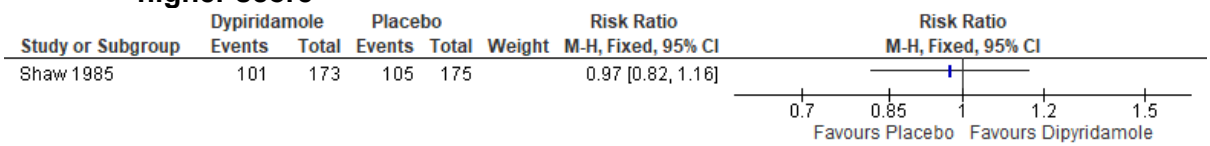
4

Figure 5: GOS 4 - moderate disability (Glasgow outcome scale 1-5) - better indicated by higher score



5

Figure 6: GOS 5 - low disability (Glasgow outcome scale 1-5) - better indicated by higher score



6

E.21 Aspirin +/- Clopidogrel vs Control: No antiplatelet therapy

Figure 7: mRS <3 at 6 months (modified Rankin scale 0 – 6) - better indicated by lower score

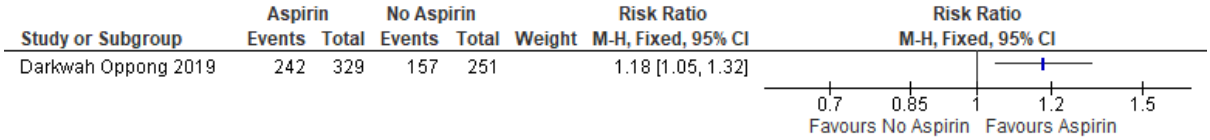
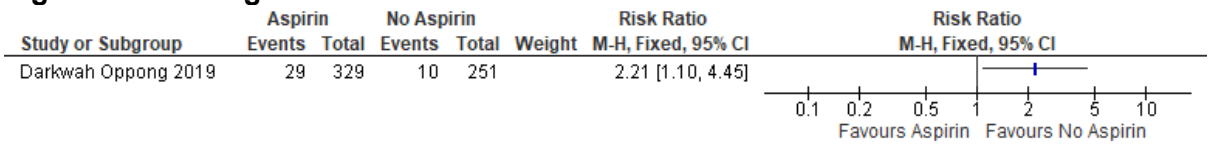


Figure 8: Bleeding events



E.33 Dual antiplatelet therapy vs Control: No Dual Antiplatelet 4 Therapy

Figure 9: DCI

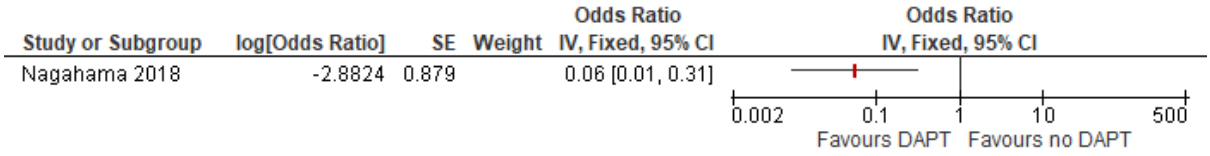
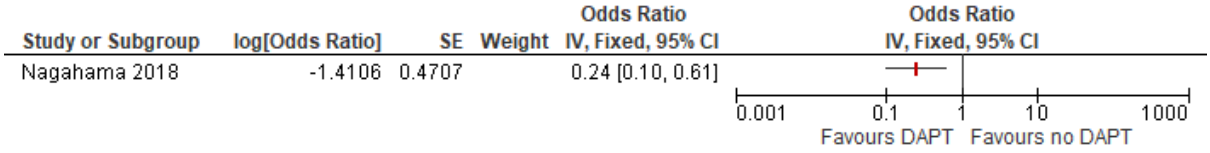


Figure 10: Vasospasm



1 Appendix F: GRADE tables

2 Table 11: Clinical evidence profile: Dipyridamole vs Placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dipyridamole	Placebo	Relative (95% CI)	Absolute		
GOS 1 (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	21/173 (12.1%)	20/175 (11.4%)	RR 1.06 (0.60 to 1.89)	7 more per 1000 (from 46 fewer to 102 more)	⊕⊕OO LOW	CRITICAL
GOS 2												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/173 (1.2%)	0/175 (0%)	Peto 7.52 (0.47 to 120.69)	-	⊕⊕OO LOW	CRITICAL
GOS 3												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/173 (6.4%)	20/175 (11.4%)	RR 0.56 (0.27 to 1.13)	50 fewer per 1000 (from 83 fewer to 15 more)	⊕⊕⊕O MODERATE	CRITICAL
GOS 4												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	25/173 (14.5%)	18/175 (10.3%)	RR 1.40 (0.80 to 2.48)	41 more per 1000 (from 21 fewer to 152 more)	⊕⊕⊕O MODERATE	CRITICAL
GOS 5												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	101/173 (58.4%)	105/175 (60%)	RR 0.97 (0.82 to 1.16)	18 fewer per 1000 (from 108 fewer to 96 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence profile: Aspirin +/- Clopidogrel vs Control: No antiplatelet therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aspirin**	**Control**	**Relative (95% CI)**	**Absolute**		
mRS <3 (follow-up 6 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	242/329 (73.6%)	62.6%	RR 1.18 (1.05 to 1.32)	113 more per 1000 (from 31 more to 200 more)	⊕OOO VERY LOW	CRITICAL
Bleeding events												

1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	strong association	29/329 (8.8%)	10/251 (4%)	RR 2.21 (1.1 to 4.45)	48 more per 1000 (from 4 more to 137 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

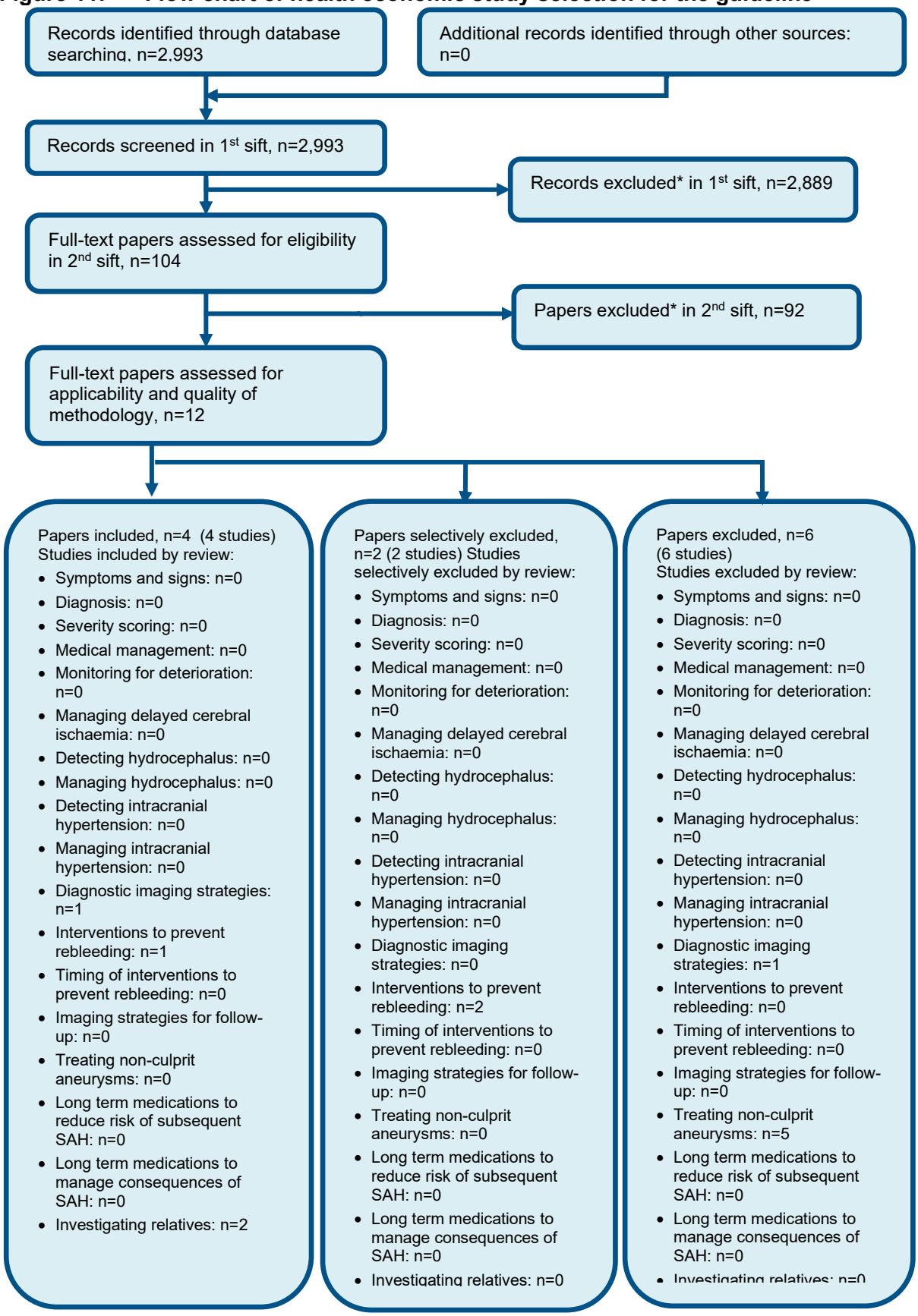
Table 13: Clinical evidence profile: Dual Antiplatelet therapy vs No Dual Antiplatelet therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DAPT**	**No DAPT**	**Relative (95% CI)**	**Absolute**		
DCI												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Adjusted OR 0.06 (0.01 to 0.31)	-	⊕⊕OO LOW	IMPORTANT
Vasospasm												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Adjusted OR 0.24 (0.10 to 0.61)	-	⊕⊕OO LOW	IMPORTANT
										-		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[1]

Appendix G: Health economic evidence selection

Figure 11: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

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Appendix H: Health economic evidence tables

None.

1 Appendix I: Excluded studies

I.1 2 Excluded clinical studies

3 **Table 14: Studies excluded from the clinical review**

Study	Reason for exclusion
Al-Shahi Salman 2018[1]	Inappropriate comparison – medications for ICH
Asano 1996[2]	Inappropriate intervention - Medication not licensed for the UK
Baharoglu 2013[3]	Inappropriate intervention – anti-fibrinolytics
Behrouz 2015[4]	Systematic review – references checked
Bruder 2017[5]	Inappropriate intervention – acute hospital intervention
Buchner 1985[6]	Paper not available
Cagnazzo 2018[8]	Inappropriate population – post ventriculostomy haemorrhage
Cagnazzo 2019[7]	Systematic review – references checked
Cagnazzo 2019[9]	Systematic review – references checked
Chalmers 2014[10]	Citation only
Cho 2019[11]	Inappropriate intervention – pre surgery intervention
Curran 2006[12]	Literature review – references checked
Dorhout Mees 2006[16]	Systematic review – references checked
Dorhout Mees 2007[15]	Systematic review – references checked
Dorhout Mees 2008[14]	Inappropriate study design - Clinical trial protocol
Guo 2020[17]	Inappropriate population – hypertensive cerebral haemorrhage, no reference to subarachnoid bleeding
Haley 1997[18]	Inappropriate intervention – short-term Tirilizad
Harrigan 2010[19]	Inappropriate study design - Review / commentary paper
Hasan 2011[20]	Inappropriate population – ISUIA cohort with pre interventional or historical aspirin usage
Heeley 2010[21]	Citation only
Hillman 2002[22]	Inappropriate intervention – anti-fibrinolytics
Hop 2000[23]	Inappropriate intervention – acute hospital intervention
Juvela 1995[24]	Inappropriate population – historical aspirin usage before intervention
Kassell 1996[25]	Inappropriate intervention – short-term Tirilizad
Keir 2002[26]	Systematic review – references checked
Khattar 2020[27]	Systematic review – references checked
Lanzino 1999[28]	Inappropriate intervention – short-term Tirilizad
Mendelow 1982[29]	Inappropriate intervention – anti-fibrinolytics
Neil-Dwyer 1983[32]	Inappropriate intervention - Unclear methodology of intervention

Study	Reason for exclusion
Neil-Dwyer 1985[33]	Inappropriate intervention - Unclear methodology of intervention
Ono 1984[35]	Inappropriate intervention – Ticlodipine
Roos 2000[36]	Inappropriate intervention – anti-fibrinolytics
Sedat 2017[37]	Inappropriate population – non ruptured aneurysms
Siironen 2003[39]	Inappropriate intervention – short term enoxaparin
Simard 2013[40]	Inappropriate intervention – short term heparin
Toussaint 2004[41]	Inappropriate population – cohort with historical aspirin usage
van den Bergh 2006[43]	Inappropriate intervention – short term aspirin usage
van Den Bergh 2009[42]	Inappropriate intervention – short term aspirin and magnesium usage
van den Bergh 2009[44]	Inappropriate intervention – multiple antiplatelet therapy in post ISAT cohort
Vergouwen 2011[45]	Systematic review – references checked
Vermeulen 1984[46]	Inappropriate intervention – anti-fibrinolytics
Wurm 1999[47]	Citation only
Young 2012[48]	Inappropriate intervention – NSAIDS for SAH

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 15: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	