National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[N] Evidence review for risk of subsequent subarachnoid haemorrhage

NICE guideline NG228

Methods, evidence and recommendations

November 2022

Final

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Evidence review underpinning recommendation 1.5.8 and research recommendations in the NICE guideline.

1.1 Review question: What is the risk of subsequent subarachnoid haemorrhage in adults with confirmed subarachnoid haemorrhage?

1.2 Introduction

People with aneurysmal subarachnoid haemorrhage are at high early risk of rebleeding from the ruptured arterial aneurysm, which can be mitigated by neurosurgical clipping or endovascular intervention to secure the aneurysm.

In the longer-term people with subarachnoid haemorrhage remain at risk of subsequent subarachnoid haemorrhage because of recurrence of the culprit aneurysm or because of bleeding from a non-culprit aneurysm.

This review aimed to quantify the risk of recurrent subarachnoid haemorrhage.

1.3 PICO table

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm.
Exposure variable under consideration	Previous aneurysmal subarachnoid haemorrhage
Outcome	A confirmed subsequent aSAH (confirmed by CT/LP +/- angiography)

1.4 Clinical evidence

1.4.1 Included studies

In order to judge the risk of subsequent SAH, a search was conducted for observational studies investigating the incidence of subsequent SAH in people with a previous SAH.

Thirty-five papers from 28 studies were included in the review,[2, 9-12, 39-42, 53, 59-63, 65-67, 76, 79, 80, 86, 88, 91-94, 97, 99, 102, 103, 105, 107, 108, 110] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

A search was initially conducted to identify the prognostic association of a previous subarachnoid haemorrhage with subsequent subarachnoid haemorrhage. On review of the evidence available, the outcome data provided information on the incidence of subsequent subarachnoid haemorrhage within a population of people who had experienced a previous subarachnoid haemorrhage. As such, a change in the review approach was made from

measuring the prognostic association of a previous subarachnoid haemorrhage to reviewing the incidence rate of subsequent subarachnoid haemorrhage within this target population.

The overall risk of subsequent SAH is reported (n=28) and then risk is reported according to the timing of study follow up since initial SAH (including under 1 year (n=8), over 1 year (n=23)), type of intervention (including neurosurgical (n=8),endovascular (n=18), craniotomy (n=1) and conservative management (n=1)) and age (under 65 years (n=1) and over 65 years (n=1)). Table 4 outlines the risk for subsequent SAH reported by the individual studies and Table 5-Table 7 report the risk by study for each of the factors listed in Table 3.

Follow-up of studies ranged from 1 month to 18.5 years. The incidence of subsequent SAH was recorded and total follow-up was used to determine the incidence rate of subsequent SAH per 100,000 person-years.

The incidence rate of the subsequent SAH was recorded for populations with previous SAH. Data on the sum of SAH events relative to the total number of participants under investigation was used to assess pooled incidence rate per 100 people and per 100,000 people. This value was used to estimate the incidence rate of SAH.

See also the study selection flow chart in Appendix C study evidence tables in Appendix D, and incidence plots in Appendix E.

1.4.2 Excluded studies

See the excluded studies list in Appendix F.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Outcomes	Follow-up	Stratification strategy
Aikawa 2007[2]	N=227 Patients with ruptured solitary cerebral aneurysm who underwent endovascular embolization with detachable coils. Mean age (range): 63.9 years (27-94) Study design: Retrospective case-series Japan	Incidence of rebleeding after endovascular treatment for ruptured cerebral aneurysm	Mean follow up 4.2 years	No stratification
BRAT: McDougall 2012[61] Merged with: Spetzler 2013[11] Spetzler 2015[93] Spetzler 2018[94] Mooney 2018[67]	N=472 Patients with acute SAH, confirmed by CT scan or lumbar puncture. Participants underwent either neurosurgical clipping (n=239) or endovascular coiling (n=233). Mean age: Clipping 53.1 ±12.8; Coiling 54.3 ±12	Incidence of aneurysmal re-bleed	6 years	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	Study design: RCT USA			
Brawanski 2017[9]	N=1493 Patient records from 1999 to 2013, of patients who had suffered from SAH and were treated with clipping or coiling. Mean age: 56 years Study design: Prospective cohort Germany	Incidence of recurrent second SAH	Mean follow up 10.4 years	No stratification
Byrne 1999[10]	N=317 Patients previously presenting with aneurysmal subarachnoid haemorrhage having been successfully treated by coil embolization within 30 days of haemorrhage. Mean age (range): 50.5 years (22-82) Study design: Retrospective case-series	Incidence of recurrent spontaneous SAH	2 years	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	UK			
Carat Investigators 2006[12]	N=1010 Patients with subarachnoid haemorrhage attributable to rupture of an intracranial aneurysm and a treatment attempt of this index aneurysm made with surgery (n=711) or endovascular coiling (n=299). Mean age (SD): 54.8 years (14.4) Clipping: 53.5 (13.8) Coiling: 58.0 (15.1) Study design: Retrospective cohort USA	Incidence of aneurysmal re-bleed	Maximum 10 years Mean 5.7 years	No stratification
Hur 2015[39]	N=134 Medical records of 134 anterior communicating artery aneurysm patients treated by coil embolization with available angiographic and clinical follow-up results. 101/134 patients had SAH, 33/134 had unruptured aneurysms. Mean age (range):	Incidence of DSA confirmed aneurysmal recurrence and rebleeding	Mean follow up 16 months	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	57.5 (23-80) Study design: Retrospective case-series Korea			
ISAT Molyneux 2002[62] Merged with: Molyneux 2005[66] Molyneux 2009[65] Molyneux 2015[63]	N=2143 Patients were eligible for the trial if they had a definite SAH, proven by CT or LP, within the preceding 28 days and an intracranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage. Participants underwent either neurosurgical clipping (n=1070) or endovascular coiling (n=1073). Mean age (range): Clipping 52 (18-84); Coiling 52 (18-87) Study design: RCT UK	Incidence of recurrent aSAHs more than 1 year after treatment of target aneurysm. Data collection through questionnaire and medical records.	10 years	No stratification
ISUIA Wiebers 1998[105]	N=615 Patients with unruptured aneurysm included in the	Incidence of subsequent SAH	6 years	Incidence of subsequent SAH in prospective cohort of patients treated with

Study	Population	Outcomes	Follow-up	Stratification strategy
Wiebers 2003[106]	International Study of Unruptured Intracranial Aneurysms (ISUAI). Subgroup of cohort with separate SAH and incidental unruptured aneurysm included. Unruptured aneurysm treated with conservative management (no surgery). Study design: Retrospective + prospective case-series USA			clipping or coiling not available. Treatment of previous SAH not reported.
Juvela 1989[40]	N=236 Consecutive patients with proven aneurysmal SAH admitted within 72 hours after SAH. Rebleeding was confirmed via CT; angiography or LP. Patients treated with neurosurgical clipping (n=236) Age (range): 19 – 55 years Finland	Incidence of rebleed	Follow up over 6 months to 3 years.	No stratification
Kassell 1990a[41] Kassell 1990b[42]	N=3521 International cooperative study on timing of aneurysm surgery. Patients included in the study had a SAH and admitted within 3 days to a neurosurgical centre.	Incidence of rebleeding / intracerebral haemorrhage	6 months	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	Patients underwent surgical intervention or medical management. Mean age: 50.4 years 68 medical centres globally (majority within USA and Japan) Study design: Prospective case-series			
Li 2012[53]	N=186 Consecutive patients with acute aSAH. 94 received endovascular treatment and 92 received surgical treatment. Mean age: 54.2 Study design: RCT China	Incidence of aneurysmal rebleed	1 year follow-up	No stratification
McAuliffe 2012[59]	N=11 Cases of recent aneurysmal SAH treated with pipeline embolization devices. Mena age (range): 51.6 years (41-69) Study design: Retrospective case-series Australia	Incidence of aneurysmal re-bleed	6 months follow-up	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
Mcdougall 2014[60]	N=228 Adult with ruptured intracranial saccular aneurysm for which both polymer-modified coils and bare metal coils (BMCs) were treatment options. Participants received either bare metal coiling (n=119) or Matrix 2 coiling (n=109). Mean age: Bare metal coiling 54.4 ±13.2 Matrix2: 55.7 ±11.6 Study design: RCT USA	Incidence of aneurysms rupture or re-rupture	Mean follow up 1.2 years	No stratification
Pierot 2020[76]	N= 794 Adults with at least one ruptured intracranial aneurysm. Treated by endovascular coiling (n=461) or balloon assisted coiling (n=356) Mean age: 54 years ± 13.1 Study design: Prospective case-series France	Incidence of rebleeding	Mean follow-up 12.2 ± 6.3 months	Patients treated for unruptured aneurysms were not included in the analysis.

Study	Population	Outcomes	Follow-up	Stratification strategy
Plowman 2011[79]	N=570 Consecutive patients presenting acute aneurysmal SAH treated with endosaccular coil embolization within 30 days of haemorrhage. Clinical follow up confirmed with angiography Patients treated with endovascular coiling (n=570) Mean age: 53 years Study design: Prospective case-series UK	Incidence of rebleeding	Mean follow up 73.7 months Angiography performed at 6 and 24 months	No stratification
Pyysalo 2010[80]	N=109 SAH patients who received coiling for ruptured aneurysms. Study design: Retrospective case-series Finland	Incidence of MR confirmed re-bleeding of ruptured aneurysm.	11 years	No stratification
Schaafsma 2009[86]	N=283 Patients with ruptured intracranial aneurysms coiled with adequate aneurysm occlusion at 6-month follow-up angiograms.	Incidence of recurrent SAH	mean of 6.3 years	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	Mean age (range): 51 years (26-82) Study design: Prospective case-series The Netherlands			
Sedat 2002[88]	N=195 Patients hospitalised for SAH resulting from aneurysm rupture. Aneurysms were secured by endovascular treatment. Mean age: 53.5 years Study design: Retrospective case-series France	Incidence of recurrent haemorrhage after treatment	1 year	Cohort divided into those aged <65 (n=52) and those aged ≥65 years (n=143)
Sluzewski 2005[91]	N=392 Consecutive patients with aSAH were treated with detachable coils. Mean age: 52.9 years Study design: Retrospective case-series The Netherlands	Incidence of aneurysmal re-bleeding	4 years	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
Sokolowski 2019[92]	N=33 Consecutive patients with intracranial aneurysms who underwent endovascular treatment using SMART coils and had follow up angiographic data Patients underwent endovascular coiling (n=33) Mean age (SD): 56.8 (11.5) Study design: Retrospective case-series USA	Incidence of retreatment for aneurysm reoccurrence	mean of 7.7 months	No stratification
Tanno 2007[97]	N=5612 Patients with ruptured intracranial aneurysms. Rebleeding diagnosed via CT. Age demographics not specified Study design: Retrospective case-series 49 institutions across Japan	Incidence of rebleeding (within 4 weeks of intervention)	1 month	No stratification
Todd 1989[99]	N=181 Patients included with single anterior circulation aneurysm,	Incidence of late recurrent subarachnoid haemorrhage, >6 months after initial bleed	10 years	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	which was either clipped or wrapped. SAH confirmed on angiography. Patients underwent either neurosurgical clipping (n=121) or wrapping (n=60) Mean age (range): 46 years (15 to 69 years) Study design: Prospective cohort study Scotland			
Tsutsumi 1998[102]	N=220 Patients with SAH surgically treated cases with aneurysms detected by 3- or 4-vessel cerebral angiography clipped, complete obliteration of aneurysm(s) confirmed by postoperative angiography. Mean age (range): 55.8 years (24-79) Study design: Retrospective case-series Japan	Incidence of recurrent SAH	Mean follow up 9.9 years	No stratification
Wermer 2005[103]	N=752	Incidence of recurrent SAH confirmed by CT/LP/autopsy.	8 years	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	Patients admitted with CT confirmed SAH, presence of a saccular aneurysm confirmed by conventional angiography or CT-angiography and clipping of the ruptured aneurysm and all additional aneurysms. Mean age (range): 50.1 (20-83) Study design: Retrospective case-series The Netherlands			
Willinsky 2009[107]	N=292 Consecutive patients who presented with SAH from a ruptured intracranial aneurysm and were successfully treated by coiling. Mean age (SD): 54.8 years (15) Study design: Retrospective case-series Canada	Incidence of aneurysmal rebleeding	Mean follow up 22 months	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
Winn 1983[108]	N = 182 Patients with multiple subarachnoid aneurysms leadings to SAH. Patients underwent conservative treatment (n=132) or craniotomy (n=50). 38 of the surgically treated patients were alive at 6 months and followed up Mean age (SD): Conservative: 51 (1); Surgical treatment: 47 (1) Study design: Retrospective case-series UK	Incidence of recurrent bleed from 6 months to 10 years of initial SAH.	6 months – 10 years	Type of intervention
Yu 2019[110]	N=6008 Patients treated at the centre for intracranial aneurysms. Angiographic follow up with DSA or 3D CTA. Patients treated with endovascular coiling (n=6008) Mean age (SD): 47.4 (11.5) Study design: Retrospective case-series	Incidence of recurrences over a 6 year period with minimal interval 6 months post intervention	6 months	No stratification

Study	Population	Outcomes	Follow-up	Stratification strategy
	China			

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: Risk of recurrent SAH (pooled data)

Risk factor (population)	Number of studies (participants)	Pooled incidence per 100000 person-years (95% CI)	Pooled incidence per 100 person-years (95% CI)	Risk of Bias
Previous SAH	28 (27055)	1198 (1122-1278)	1.2 (1.12-1.28)	Moderate[1]
Timing of follow up				
Including studies with ≤1 year follow-up	*8 (11946)*	*12678 (11722-13690)*	*12.68 (11.72-13.69)*	High[1,2]
Including studies with >1 year follow-up	*20 (15109)*	*379 (336-427)*	*0.38 (0.34-0.43)*	Moderate[1]
Including data from follow-up after 1 year	*3 (2990)*	*158 (109-221)*	*0.16 (0.11-0.22)*	Moderate[1]
Stratification by subgroup				
Intervention:				
Neurosurgical	*8 (3159)*	*607 (511-716)*	*0.61 (0.41-0.72)*	Moderate[1]
Endovascular	*18 (9878)*	*404 (339-477)*	*0.4 (0.34-0.48)*	Moderate[1]
Craniotomy	*1 (50)*	*3968 (1900-7298)*	*3.97 (1.9-7.3)*	High[1,3]
Conservative management	*1*	3770 (2333-5763)	*3.77 (2.33-5.73)*	Moderate[1]

Risk factor (population)	Number of studies (participants)	Pooled incidence per 100000 person-years (95% CI)	Pooled incidence per 100 person-years (95% CI)	Risk of Bias
	(132)			
Age				
Aged <65 years	*1 (143)*	*0 (0-2580)*	*0 (0-2.58)*	Moderate[1]
Aged ≥65 years	*1 (52)*	*0 (0-7094)*	*0 (0-7.09)*	High[1,3]

1) *Unclear if valid methods used for the identification of the target condition – unclear in the majority of included studies if subsequent SAH was confirmed by CT/LP +/- angiography.*
2) *Unclear if valid methods used for the measurement of the target condition – majority of included studies allowed for insufficient follow-up time to provide an accurate estimation of recurrence incidence.*
3) *Sample size considered to be inadequate to accurately record incidence and ensure good precision of the final estimate.*

Table 4: Clinical evidence: Risk of recurrent SAH (individual studies)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Aikawa 2007[2]	224	64	4.2	953	6	630 (231-1370.4)
BRAT[94]	336	53.7	6	2016	0	0 (0-182)
Brawanski 2017[9]	1493	56	10.4*	15527	18	116 (68.7-183)
Byrne 1999[10]	317	51	1.9†	792	5	632 (205-1473)
CARAT[12]	1010	55	5.7	4216	19	451 (271-704)
Hur 2015[39]	134	58	1.4	182	0	0 (0-2027)
ISAT[62] (<1 year)	1594	52	1	1594	73	4579.7 (3589.6-5758.3)
ISAT[63] (>1 year)	1644	52	10 to 18.5	16579	33	199 (137-280)
ISUIA[106]	615	52	6	1145	10	873.4 (418.1-1606.2)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Juvela 1989[40]	236	37	3	708	55	7768 (5852-10112)
Kassell 1990[41, 42]	3521	50.4	0.5 (6 months)	1760.5	333	18915.1 (16937.8-21059.8)
Li 2012[53]	186	54.2	1	186	6	3260.9 (1196.7-7097.5)
McAuliffe 2012[59]	11	51.6	0.5	5.5	2	36363.6 (4403.8-131358)
McDougall 2014[60]	228	55	1.25	285	3	659 (136-1927)
Pierot 2020[76]	794	54	1.02	807.2	8	1007.6 (435 - 1985.3)
Plowman 2011[79]	452	53	6.2 years	2802.4	9	321 (147- 610)
Pyysalo 2010[80]	109	54	11‡	688	9	659 (136-1927)
Schaafsma 2009[86]	283	51	6.3	1778	1	56 (6-311)
Sedat 2002[88]	195	54	1	195	0	0 (0-1892)
Sluzewski 2005[91]	392	53	4	1159	5	431 (140-1007)
Sokolowski 2019[92]	33	56.8	0.77	25.41	5	19677.3 (6389.2-45920.2)
Tanno 2007[97]	5612	64.6	0.1 (1 month follow up)	561.2	224	39914.5 (34858.0-45498.2)
Todd 1989[99]	182	46	10 (max)	809	31	3832 (2603-3439)
Tsutsumi 1998[102]	220	56	9.9	2175	6	276 (101-600)
Wermer 2005[103]	752	50	8	6016	18	299 (177-473)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Willinsky 2009[107]	292	55	1.8	546	8	1474 (637-2905)
Winn 1983[108]	182	47	10	809	31	3832 (2603-3439)
Yu 2019[110]	6008	47.4	2.13	12797	6	47 (17-102)
Pooled data	**27055**	**53**	**4.47**	**77117**	**924**	**1198 (1122-1278)**

*Mean time to second SAH

†Value represents median follow-up

‡Total cohort follow-up (included unruptured aneurysms)

Table 5: Clinical evidence: Risk of recurrent SAH (sensitivity analysis by timing of follow up)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Studies with ≤1 year follow-up						
ISAT[62] (<1 year)	1594	52	1	1594	73	4579.7 (3589.6- 5758.3)
Kassell 1990[41, 42]	3521	50.4	0.5 (6 months)	1760.5	333	18915.1 (16937.8-21059.8)
Li 2012[53]	186	54.2	1	186	6	3260.9 (1196.7-7097.5)
McAuliffe 2012[59]	11	51.6	0.5	5.5	2	36363.6 (4403.8-131358)
Pierot 2020[76]	794	54	1.02	807.2	8	1007.6 (435 - 1985.3)
Sedat 2002[88]	195	54	1	195	0	0 (0-1892)
Sokolowski 2019[92]	33	56.8	0.77	25.41	5	19677.3 (6389.2-45920.2)
Tanno 2007[97]	5612	64.6	0.1 (1 month)	561.2	224	39914.5 (34858.0-45498.2)
Pooled	**11946**	**54.7**	**0.74**	**5135**	**651**	**12678 (11722-13690)**

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Studies with >1 year follow-up						
Aikawa 2007[2]	224	64	4.2	953	6	630 (231-1370.4)
BRAT[94]	336	53.7	6	2016	0	0 (0- 182)
Brawanski 2017[9]	1493	56	10.4*	15527	18	116 (68.7-183)
Byrne 1999[10]	317	51	1.9†	792	5	632 (205-1473)
CARAT[12]	1010	55	5.7	4216	19	451 (271-704)
Hur 2015[39]	134	58	1.4	182	0	0 (0-2027)
ISAT[63] (>1 year)	1644	52	10 to 18.5	16579	33	199 (137-280)
ISUIA[106]	615	52	6	1145	10	873.4 (418.1-1606.2)
Juvela 1989[40]	236	37	3	708	55	7768 (5852- 10112)
McDougall 2014[60]	228	55	1.25	285	3	659 (136-1927)
Plowman 2011[79]	452	53	6.2 years	2802.4	9	321 (147- 610)
Pyysalo 2010[80]	109	54	11‡	688	9	659 (136-1927)
Schaafsma 2009[86]	283	51	6.3	1778	1	56 (6-311)
Sluzewski 2005[91]	392	53	4	1159	5	431 (140-1007)
Todd 1989[99]	182	46	10 (max)	809	31	3832 (2603-3439)
Tsutsumi 1998[102]	220	56	9.9	2175	6	276 (101-600)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Wermer 2005[103]	752	50	8	6016	18	299 (177-473)
Willinsky 2009[107]	292	55	1.8	546	8	1474 (637-2905)
Winn 1983[108]	182	47	10	809	31	3832 (2603-3439)
Yu 2019[110]	6008	47.4	2.13	12797	6	47 (17-102)
Pooled	**15109**	**52.3**	**4.76**	**71982**	**273**	**379 (336-427)**
Including studies with follow-up from year 1 after initial SAH						
BRAT[94]	336	54	years 1-6	1726	0	0 (0-214)
CARAT[12]	1010	55	years >1	3206	1	31 (1-174)
ISAT[63] (>1 year)	1644	52	10 to 18.5	16579	33	199 (137-280)
Pooled	**2990**	**53.7**	**7.2 (→1 year)**	**21514**	**34**	**158 (109-221)**

*Mean time to second SAH
†Value represents median follow-up
‡Total cohort follow-up (included unruptured aneurysms)

Table 6: Clinical evidence: Risk of recurrent SAH (subgroup stratification by initial intervention)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Neurosurgery						
BRAT[94]	174	53	6	1044	0	0 (0-353)
CARAT[12]	711	54	4.4	3127	9	288 (132-547)
ISAT[62] (<1 year)	853	52	1	793	33	4161.4 (2864.1- 5844.4)
ISAT[63] (>1 year)			10 to 18.5	8228	12	146 (75-255)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Juvela 1989[40]	236	37	3	708	55	7768 (5852-10112)
Li 2012[53]	92	54	1	92	3	3191.5 (658.2-9326.9)
Todd 1989[99]	121	46	10	1210	6	332 (122-722)
Tsutsumi 1998[102]	220	56	9.9	2175	6	276 (101-600)
Wermer 2005[103]	752	50	8	6016	18	299 (177-473)
Pooled data	**3159**	**50**	**7.41**	**23393**	**142**	**607 (511-716)**
Endovascular intervention						
Aikawa 2007[2]	224	64	4.2	953	6	630 (231-1370)
BRAT[94]	162	54	6	2016	0	0 (0- 398)
Byrne 1999[10]	317	51	1.9*	792	5	632 (205-1473)
CARAT[12]	299	58	3.7	1089	10	918 (440-1689)
Hur 2015[39]	134	58	1.4	182	0	0 (0-2027)
ISAT[62] (<1 year)	809	52	1	801	40	4993.8 (3567.2- 6800.3)
ISAT[63] (>1 year)			10 to 18.5	8351	21	252 (116-384)
Li 2012[53]	94	54	1	92	3	3260.9 (672.5-9529.6)
McAuliffe 2012[59]	11	51.6	0.5	5.5	2	36363.6 (4403.8-131358)
Mcdougall 2014[60]	228	55	1.25	285	3	659 (136-1927)
Plowman 2011[79]	452	53	6.2	2802.4	9	321.2 (147-610)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Pyysalo 2010[80]	109	54	11†	688	9	659 (136-1927)
Schaafsma 2009[86]	283	51	6.3	1778	1	56 (6-311)
Sedat 2002[88]	195	54	1	195	0	0 (0-1891.7)
Sluzewski 2005[91]	392	53	4	1159	5	431 (140.1-1006.8)
Sokolowski 2019[92]	33	56.8	0.77	25.41	5	19677.3 (6389.2-45920.2)
Todd 1989[99]	60	46	10	600	11	1833 (914-3281)
Willinsky 2009[107]	292	55	1.8	546	8	1474 (637-2905)
Yu 2019[110]	6008	47	2.13	12797	6	47 (17- 102)
Pooled data	**9878**	**53**	**3.47**	**34259**	**99**	**404 (339-477)**
Craniotomy						
Winn 1983[108]	50	46	10	252	10	3968 (1900-7298)
Conservative management						
Winn 1983[108]	132	46	10	557	21	3770 (2333-5763)

*Mean time to second SAH
‡Value represents median follow-up

Table 7: Clinical evidence: Risk of recurrent SAH (subgroup stratification by age)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Aged <65 years						
Sedat 2002[88]	143	47	1	195	0	0 (0-2580)

Study	Number of participants	Mean age (years)	Mean follow-up (years)	Number of person-years	Subsequent aSAH (total number)	Incidence per 100000 person-years (95% CI)
Aged ≥65 years						
Sedat 2002[88]	52	72	1	195	0	0 (0-7094)

1.5 Economic evidence

The committee agreed that health economic studies would not be relevant to this review question, and so none were sought.

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

The committee considered the incidence of subsequent aSAH, confirmed by CT, lumbar puncture, or angiography, to be the primary focus of this review. Studies reporting rebleeding or subsequent aSAH were included for analysis. Patient follow-up was recorded to produce the pooled measure of incidence rate of subsequent aSAH per 100 and 100,000 patient-years.

1.6.1.2 The quality of the evidence

The evidence reviewed was considered to be of low quality. Most of the evidence was downgraded as there was a moderate or high risk bias. This was mostly due to a lack of clarity as to whether valid methods were used, such as CT and/or LP +/- angiography, for the identification of subsequent SAH. There were also concerns regarding the short follow-up times of some of the included studies. The committee noted that some studies may have included patients with rebleeding before the aneurysm had been secured and this may have contributed to the inconsistency and imprecision. The committee also noted the small sample size of some included studies as a potential bias. Some evidence was also considered to be of lower quality because of a high level of imprecision with wide confidence intervals around the pooled summary measure.

As such, the committee were unable to provide a specific recommendation for the risk of subsequent subarachnoid haemorrhage in people who have had a subarachnoid haemorrhage. The committee highlighted that information on future risk of subarachnoid haemorrhage may be desirable for people following a subarachnoid haemorrhage. As such, the committee made a consensus recommendation to give people who wish to receive it information about their estimated future risk of another subarachnoid haemorrhage. The committee recommended that this information should be based on specialist assessment by a multidisciplinary team, taking into account the person's medical circumstances.

1.6.1.3 The committee discussion of the evidence

Summary of the evidence

The evidence suggested an overall risk of subsequent aSAH, independent of management of the previous aSAH, of approximately 1% per annum. When studies were stratified by length of follow-up, the evidence showed a 13% risk of subsequent aSAH within the first year following initial haemorrhage, with the risk decreasing to approximately 0.4% per annum thereafter. The risk after intervention showed under a 1% risk for neurosurgical and endovascular intervention (0.61 and 0.4% respectively), and under a 4% risk after craniotomy and conservative management (3.97 and 3.77% respectively). The evidence for age (under and above 65 years) was from 2 small studies and neither reported any rebleeds.

Committee discussion

The committee discussed the low quality of the evidence for data recorded within the first year of follow-up and agreed that it was less helpful for their decision making than the studies

with longer term follow up. The studies reporting longer-term follow-up included rebleeding following endovascular and neurosurgical intervention.

The committee discussed the evidence noting the 13% risk during the first year and the ~1% per annum risk from the total dataset were higher than expected. The committee suggested that the dataset may have included episodes of early rebleeding of the culprit aneurysm before the aneurysm had been secured, although it was not possible to ascertain this level of detail from the evidence. The committee considered that the inclusion of such data on rebleeding may have artificially inflated the overall incidence rates of subsequent SAH. They noted the low quality of the evidence and the imprecision also contributed to the uncertainty in the data. The committee agreed that the data showing the average risk of subsequent aSAH after neurosurgical clipping or endovascular coiling of approximately 0.4% per annum (or 1 in 200) is more reflective of clinical experience. The committee agreed that there was insufficient evidence to draw any firm conclusions on the incidence of subsequent aSAH following conservative management or craniotomy for the initial haemorrhage.

The committee discussed that patients often ask about their risk of having another subarachnoid haemorrhage in the future and concluded that consensus recommendations should be made to ask the person if they would like information about their risk and then discuss an individual's estimated risk of recurrence if requested. The committee also acknowledged that some people may not wish to discuss their risk of subsequent SAH, and this should be taken into consideration.

The committee suggested that from their experience, the incidence of aSAH in the general population is typically around 8 per 10,000 per annum, and this may inform discussions around risk of subsequent aSAH in people with previous SAH. The committee agreed that the incidence of subsequent aSAH may be influenced by several factors. These include the size, location and treatment of the original ruptured aneurysm; the presence, location and characteristics of any non-culprit aneurysms; the recurrence of treated aneurysm(s) detected during follow up; or occurrence of new aneurysms. In addition, there will be patient specific risks such as smoking and uncontrolled hypertension. The committee recommended these should be taken into consideration when discussing subsequent risk.

Information about the risk should be provided in an understandable form and may include the absolute risk of subsequent aSAH and the risk relative to the general population. The committee agreed that the discussion with the person with aSAH about the risk of subsequent SAH should involve an appropriately qualified healthcare professional.

The committee were aware that smoking is a risk factor for initial aSAH. The committee agreed that smoking would continue to be a risk factor for subsequent aSAH following an initial episode and should be considered when reviewing future risk, and decided cross-reference should be made to the NICE guidance on stop smoking interventions and services.

1.6.2 Cost effectiveness and resource use

Economic evidence was not sought for this review as identifying the risk of subsequent subarachnoid haemorrhage is intended primarily for patient information.

No changes in resource use are expected as a consequence of the recommendation.

1.6.3 Other factors the committee took into account

The committee discussed the lack of a validated risk tool to provide a person with an estimate of their individual risk of a subsequent SAH. This information is frequently asked for and the availability of such a tool to provide such information for those who wanted it would be of benefit to patients. The committee agreed this should be a high priority research recommendation (see Appendix G:). The committee felt this research would be of greater

value than further research into the incidence of subsequent SAH in people who have experience a SAH.

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Appendices

Appendix A: Review protocols

Table 8: Review protocol: Risk of subsequent SAH

ID	Field	Content
0.	PROSPERO registration number	CRD42019160093
1.	Review title	What is the risk of subsequent subarachnoid haemorrhage in adults with confirmed subarachnoid haemorrhage?
2.	Review question	What is the risk of subsequent subarachnoid haemorrhage in adults with confirmed subarachnoid haemorrhage?
3.	Objective	To determine the risk of subsequent subarachnoid haemorrhage in people with confirmed subarachnoid haemorrhage.
4.	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 only The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
6.	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.
7.	Exposure	• Previous aneurysmal subarachnoid haemorrhage
8.	Comparator	• n/a

9.	Types of study to be included	• Case series studies will be included. Studies stratifying groups by age will be prioritised to consider age as a confounding factor.
	Addendum to review protocol	• To allow for the collection of incidence data, studies of RCT, cohort, and case series study designs were considered for inclusion. Population data was assessed as a whole, recording the rate of outcome incidence within the predefined population.
10.	Other exclusion criteria	Exclusions: • Studies not in English • Conference abstracts
11.	Context	n/a
12.	Primary outcomes (critical outcomes)	• A confirmed subsequent aSAH (confirmed by CT/LP +/- angiography) • Measured by a weighted pooled risk Outcomes will be captured after the point of an initial assessment for primary aSAH.
13.	Secondary outcomes (important outcomes)	n/a
14.	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. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. 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. • papers were included /excluded appropriately • a sample of the data extractions • 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.

	Addendum to protocol	The quality assessment for included studies was performed based on risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data for incidence studies.	
16.	Strategy for data synthesis	Aggregate data on risk association of subsequent subarachnoid haemorrhage will be collected and synthesized in a quantitative data analysis. If more than one study covered the same combination of population and outcome then meta-analysis will be used to pool results. Meta-analysis will be carried out using a weighted pooled risk calculation. Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer. Endnote will be used for bibliography, citations, sifting and reference management.	
	Addendum to protocol	Incidence data will be pooled to provide a weighted pooled incidence rate per 100 people per year and per 100,000 people per year. The summary statistics will be presented in summary tables alongside overall risk of bias of pooled estimates. Incidence rates from each study population will also be reported.	
17.	Analysis of sub-groups	Strata: • n/a Subgroups: • Treatment of previous aneurysm: ○ Clipping ○ Coiling ○ Conservative management • Presence of non-culprit aneurysm(s) ○ Yes ○ No • Smoking status ○ Smoker ○ Non-smoker • Family history ○ aSAH history in first degree relative ○ No aSAH history in first degree relative • Gender ○ Male ○ Female • Age ○ <60 ○ ≥60 • Blood pressure ○ Hypertensive (>140/90) ○ Non-hypertensive (<140/90)	
18.	Type and method of review	☐	Intervention

		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☒	Other (please specify) Incidence review
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date		
22.	Anticipated completion date	3 February 2021	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☑ / ☑
		Risk of bias (quality) assessment	☑ / ☑
		Data analysis	☑ / ☑
24.	Named contact	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	
25.	Review team members	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	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	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.	
28.	Collaborators	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 section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	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.	
32.	Keywords	Subarachnoid haemorrhage; subsequent risk	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published

		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

Table 9: 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.[70] 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.

Appendix B: Literature search strategies

This literature search strategy was used for the following review;

- What is 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[70]

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 the following approach:

- Population AND Prognostic/risk factor terms AND Study filters

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 June 2020	Exclusions

Database	Dates searched	Search filter used
		Observational studies Prognostic studies
Embase (OVID)	1974 – 26 June2020	Exclusions Observational studies Prognostic studies

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.	(rebleed* or re-bleed* or retreatment* or re-treatment*).ti,ab.
30.	((repeat* or subsequent or recur* or further or second) adj3 (event* or treat*)).ti,ab.
31.	((subsequent* or repeat* or recur*) adj3 (hemorrhag* or haemorrhag* or bleed* or blood* or aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
32.	or/29-31
33.	28 and 32
34.	((subsequent* or repeat* or recur*) adj3 (subarachnoid* or arachnoid* or aSAH or SAH)).ti,ab.

35.	((subsequent* or repeat* or recur*) adj3 (cerebral or intracranial or intra-cranial or brain) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
36.	34 or 35
37.	36 not 24
38.	28 and 37
39.	38 not 26
40.	33 or 39
41.	risk/
42.	Risk Assessment/
43.	Risk Factors/
44.	risk*.ti.
45.	or/41-44
46.	predict.ti.
47.	(validat* or rule*).ti,ab.
48.	(predict* and (outcome* or risk* or model*)).ti,ab.
49.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
50.	decision*.ti,ab. and Logistic models/
51.	(decision* and (model* or clinical*)).ti,ab.
52.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
53.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
54.	ROC curve/
55.	or/46-54
56.	Epidemiologic studies/
57.	Observational study/
58.	exp Cohort studies/
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	Controlled Before-After Studies/
63.	Historically Controlled Study/
64.	Interrupted Time Series Analysis/
65.	(before adj2 after adj2 (study or studies or data)).ti,ab.
66.	exp case control study/
67.	case control*.ti,ab.
68.	Cross-sectional studies/
69.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	or/56-69
71.	40 and (45 or 55 or 70)

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.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
25.	23 not 24
26.	limit 25 to English language
27.	(rebleed* or re-bleed* or retreatment* or re-treatment*).ti,ab.
28.	((repeat* or subsequent or recur* or further or second) adj3 (event* or treat*)).ti,ab.
29.	((subsequent* or repeat* or recur*) adj3 (hemorrhag* or haemorrhag* or bleed* or blood* or aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
30.	or/27-29
31.	26 and 30
32.	((subsequent* or repeat* or recur*) adj3 (subarachnoid* or arachnoid* or aSAH or SAH)).ti,ab.
33.	((subsequent* or repeat* or recur*) adj3 (cerebral or intracranial or intra-cranial or brain) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
34.	32 or 33
35.	34 not 22
36.	26 and 35
37.	36 not 24
38.	31 or 37
39.	risk/
40.	risk assessment/
41.	risk factor/
42.	risk*.ti.
43.	or/39-42

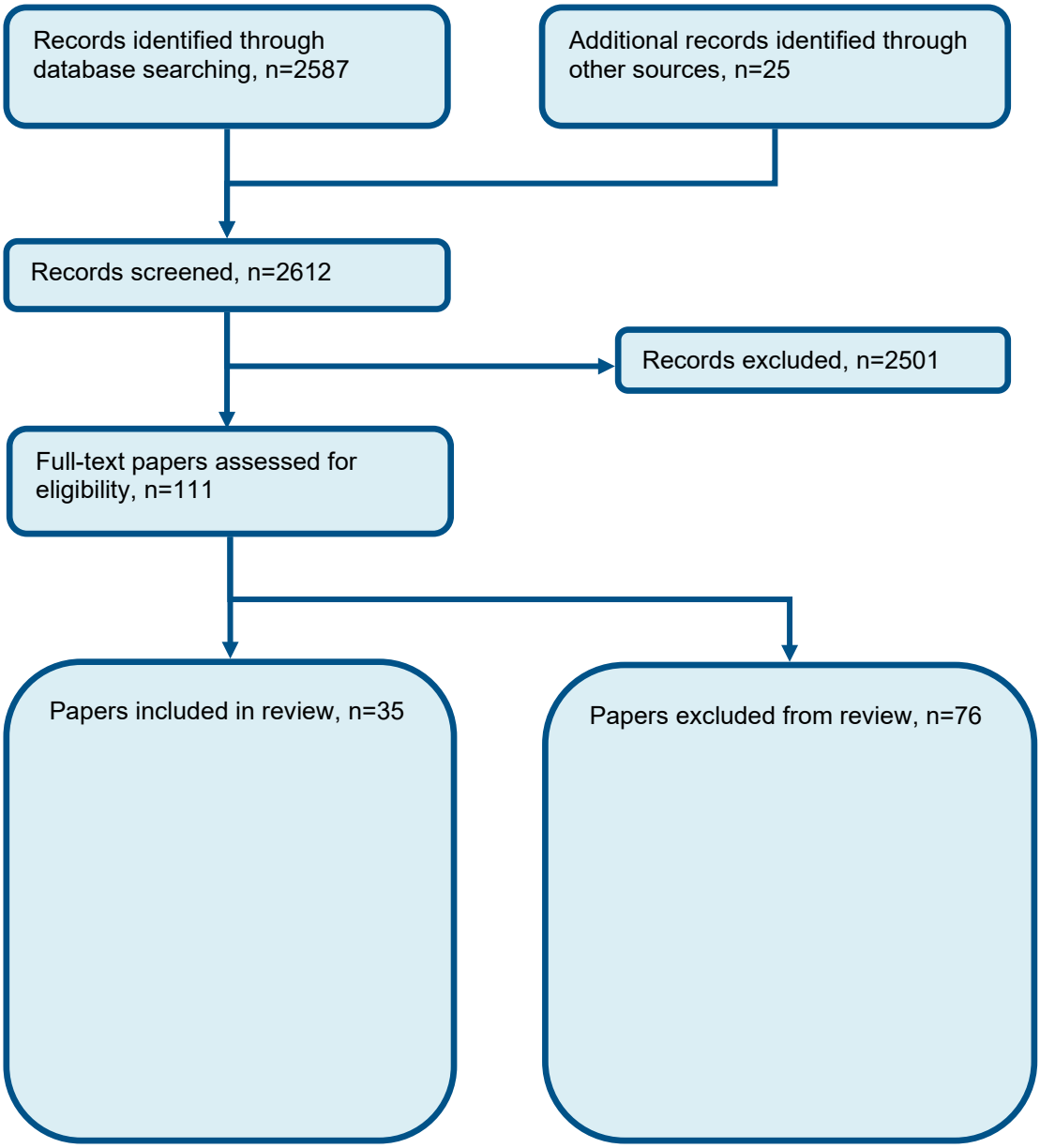
44.	predict.ti.
45.	(validat* or rule*).ti,ab.
46.	(predict* and (outcome* or risk* or model*)).ti,ab.
47.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
48.	decision*.ti,ab. and Statistical model/
49.	(decision* and (model* or clinical*)).ti,ab.
50.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
51.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
52.	Receiver operating characteristic/
53.	or/44-52
54.	Clinical study/
55.	Observational study/
56.	family study/
57.	longitudinal study/
58.	retrospective study/
59.	prospective study/
60.	cohort analysis/
61.	follow-up/
62.	cohort*.ti,ab.
63.	61 and 62
64.	(cohort adj (study or studies or analys* or data)).ti,ab.
65.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
66.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
67.	(before adj2 after adj2 (study or studies or data)).ti,ab.
68.	or/54-60,63-67
69.	exp case control study/
70.	case control*.ti,ab.
71.	cross-sectional study/
72.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
73.	or/68-72
74.	38 and (43 or 53 or 73)

B.2 Health Economics literature search strategy

Health economic evidence was not required for this review.

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of Risk of subsequent SAH



Appendix D: Clinical evidence tables

Reference	Aikawa 2007[2]
Study type	Retrospective case-series. Japan
Number of participants and characteristics	Total n= 227 Inclusion and exclusion criteria: Patients underwent endovascular embolization using Guglielmi detachable coils between March 1997 and March 2006. Complete clinical data were available for patients who continue to receive regular follow-up examinations. This study included 227 of these patients, treated for ruptured solitary cerebral aneurysm to simplify the evaluation of the efficacy and the outcome of the treatment. Four-vessel angiography confirmed the presence of solitary aneurysm at the onset of the initial SAH. Follow-up examinations included routine magnetic resonance angiography every 6 months and cerebral angiography if revascularization was suspected. Mean age: 63.9 years (27-94) Gender (m:f): 73/154 Primary intervention of initial SAH: Guglielmi detachable coils
Outcome	Incidence of rebleeding after endovascular treatment for ruptured cerebral aneurysm
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: 4.2 years Person-years: 953
Incidence:	Total subsequent SAH: 6

Reference	Aikawa 2007[2]
	Incidence per 100000 person-years (95% CI): 630 (231 – 1370.4)
Comments	Low risk of bias

Reference	BRAT (McDougall 2012[61]; Spetzler 2013[11]; Spetzler 2015[93]; Spetzler 2018[94]; Mooney 2018[67])
Study type	RCT (Patient randomised; Parallel) USA
Number of participants and characteristics	Total n=472 Inclusion and exclusion criteria: Acute subarachnoid haemorrhage (SAH) with confirmed by CT scan or lumbar puncture, aged 18-80 years and the ability to give informed consent (subject or legally authorized representative). Mean age (SD): Clipping 53.1 ±12.8; Coiling 54.3 ±12 Gender (m:f): Clipping group 72/166; coiling 67/166. Primary intervention of initial SAH: Participants underwent either neurosurgical clipping (n=239) or endovascular coiling (n=233).
Outcome	Aneurysmal rebleed
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: Mean 6 years

Reference	BRAT (McDougall 2012[61]; Spetzler 2013[11]; Spetzler 2015[93]; Spetzler 2018[94]; Mooney 2018[67])
	Person-years: Total: 2016 Clipped patients: 1044 person-years Coiled patients: 972 person-years
Incidence:	Total subsequent SAH: Total: 0 Rebleeding at 1 year; Clipping 1: 0/180, Coiling: 0/109 rebleeding at 3 years; Clipping 1: 0/175, Coiling: 0/106 rebleeding at 6 years; Clipping 1: 0/174, Coiling: 0/162 Incidence per 100000 person-years (95% CI): Total: 0 (0-183) Clipping: 0 (0-353.3) Coiling: 0 (0-397.5)
Comments	Moderate risk of bias

Reference	Brawanski 2017[9]
Study type	Prospective cohort Germany
Number of participants and characteristics	Total n= 1493 Inclusion and exclusion criteria: Patient records from 1999 to 2013, of patients who had suffered from SAH. All patients with a recurrent second SAH (months or even years after the first SAH) were included in this study, whereas patients suffering from an early rebleeding (defined as a rebleeding before aneurysm treatment, during aneurysm treatment or at least in the first weeks after aneurysm treatment) were not included in this study.

Reference	Brawanski 2017[9]
	Mean age (of patients with subsequent SAH): 56 Gender of patients with subsequent SAH (m:f): 6/12 Primary intervention of initial SAH: Only patients with a secured aneurysm (by coil or clip) were included. Therefore, patients with a second SAH without aneurysm treatment or patients with an early rebleeding were excluded.
Outcome	Recurrent secondary SAH. Follow-up imaging typically carried out with DSA or MRA.
Confounders/ Stratification strategy	No stratification performed
Follow-up	Mean follow-up: Mean time between SAH events 10.4 years Clipping: 12.6 years Coiling: 6.5 years Person-years: 15527.2
Incidence:	Total subsequent SAH: 18 (Initial treatment: clipping: 6; coiling: 10; no treatment: 2) Incidence per 100000 person-years (95% CI): 116 (68.7-183.2)
Comments	Low risk of bias

Reference	Byrne 1999[10]
Study type	Retrospective case-series UK
Number of participants	Total n= 317

Reference	Byrne 1999[10]
and characteristics	Inclusion and exclusion criteria: Patients previously presenting with aneurysmal subarachnoid haemorrhage having been successfully treated by coil embolization within 30 days of haemorrhage. Mean age: 50.5 years (22-82) Gender (m:f): 126/191 Primary intervention of initial SAH: Coil embolization
Outcome	Recurrent spontaneous SAH
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: Clinical review follow up 6 to 65 months. Median follow-up 22.3 months Person-years: 792 Participant follow up by year: Year 1: 317 Year 2: 234 Year 3: 139 Year 4: 69 Year 5: 28 Year 6: 5
Incidence:	Total subsequent SAH: 5 Incidence per 100000 person-years (95% CI): 632 (205-1473.3)
Comments	Moderate risk of bias

Reference	Carat Investigators 2006[12]
Study type	Retrospective cohort USA
Number of participants and characteristics	Total n=1010 Inclusion and exclusion criteria: All patients discharged between January 1, 1996 and December 31, 1998 with a primary diagnosis of subarachnoid haemorrhage were identified by a medical record search through hospital administrative databases. Detailed medical records were reviewed. Patients were included if subarachnoid haemorrhage was attributable to rupture of an intracranial aneurysm and a treatment attempt of this index aneurysm was made with surgery or endovascular coiling, at the discretion of the treating physicians, but not both. Mean age (SD): 54.8 (14.4) Clipping: 53.5 (13.8) Coiling: 58.0 (15.1) Gender (m:f): 314/696 Primary intervention of initial SAH: 711 treated with surgical clipping and 299 with coil embolization.
Outcome	Aneurysmal rebleed For all instances of possible subarachnoid haemorrhage and all deaths, associated medical records for the patient were gathered. After masking of information that could reveal the treatment modality or the identity of the patient, records were reviewed independently by members of an adjudication panel composed of 1 neurologist, 1 neurosurgeon, and 1 neuro-interventionalist. Adjudicators were asked to determine whether, more likely than not, the treated index aneurysm re-ruptured. Agreement of 2 of 3 reviewers was required to classify an event as a re-rupture.
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: Mean 5.7 years Maximum duration of follow-up was 9.6 years (mean 4.4 years) for clipped patients and 8.9 years (mean 3.7 years) for coiled patients

Reference	Carat Investigators 2006[12]
	Person-years: Total: 4216 Clipped patients: 3127 person-years Coiled patients: 1089 person-years
Incidence:	Total subsequent SAH: Total: 19 Clipping: 9 (9 in the first year, none thereafter) Coiling: 10 (9 in the first year, 1 thereafter) Incidence per 100000 person-years (95% CI): Total: 450.7 (271.2-703.8) Clipping: 287.8 (131.6-546.4) Coiling: 918.3 (439.6-1688.8)
Comments	Moderate risk of bias

Reference	Hur 2015[39]
Study type	Retrospective case-series Korea
Number of participants and characteristics	Total n=134 Inclusion and exclusion criteria: Medical records of 134 anterior communicating artery aneurysm patients treated by coil embolization with available angiographic and clinical follow-up results. 101/134 patients had SAH, 33/134 had unruptured aneurysms. Mean age: 57.5 (23-80) Gender (m:f): 65/69 Primary intervention of initial SAH: coil embolization

Reference	Hur 2015[39]
Outcome	DSA confirmed aneurysmal rebleeding
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: Mean follow-up with DSA 16.3 months (1.36 years) (mean clinical follow up of 49.7 months) Person-years: 182
Incidence:	Total subsequent SAH: Total cohort 20 cases of aneurysmal recurrence (18 recurrences from 101 cases of SAH) No cases of rebleeding Incidence per 100000 person-years (95% CI): 0 (0-2027)
Comments	Moderate risk of bias Serious indirectness. Follow-up duration of SAH cohort not available. Only total cohort follow-up including 33 unruptured aneurysms.

Reference	ISAT (Molyneux 2002[62]; Molyneux 2005[66]; Molyneux 2009[65]; Molyneux 2015[63])
Study type	RCT (Patient randomised; Parallel) Conducted in United Kingdom; Setting: 43 neurological centres
Number of participants and characteristics	Total n=2143 Inclusion and exclusion criteria: Patients were eligible for the trial if:1. they had a definite subarachnoid haemorrhage, proven by computed tomography (CT) or lumbar puncture, with the preceding 28 days; 2. they had an intercranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage; 3. they were in the clinical state that justified treatment, at some time, by either neurosurgical or endovascular means; 4. they had an intracranial aneurysm that was judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique on the basis of its angiographic anatomy; (5) there was uncertainty as to whether the ruptured aneurysm should be treated by neurosurgical or endovascular means; and (6) they gave appropriate informed consent, according to the criteria laid down by the local ethics committee. If a patient was not competent to

<table>
<tr><th>Reference</th><th>ISAT (Molyneux 2002[62]; Molyneux 2005[66]; Molyneux 2009[65]; Molyneux 2015[63])</th></tr>
<tr><td></td><td>give consent (because of his or her cognitive state), assent from relatives was obtained if the ethics committee regarded it as an acceptable alternative.

Age - Mean (range): Clipping 52 (18-84); coiling 52 (18-87).
Gender (M:F): clipping 399/671; coiling 400/673.

Primary intervention of initial SAH:
(n=1070) Intervention 1: Neurosurgical intervention - Neurosurgical clipping.
(n=1073) Intervention 2: Endovascular intervention - Detachable platinum coils.</td></tr>
<tr><td>Outcome</td><td>Number of patients who had recurrent subarachnoid haemorrhage</td></tr>
<tr><td>Confounders/ Stratification strategy</td><td>No stratification by age was made. Crude results are reported</td></tr>
<tr><td>Follow-up (data from first year)</td><td>Mean follow-up: 1 year

Person-years:
Neurosurgical clipping – 793 patient-years
Endovascular coiling – 801 patient-years
Total – 1594 patient-years</td></tr>
<tr><td>Incidence:</td><td>Non-procedure related rebleeding:

<table>
<tr><th></th><th>Before the procedure</th><th>After procedure up to 30 days</th><th>30 days to 1 year</th><th>Total</th></tr>
<tr><td>Clipping</td><td>23</td><td>6</td><td>4</td><td>33</td></tr>
<tr><td>Coiling</td><td>14</td><td>20</td><td>6</td><td>40</td></tr>
<tr><td>Total</td><td>37</td><td>26</td><td>10</td><td>73</td></tr>
</table>

Incidence per 100000 person-years (95% CI):
Clipping – 4161.4 (2864.1 – 5844.4)</td></tr>
</table>

Reference	ISAT (Molyneux 2002[62]; Molyneux 2005[66]; Molyneux 2009[65]; Molyneux 2015[63])
	Coiling – 4993.8 (3567.2 – 6800.3) Total – 4579.7 (3589.6 – 5758.3)
Follow-up (data from >1 year)	Mean follow-up: minimum of 10 years, maximum of 17.6 years Person-years: Neurosurgical clipping – 8228 patient-years Endovascular coiling – 8351 patient-years Total – 16579 patient-years
Incidence:	Total subsequent SAH:

	Rebleeding from target aneurysms	Rebleeding from aneurysms known at baseline	De-novo aneurysm	Aneurysm from unknown source	Total
Clipping	4	2	6	0	12
Coiling	13	4	3	1	21
Total	17	6	9	1	33

Incidence per 100000 person-years (95% CI):
Clipping – 146 (75.3 – 254.8)
Coiling – 252 (115.6 – 384.4)
Total – 199 (137 – 279.5)

Comments	Low risk of bias

Reference	ISUIA (Wiebers 2003[106], Wiebers 1998[105])
Study type	Retrospective + prospective case-series Conducted in USA, Canada + Europe

Reference	ISUIA (Wiebers 2003[106], Wiebers 1998[105])
Number of participants and characteristics	Total n = 615 Inclusion criteria: People with at least 1 saccular UIA of at least 2 mm in maximum diameter confirmed by cerebral arteriography. Exclusion criteria: Patients with a neurologically devastating prior haemorrhage. Patients in whom the sole UIA was previously manipulated by wrapping, packing, coil placement, proximal arterial ligation, bypass, balloon occlusion, or clip placement before entry into the study were not eligible. Patients with a history of intracranial haemorrhage from an unrepaired underlying structural lesion, primary intracerebral haemorrhage (without an underlying structural lesion), or SAH from an undetermined origin were excluded from the study. Patients with a malignant brain tumour were also excluded from the study. Age - Mean (range): No surgery: 55.2 years (13.1) Gender (M:F): Male 25.5% (total cohort) Primary intervention of initial SAH: Unoperated unruptured aneurysm. Treatment of previous SAH not reported.
Outcome	Number of patients who had subsequent subarachnoid haemorrhage
Confounders/ Stratification strategy	No stratification by age was made.
Follow-up	Mean follow-up: 6 years Baseline: 608 Year 1: 507 Year 2: 298 Year 4: 129 Year 6: 41 Person-years: 1145
Incidence:	Subsequent SAH: 51 patients with rebleeding in total cohort – 41 from cohort with no history of SAH, 10 from cohort with separate SAH

Reference	ISUIA (Wiebers 2003[106], Wiebers 1998[105])
	Incidence per 100000 person-years (95% CI): 873.4 (418.1-1606.2)
Comments	Low risk of bias

Reference	Juvela 1989[40]
Study type	Prospective case-series study
Number of participants and characteristics	Total n= 236 Primary intervention of initial SAH: neurosurgical clipping Inclusion and exclusion criteria: patients who had a proven aneurysmal SAH and who were admitted within 72 hours after SAH to the emergency room. Median age (range): 37 (19 to 55)
Outcome	Rebleeding with 6 months and up to 3 years post intervention Rebleeding was verified by computed tomography and/or by extravasation of contrast medium during angiography and or autopsy. Lumbar puncture was used for verification of a rebleed in only a minority of patients. Gradual deterioration of neurological condition from 4 to 14 days after SAH was thought to be due to DCI.
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 3 years Person-years: 708

Reference	Juvela 1989[40]
Incidence:	Total subsequent SAH: 55 53 within first six months (9 within 24 hours, 28 within first week) 2 > 6 months Incidence per 100000 person-years (95% CI): 7768.4 (5851.8-10111.8)
Comments	Moderate risk of bias. Incidence of aSAH in cohort treated with clipping or coiling not reported.

Reference	Kassell 1990[41, 42]
Study type	Prospective case-series study Multiple medical centres globally
Number of participants and characteristics	Total n= 3521 Primary intervention of initial SAH: surgical intervention or medical management Inclusion and exclusion criteria: Inclusion: Patients admitted on day 0 to 3 following their first major SAH; day 0 was defined as the calendar day of the haemorrhage. Exclusion: not specified Mean age: 50.4 years M/F ratio: 1.6/1
Outcome	Rebleeding within 6 months ± 2 weeks of intervention Intracerebral haemorrhage The central registry consisted of that group of statisticians, epidemiologists, computer programmers neurologists, neurosurgeons and neurosurgical nurses who were responsible for day to day operation of the study. Participants included 68 neurosurgical centres in 14 countries. Each centre had a reporting investigator who was responsible for the conduct of the study at that study site, one or more operating surgeons who performed the operative and perioperative patient care, and an evaluator (usually a neurologist) who conducted the follow up examination and was independent of the management of the patients and blind to the timing of the surgery.

Reference	Kassell 1990[41, 42]
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 0.5 (6 months) Person-years: 1760.5
Incidence:	Total subsequent SAH: 333 Incidence per 100000 person-years (95% CI): 18915.1 (16937.8 – 21059.8)
Comments	High risk of bias

Reference	Li 2012[53]
Study type	Randomised controlled trial. China
Number of participants and characteristics	Total n=186 Inclusion and exclusion criteria: Consecutive patients with acute aSAH. Mean age: 54.2 years Gender (m:f): 130/56 Primary intervention of initial SAH: 94 Endovascular coiling 92 Surgical clipping
Outcome	Re-bleed

Reference	Li 2012[53]
	Follow-up imaging was performed by digital subtraction angiography, CT angiography to evaluate the occurrence of angiographic vasospasm or CT for detection of infarction. Following endovascular coil treatment, imaging follow-up was routinely performed at 3 and 12 months.
Confounders/ Stratification strategy	No stratification by age Groups allocated to one of two interventions.
Follow-up	Mean follow-up: 1 year Person-years: 184 patient years
Incidence:	Total subsequent SAH: Total 6 Clipping: 3 Coiling: 3 Incidence per 100000 person-years (95% CI): 3260.9 (1196.7-7097.5) Clipping: 3191.5 (658.2-9326.9) Coiling: 3260.9 (672.5-9529.6)
Comments	Low risk of bias

Reference	McAuliffe 2012[59]
Study type	Retrospective case-series Australia
Number of participants and characteristics	Total n=11 Inclusion and exclusion criteria: Cases of recent aneurysmal SAH treated with pipeline embolization devices. Mean age (range): 51.6 years (41-69) Gender (m:f): 4/7

Reference	McAuliffe 2012[59]
	Primary intervention of initial SAH: Cases of recent aneurysmal SAH treated with pipeline embolization devices. Six patients were treated between day 1 and 14 post-SAH. Five others were treated between day 15 and 26.
Outcome	Aneurysmal re-bleed
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: 6 months (0.5 years) Person-years: 5.5
Incidence:	Total subsequent SAH: 2 (experienced during acute admission) Incidence per 100000 person-years (95% CI): 36363.6 (4403.8-131358)
Comments	High risk of bias

Reference	McDougall 2014[60]
Study type	RCT (Patient randomised; Parallel)
Number of participants and characteristics	Total n= 228 (ruptured aneurysm cohort included) Inclusion and exclusion criteria: The study population included subjects 18–80 years of age with a single untreated, intracranial saccular aneurysm (4–20mm;Hunt and Hess scale score, I–III; mRS score, 0–3), ruptured or unruptured, for which both polymer-modified coils and bare metal coils (BMCs) were treatment options and for which primary coiling treatment was planned to be completed during a single procedure. Cohort of ruptured aneurysms included for analysis. Mean age: BMC 54.4 (13.2); Matrix2 55.7(11.6). Gender (m:f): BMC 104/211 Matrix2 82/229

Reference	McDougall 2014[60]
	Primary intervention of initial SAH: (n=109) Intervention 1: Endovascular intervention – Coiling (polylactic acid biopolymer-modified coils). (n=119) Intervention 2: Endovascular intervention – Coiling (bare metal coiling).
Outcome	Aneurysm rupture or re-rapture during follow-up
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: 455 days (1.25 years) Person-years: 285
Incidence:	Total subsequent SAH: 3 Incidence per 100000 person-years (95% CI): 659 (136-1927)
Comments	Moderate risk of bias

Reference	Pierot 2020[76]
Study type	Prospective case-series study.
Number of participants and characteristics	Total n= 794 Primary intervention of initial SAH: endosaccular coil embolization (n=461 (54.2%)) or balloon assisted coiling (n=356 (43.6%)) Inclusion and exclusion criteria: age >18 years, saccular IA, ruptured or unruptured IA, and IA treated by any endovascular technique (coiling, balloon-assisted coiling (BAC), stent-assisted coiling (SAC), flow diversion, flow disruption). Exclusion criteria included dissecting or fusiform IA, IA associated with a brain arteriovenous malformation, and IA already treated by clips or coils. Participants with at least one IA treated with a technique other than coiling or BAC (i.e., stent-assisted coiling, flow diversion, flow disruption) were excluded.

Reference	Pierot 2020[76]
	Mean age (SD): 54 years (13.1) M/F ratio: 274/520
Outcome	Rebleeding - mean follow up period of 12.2 months post intervention.
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 12.2 months Person-years: 807.23
Incidence:	Total subsequent SAH: 8 Incidence per 100000 person-years (95% CI): 1007.6 (435 - 1985.3)
Comments	Low risk of bias

Reference	Plowman 2011[79]
Study type	Prospective case-series study.
Number of participants and characteristics	Total n= 452 Primary intervention of initial SAH: endosaccular coil embolization Inclusion and exclusion criteria: 1) clinical diagnosis of SAH supported by either CT scanning or a xanthrochromic CSF sample; and 2) coil embolization by endosaccular packing performed within 30 days of the last haemorrhage and which successfully occluded the aneurysm. Mean age (range): 53 (21 – 87) M/F ratio: 191/379

Reference	Plowman 2011[79]
Outcome	Rebleeding - mean follow up period of 73.7 months post intervention. Angiography performed at 6 and 24 months After discharge from the surveillance imagine protocol, patients were contacted by mail and asked to fill out a follow up questionnaire. All patients were contacted by mail in 5-year audits. Specific inquiries were made about further intracranial haemorrhages, and patients, families or their referring physicians were contacted to provide details of the current status for patients who failed to respond to the questionnaire
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 6.2 years Person-years: 2802.4
Incidence:	Total subsequent SAH: 9 Incidence per 100000 person-years (95% CI): 321.2 (146.9 – 609.6)
Comments	Low risk of bias

Reference	Pyysalo 2010[80]
Study type	Retrospective case-series Finland
Number of participants and characteristics	Total n=109 Inclusion and exclusion criteria: SAH patients who received coiling for ruptured aneurysms. Those with unruptured aneurysm Mean age of subgroup with MRI data (n=34): 54 years (34-73) Gender (m:f): 15/19 Primary intervention of initial SAH: aneurysms were treated with endovascular coiling

Reference	Pyysalo 2010[80]
Outcome	MR confirmed rebleed of ruptured aneurysm
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: 11 years Person-years: 688 years
Incidence:	Total subsequent SAH: 9 Incidence per 100000 person-years (95% CI): 1308 (598.2-2483.3)
Comments	Moderate risk of bias

Reference	Schaafsma 2009[86]
Study type	Retrospective case-series The Netherlands
Number of participants and characteristics	Total n=283 Inclusion and exclusion criteria: Patients with ruptured intracranial aneurysms coiled with adequate aneurysm occlusion at 6-month follow-up angiograms. Mean age: 51 (26-82) Gender (m:f): 82/201 Primary intervention of initial SAH: Patients received endovascular coiling for ruptured intracranial aneurysms.
Outcome	Recurrent SAH.

Reference	Schaafsma 2009[86]
	All brain imaging was reviewed to assess the cause of stroke and to evaluate the degree of occlusion of the coiled aneurysm at the time of recurrent SAH. In case patients had died suddenly without being admitted, the event was classified a possible recurrent SAH if no further information was available.
Confounders/ Stratification strategy	No stratification performed
Follow-up	Mean follow-up: 6.3 years (1 – 12.2) Person-years: 1778
Incidence:	Total subsequent SAH: 1 confirmed 2 possible Incidence per 100000 person-years (95% CI): Confirmed recurrent SAH only: 56 (6-311) Including possible recurrent SAH: 171 (31-494))
Comments	Moderate risk of bias

Reference	Sedat 2002[88]
Study type	Retrospective case-series France
Number of participants and characteristics	Total n=195 Inclusion and exclusion criteria: Patients hospitalised for SAH resulting from aneurysm rupture. SAH confirmed by CT or LP, with aneurysms identified by angiography. Mean age: 53.5 (14.6) Group 1: 71.5 (5)

Reference	Sedat 2002[88]
	Group 2: 47 (11) Gender (m:f): 87/108 Primary intervention of initial SAH: Aneurysms were secured by endovascular treatment.
Outcome	Recurrent haemorrhage after treatment
Confounders/ Stratification strategy	Cohort divided into those aged <65 (n=143) and those aged ≥65 years (n=52)
Follow-up	Mean follow-up: 1 year Person-years: 195
Incidence:	Total subsequent SAH: No episodes of rebleeding in either groups Incidence per 100000 person-years (95% CI): Total cohort: 0 (0-1891.7) aged ≥65 years: 0 (0-7094) aged <65 years: 0 (0-2579.6)
Comments	High risk of bias

Reference	Sluzewski 2005[91]
Study type	Retrospective case-series The Netherlands
Number of participants and characteristics	Total n= 392 Inclusion and exclusion criteria: Between January 1995 and January 2003, 393 consecutive patients with aneurysmal subarachnoid haemorrhage were treated with detachable coils. The indication for coiling of the ruptured aneurysm was assessed in a weekly joint meeting of 2 neurosurgeons, 2 neurologists, and 2 interventional neuroradiologists.

Reference	Sluzewski 2005[91]
	Mean age: 52.9 years Gender (m:f): 120/275 Primary intervention of initial SAH: All patients treated with detachable coils.
Outcome	Aneurysmal rebleeding. Patients followed up with angiographic imaging at 6 and 18 months. Data also collected by standard questionnaire regarding the occurrence of rebleeding (severe headache that necessitated family doctor's attention or hospital admission).
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: 4 years Person-years: 1159
Incidence:	Total subsequent SAH: 5 Three patients died from a late rebleeding after coiling of a ruptured aneurysm. Two additional patients survived CT-confirmed late rebleeding from coiled aneurysms, 12 and 30 months after coiling. Incidence per 100000 person-years (95% CI): 431.4 (140.1-1006.8)
Comments	Moderate risk of bias

Reference	Sokolowski 2019[92]
Study type	Retrospective case-series study
Number of participants and characteristics	Total n= 33 Primary intervention of initial SAH: endovascular treatment using SMART coils

Reference	Sokolowski 2019[92]
	Inclusion and exclusion criteria: Consecutive patients with intracranial aneurysms who underwent endovascular treatment using SMART coils. Patients were excluded if no follow up angiographic data was available. Mean age (SD): 56.8 (11.5) M/F ratio: 6/27
Outcome	Retreatment for aneurysm reoccurrence. Follow up of aneurysms was classified by the modified Raymond Roy occlusion classification (class 1 complete occlusion; class II residual neck; class IIIa permeability within the coil interstices; class IIIb is permeability along the residual aneurysm wall). Aneurysm reoccurrence and retreatment was also recorded.
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 0.77 years Person-years: 25.41
Incidence:	Total subsequent SAH: 5 Incidence per 100000 person-years (95% CI): 19677.3 (6389.2 – 45920.2)
Comments	High risk of bias

Reference	Tanno 2007[97]
Study type	Retrospective case-series study 49 major hospitals across the north eastern province of Japan
Number of participants and characteristics	Total n= 5612 Primary intervention of initial SAH: Not specified

Reference	Tanno 2007[97]
	Inclusion and exclusion criteria: Case investigation forms for this retrospective study were prepared by a committee consisted of the neurology and neurosurgery representatives of six sub-regions. They were requested the Tohoku society of stroke research to fill out the questionnaires. Inclusion: rebleeding from ruptured intracranial aneurysms that occurred in the hospital setting of up to 4 weeks from January 1997 to December 2001; after the initial SAH, at least brain CT was performed to confirm the bleed in the subarachnoid space; the rebleeding was diagnosed from the neurological symptoms, or from CT or from both; the ruptured intracranial aneurysm was confirmed by cerebral angiography, 3D-CTA, MRA. Exclusion: not specified Mean age: demographics not specified for this part of the study M/F ratio: demographics not specified for this part of the study
Outcome	Rebleeding within the first 4 weeks after intervention
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 1 month Person-years: 561.2
Incidence:	Total subsequent SAH: 224 Incidence per 100000 person-years (95% CI): 39914.5 (34858.0 – 45498.2)
Comments	High risk of bias

Reference	Todd 1989[99]
Study type	Prospective cohort study

Reference	Todd 1989[99]
Number of participants and characteristics	Total n= 181 Primary intervention of initial SAH: neurosurgical clipping (n=121) or wrapping (n=60) Inclusion and exclusion criteria: This study included only patients with a single anterior circulation aneurysm, which was either clipped or wrapped. Patients were excluded if there was a posterior circulation aneurysm, arteriovenous malformation, or multiple aneurysms, or if previous surgery or another operation such as carotid artery ligation had been performed Mean age (range): 46 (15 – 69 years) M/F ratio: 148-212
Outcome	Recurrent subarachnoid haemorrhage 10 years after treatment of primary aneurysm. Outcome was examined prospectively for 10 years following the operation to define 1) the rate of rebleeding 2) overall mortality rate and 3) clinical status in survivors at 10 year. This series only included patients undergoing surgery for an aneurysm.
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 10 years Person-years: 1810 Clipped:1210 Wrapped: 600
Incidence:	Total subsequent SAH: 17 (15 absolute or probably, 2 possible) Clipping: 6 (4 absolute or probably, 2 possible) Wrapped: 11 (11 absolute or probably, 0 possible) Incidence per 100000 person-years (95% CI): Total: 828.7 (463.5 – 1366.9) Clipped: 331.5 (121.7-721.5) Coiling: 1833.3 (913.9-3280.5)

Reference	Todd 1989[99]
	Absolute and probable SAH included for analysis
Comments	Moderate risk of bias

Reference	Tsutsumi 1998[102]
Study type	Retrospective case-series Japan
Number of participants and characteristics	Total n= 425 Inclusion and exclusion criteria: Patients with SAH surgically treated in Aizu Chuou Hospital from 1976 to 1994, 220 cases meeting the following criteria were studied: (1) all aneurysms detected by 3- or 4-vessel cerebral angiography were clipped, (2) complete obliteration of aneurysm(s) was confirmed by postoperative angiography, and (3) the patient survived <3 years. Mean age: 55.8 (24-79) Gender (m:f): 104/116 Primary intervention of initial SAH: All patients underwent neurosurgical clipping
Outcome	Recurrent SAH Follow-up information was obtained by interviews at the clinic, by telephone calls, or by letters to identify the cause of death or incidents suggestive of recurrent SAH. In all cases, SAH was diagnosed by CT scans
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: 9.9 years Person-years: 2175.1
Incidence:	Total subsequent SAH: 6

Reference	**Tsutsumi 1998[102]**
	Incidence per 100000 person-years (95% CI): 275.8 (101.2-600.4)
Comments	Moderate risk of bias

Reference	**Wermer 2005[103]**
Study type	Retrospective case-series The Netherlands
Number of participants and characteristics	Total n=752 Inclusion and exclusion criteria: Patients admitted with CT confirmed SAH, presence of a saccular aneurysm confirmed by conventional angiography or CT-angiography and clipping of the ruptured aneurysm and all additional aneurysms. Records attained through medical database. Mean age: 50.1 (12.3) Gender (m:f): 236/516 Primary intervention of initial SAH: Only patients with clipping of the ruptured aneurysm and all additional aneurysms were included
Outcome	Recurrent SAH New episodes of SAH were defined as SAH proven by CT, lumbar puncture, or autopsy after treatment of all aneurysms that had been found at the time of the initial SAH.
Confounders/ Stratification strategy	No stratification
Follow-up	Mean follow-up: 8 years Person-years: 6016

Reference	Wermer 2005[103]
Incidence:	Total subsequent SAH: 18 cases of recurrent SAH. The mean interval between the initial SAH and the recurrence was 6.5 years. There were 2 cases of sudden death with possible recurrent SAH Incidence per 100000 person-years (95% CI): 299.2 (177.2-472.9)
Comments	Low risk of bias

Reference	Willinsky 2009[107]
Study type	Retrospective case-series Canada
Number of participants and characteristics	Total n=292 Inclusion and exclusion criteria: Consecutive patients who presented with SAH from a ruptured intracranial aneurysm and were successfully treated by coiling between May 1994 and April 2008. Mean age (SD): 54.8 (15) Gender (m:f): 119/258 Primary intervention of initial SAH: All patients with aneurysmal SAH in whom endovascular treatment was completed were included.
Outcome	Episodes of aneurysmal re-bleeding Initially radiologic follow-up was performed using digital subtraction angiography (DSA) with 3D rotational angiography. Later MR angiography (MRA) became the primary follow-up imaging technique.
Confounders/ Stratification strategy	No stratification

Reference	Willinsky 2009[107]
Follow-up	Mean follow-up: 22.3 months (1.858 years) Person-years: 542.6
Incidence:	Total subsequent SAH: 8 episodes of rebleeding 6 episodes within the first 30 days 2 episodes of late rebleeding (6 months and 10 years) Incidence per 100000 person-years (95% CI): 1474 (636.5-2905.1)
Comments	Moderate risk of bias

Reference	Winn 1983[108]
Study type	Retrospective case-series study
Number of participants and characteristics	Total n= 182 Primary intervention of initial SAH: Bed rest for 6 weeks (n=132) Craniotomy (n=50) Inclusion and exclusion criteria: Patients admitted to Atkinson Morley Hospital or National Hospital following SAH. Mean age: Bed rest: 51 ± 1 Craniotomy: 47 ± 1 M/F ratio: demographics not specified

Reference	Winn 1983[108]
Outcome	Rebleeding after 6 months post intervention (only for 38 patients who survived up to 6 months post-surgical intervention). Rebleeding was separated into three categories 1) absolute proof of rebleeding was established by post mortem examination or a compatible clinical history plus arteriography or lumbar puncture or both 2) probable proof of rebleeding required a clinical history of a stiff neck, headache, and loss of consciousness or neurological impairment in keeping with the previously demonstrated aneurysm (sudden death in a few younger patients unsubstantiated by post-mortem examination was also considered in this category 3) possible proof of rebleeding required two of these 4 clinical features or a statement by the referring physician as to the cause of death.
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: 10 years Person-years: 809 Conservative: 557 Craniotomy: 252
Incidence:	Total subsequent SAH: 31 Conservative: 21 Craniotomy: 10 Incidence per 100000 person-years (95% CI): 3831.9 (2603.1-3439.2) Conservative: 3770.2 (2332.9-5763.4) Craniotomy: 3968.3 (1899.8-7298.2)
Comments	High risk of bias

Reference	Yu 2019[110]
Study type	Retrospective case-series study China
Number of participants and characteristics	Total n= 6008 Primary intervention of initial SAH: Endovascular coil embolization

Reference	Yu 2019[110]
	Inclusion and exclusion criteria: Patients treated with an intracranial aneurysm at the department of neurosurgery were included. Aneurysm obliteration was routinely recorded after initial coiling. Follow up diagnosis of aneurysms in patients who underwent endovascular coiling was based on imaged obtained using DSA or 3D CTA at least once within 6 months to 1 year of initial coiling. Mean age: 47.4 ± 11.5 M/F ratio: 1.7/1
Outcome	Recurrences over a 6 year period with minimal interval 6 months post intervention Recurrences were classified into 5 different types based only on their imaging characteristics on DSA.
Confounders/ Stratification strategy	None
Follow-up	Mean follow-up: Mean post-treatment interval was 25.6 months (range 1-167), 2.13 years Person-years: 12797
Incidence:	Total subsequent SAH: 6 (96 aneurysmal recurrence) Incidence per 100000 person-years (95% CI): 46.9 (17.2 – 102.1)
Comments	Moderate risk of bias Indirect population: patients treated for aneurysmal coil embolization, not explicitly SAH.

Appendix E: Incidence plots

E.1 Incidence rate of subsequent SAH

Figure 2: Incident rate by previous SAH

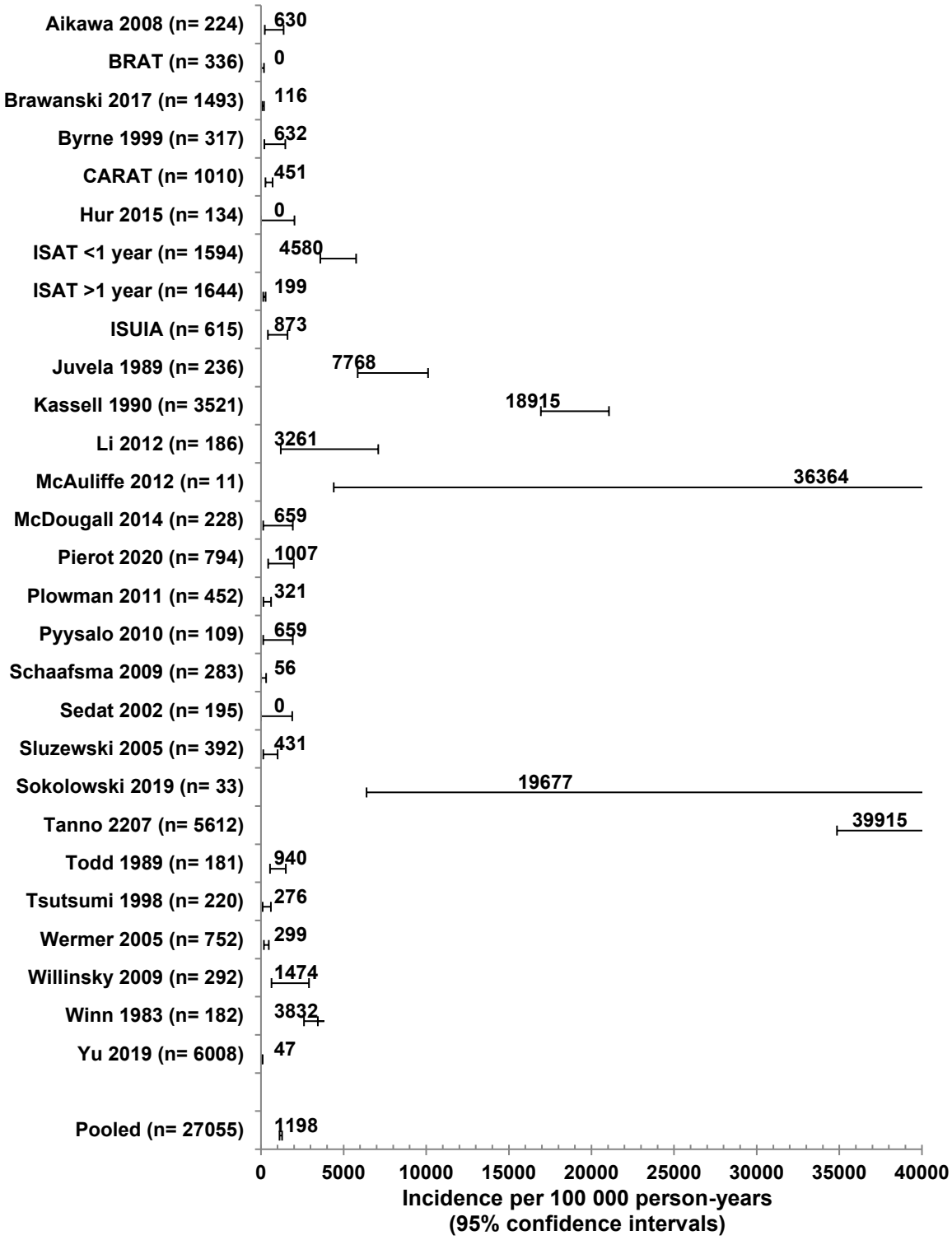


Figure 3: Incident rate by timing of follow-up (<1 year)

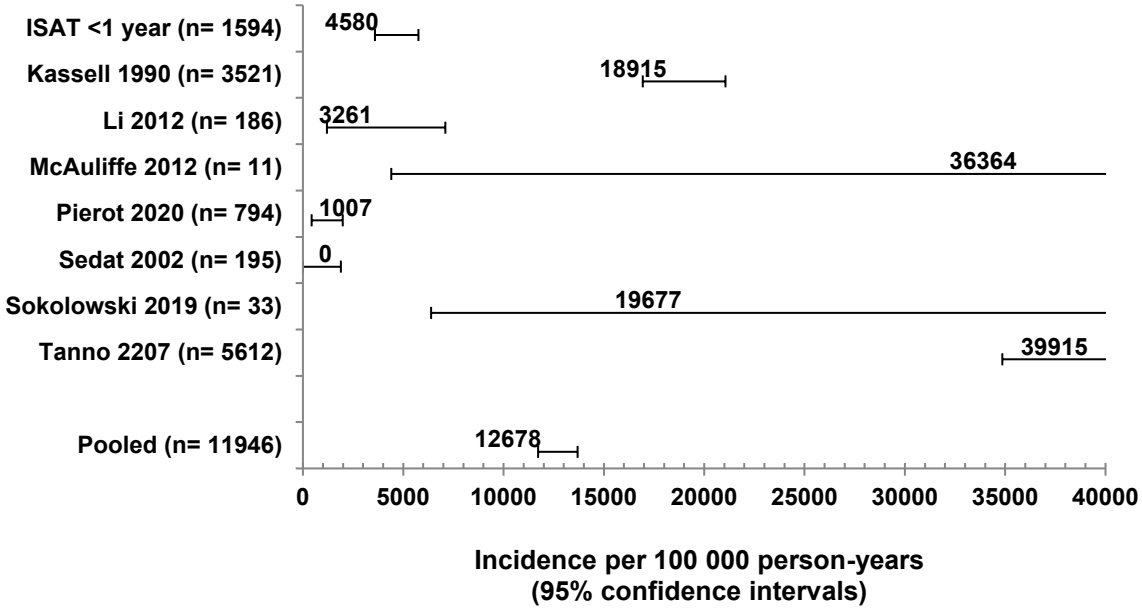


Figure 4: Incident rate by timing of follow-up (total >1 year)

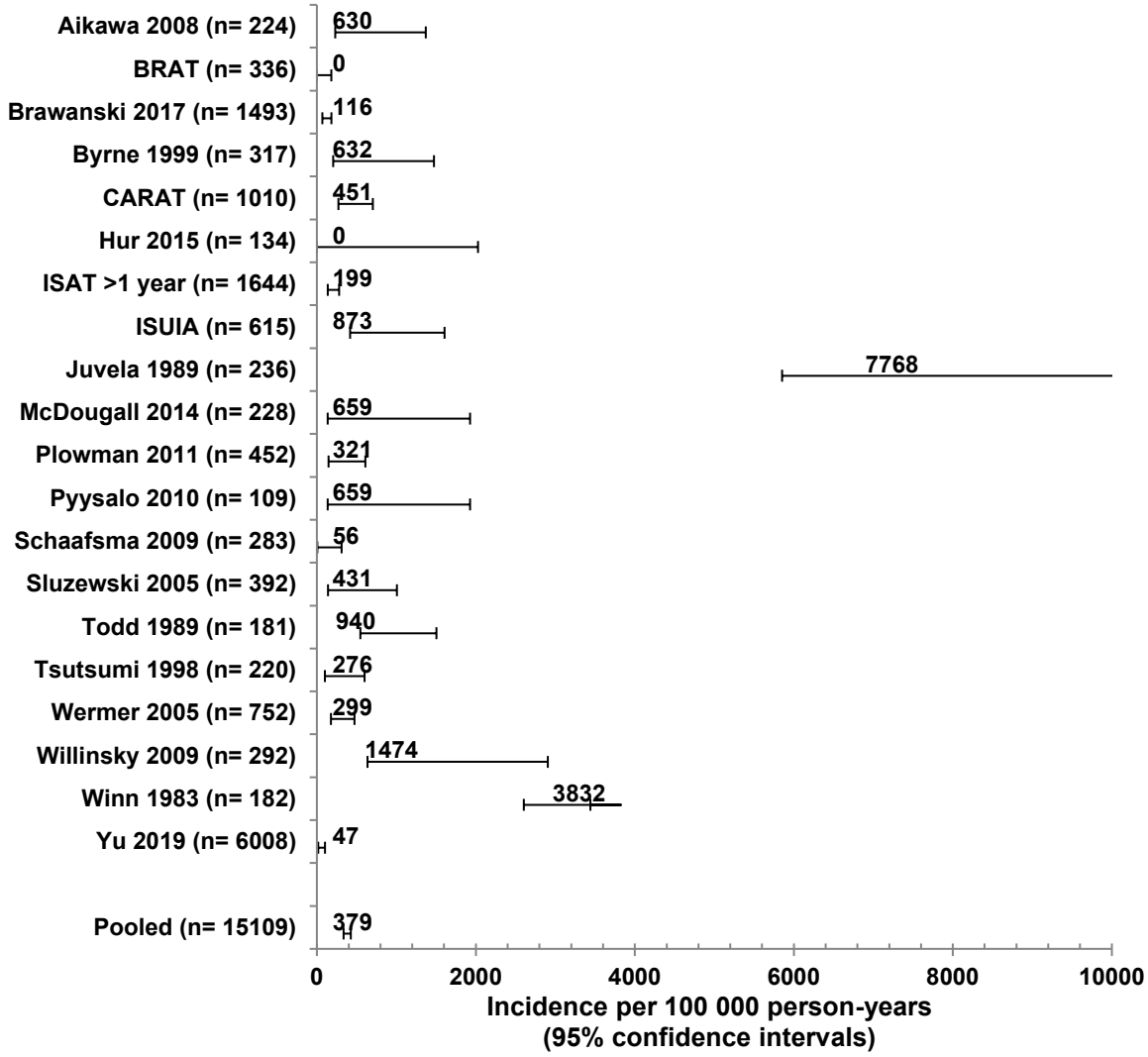


Figure 5: Incident rate by timing of follow-up (follow-up after 1 year)

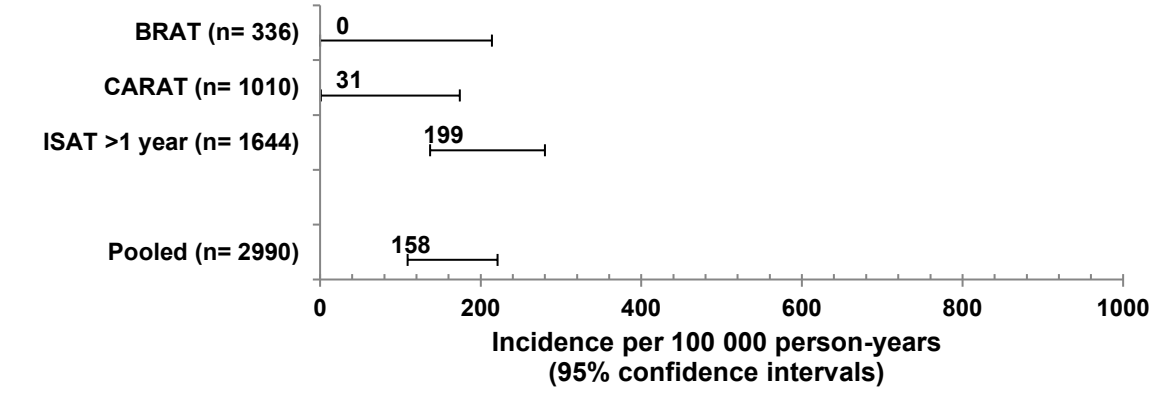


Figure 6: Incident rate by treatment of previous SAH

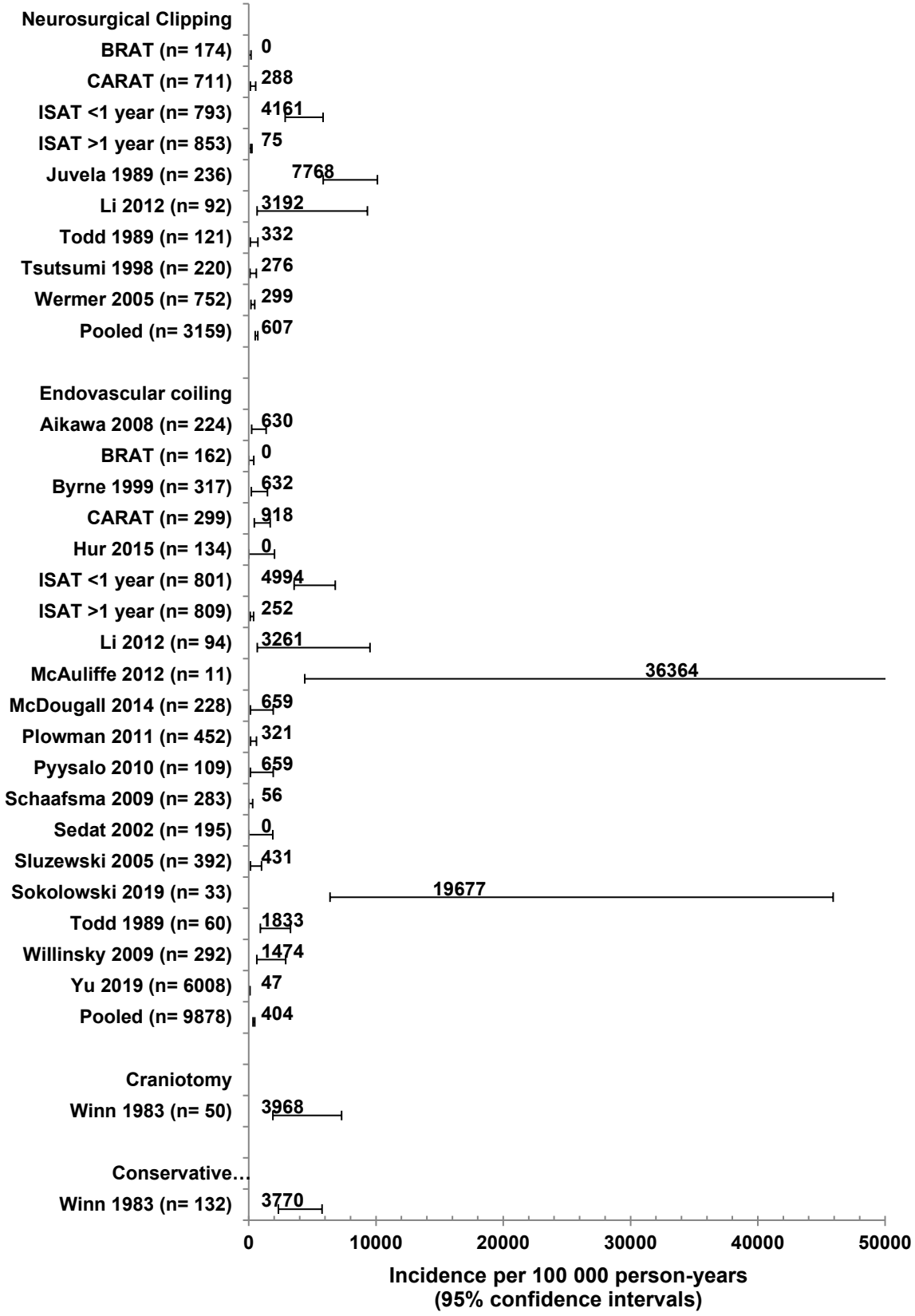
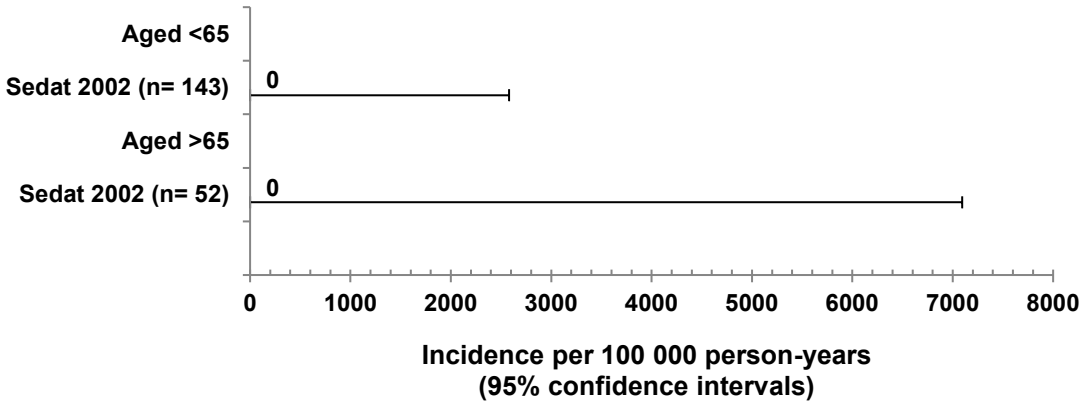


Figure 7: Incident rate by age



Appendix F:Excluded studies

F.1 Excluded clinical studies

Table 11: Studies excluded from the clinical review

Reference	Reason for exclusion
Abulhasan 2017[1]	Not available
Akyuz 2004[3]	Inappropriate population – not all SAH
AlMatter 2018[4]	Inappropriate study design - no relevant outcomes
Anzalone 2015[5]	Inappropriate comparison – MRA technique comparison
Awan 2013[6]	Inappropriate study design - no relevant outcomes
Beck 2006[7]	Inappropriate study design - no relevant outcome – (rebleeding before aneurysm obliteration)
Berenstein 2006[8]	Inappropriate population – majority unruptured aneurysms
Campi 2007[11]	Inappropriate study design - no relevant outcome
Cha 2010[13]	Inappropriate study design - no relevant outcome
Chalouhi 2014[15]	Inappropriate population – majority non SAH
Chalouhi 2017[14]	Not available
Cheung 2018[16]	Inappropriate population & length of follow-up
Choi 2010[17]	Inappropriate population – combined ruptured and unruptured aneurysm data
Cloft 2007[18]	Inappropriate population – majority unruptured aneurysms
Cognard 1999[19]	Inappropriate population – unruptured berry aneurysms
Consoli 2012[20]	Inappropriate study design - no relevant outcome
Daileda 2019[21]	Inappropriate population & outcome – retreatment of cerebral aneurysms
Deshaies 2007[22]	No relevant outcome – recurrence of aneurysm
Deutschmann 2012[23]	Inappropriate population – majority non SAH
dos Santos 2015[24]	Inappropriate population – combined ruptured and unruptured aneurysm data
Edner 2007[25]	Inappropriate study design - no relevant outcome
Fargen 2012[26]	Inappropriate population – combined elective patients and acute SAH
Fargen 2013[27]	Inappropriate population – majority unruptured aneurysms
Gaba 2006[28]	Inappropriate population & outcome – majority non SAH
Gallas 2009[29]	Inappropriate population – intradural saccular aneurysm
Gao 2012[30]	Inappropriate study design - no relevant outcome
Geyik 2008[31]	Inappropriate population – majority unruptured aneurysms
Goertz 2019[32]	Inappropriate study design - no relevant outcome
Gory 2017[33]	Inappropriate population – majority unruptured aneurysms
Gory 2017[34]	Inappropriate population – majority unruptured aneurysms
Gunnarsson 2009[35]	Inappropriate population – majority unruptured aneurysms
Gupta 2006[37]	Inappropriate study design - no relevant outcome
Gupta 2007[36]	Inappropriate population – non aSAH
Hata 2005[38]	Inappropriate population – ischemic stroke
Kaste 1978[43]	Inappropriate study design - no relevant outcome

Reference	Reason for exclusion
Kawamura 1990[44]	Inappropriate population- SAH with unknown aetiology (excluded if aneurysm seen on imaging)
Kim 2018[45]	Inappropriate population – unruptured aneurysms
King 2009[46]	Not available
Koyanagi 2018[47]	Inappropriate population – unruptured aneurysms
Kulcsar 2013[48]	Inappropriate population – majority unruptured aneurysms
Kusumi 2005[49]	Inappropriate study design - no relevant outcome
Kwon 2006[50]	Inappropriate population – cerebral aneurysms
Lago 2016[51]	Inappropriate population – non aSAH
Le Feuvre 2008[52]	Inappropriate population – SAH or third nerve palsy
Machiel Pleizier 2006[54]	Inappropriate study design - no relevant outcomes (rebleeding within admission of initial SAH)
Mansour 2011[57]	Not available
Mansour 2012[56]	Not available
Mansour 2013[55]	Inappropriate population & length of follow-up – size of aneurysm within 6 month follow up
Martin-Gaspar 2010[58]	Inappropriate study design – abstract
Molyneux 2004[64]	Inappropriate study design - no relevant outcomes
Mortimer 2015[68]	Inappropriate study design - no relevant outcomes
Naidech 2005[69]	Inappropriate study design – no relevant outcomes – (post-procedure re-bleeds not considered)
O'Hare 2010[71]	Inappropriate population – combined ruptured and unruptured aneurysm data
Park 2011[72]	Inappropriate population – majority unruptured aneurysms
Pathirana 1994[73]	Inappropriate population – combined ruptured and unruptured aneurysm data
Patzig 2018[74]	Not available
Paulsen 2010[75]	Inappropriate study design – abstract
Pierot 2008[77]	Inappropriate study design - no relevant outcomes
Pierot 2018[78]	Inappropriate study design - no relevant outcomes
Pyysalo 2011[81]	Inappropriate population – non aSAH
Qin 2017[82]	Inappropriate population – combined ruptured and unruptured aneurysm data
Raper 2010[83]	Inappropriate study design – narrative review
Renowden 2008[84]	Inappropriate study design - no relevant outcomes
Rinkel 2011[85]	Systematic review: references screened
Sedat 2009[87]	Inappropriate population – majority unruptured aneurysms
Serafin 2015[89]	Systematic review: references screened
Shtaya 2018[90]	Inappropriate study design - no relevant outcomes
Sprengers 2008[95]	Inappropriate population & outcome – aneurysm recurrence
Starke 2011[96]	Systematic review: references screened
Taschner 2018[98]	Inappropriate study design - no relevant outcomes
Tso 2010[100]	Inappropriate study design – abstract only
Tsutsumi 2001[101]	Inappropriate study design - no relevant outcomes
Wermer 2005[104]	Inappropriate population – combined ruptured and unruptured aneurysm data
Yang 2010[109]	Inappropriate population – majority unruptured aneurysms

Reference	Reason for exclusion
Yu 2012[111]	Inappropriate population – combined ruptured and unruptured aneurysm data
Zheng 2016[112]	Inappropriate population – combined ruptured and unruptured aneurysm data

Appendix G: Research recommendations

G.1 Risk score

Research question: What is the utility of a risk stratification tool to estimate the risk of subsequent aneurysmal subarachnoid haemorrhage?

Why this is important:

People with aneurysmal subarachnoid haemorrhage are at high risk of rebleeding from the ruptured arterial aneurysm, which can cause death or disability. Neuroradiological or neurosurgical interventions to secure the aneurysm reduce the risk of rebleeding, but in the longer-term recurrent haemorrhage can occur from culprit or non-culprit aneurysms.

Evidence on the risk of rebleeding is limited in quantity and quality and there are currently no reliable tools to help estimate the risk of recurrent bleeding. Importantly, uncertainty about future risk causes patient and carer anxiety. A tool that can estimate risk of further bleeding will mitigate some of this uncertainty and support decision-making about future surveillance and treatment.

Criteria for selecting high-priority research recommendations:

PICO question (prognostic review)	Population: People aged 16 or over with confirmed aneurysmal subarachnoid haemorrhage. Exposure(s): initial treatment or aneurysm(s) (clipping, coiling, conservative); patients whose aneurysmal subarachnoid haemorrhage at presentation has resulted in unconsciousness and/or needing ventilation for more than 48 hours; aneurysm size; aneurysm location; high blood load in subarachnoid space on initial CT; hypertension (systolic BP >160 mmHg); presence of non-culprit aneurysms. Confounding factors: age, gender. Outcome(s): Subsequent aneurysmal subarachnoid haemorrhage/rebleeding.
PICO question (intervention review)	Population: People aged 16 or over with confirmed aneurysmal subarachnoid haemorrhage. Intervention(s): Application of a risk assessment tool to identify and manage people at high risk of subsequent aSAH. Comparison: No risk stratification Outcome(s): Mortality, degree of disability, subsequent aSAH/rebleeding.
Importance to patients or the population	A risk score that reliably predicts subsequent subarachnoid haemorrhage will allow better informed decision-making about future management.
Relevance to NICE guidance	A validated risk assessment tool to stratify the risks of subsequent subarachnoid haemorrhage will be relevant to updates of this guideline.
Relevance to the NHS	A validated risk assessment would: • Allow better informed decision-making about future management . • Improve standardised provision of care. • Enable comparative audit of outcomes across neurosurgical centres.
National priorities	None
Current evidence base	Several tools to determine severity of aneurysmal subarachnoid haemorrhage are used widely but inconsistently. There is no validated risk assessment tool that stratifies the risk of subsequent bleeding.
Equality	None
Study design	This requires comprehensive multivariable analysis of historical registry data to develop a suitable tool; a validation exercise against a naive data set and then subsequent application in a prospective patient cohort.

Timeframe	3 years to allow for sufficient prognostic data collection and the subsequent development of a risk stratification tool.
Feasibility	This research will require collaboration between multiple neuroscience centres to collect data on unselected patients with aSAH over several years, but should be feasible within the UK, for example, the UK and Ireland SAH registry.
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.