National Institute for Health and Care Excellence

FINAL

Stroke and transient ischaemic attack in over 16s: diagnosis and initial management

[A] Evidence review for aspirin

NICE Guideline NG128

Intervention evidence review

May 2019

Final

This evidence review was developed by the National Guideline Centre

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ISBN: 978-1-4731-3386-0

Contents

1 Aspirin for suspected transient ischaemic attack (TIA)

1.1 Review question: Should people with a suspected TIA be advised to take aspirin prior to assessment in a TIA clinic?

1.2 Introduction

Aspirin is a well-recognised treatment for ischaemic stroke and TIA. It is also usual practice to administer aspirin to suspected TIA patients once they have been assessed by medical personnel. However, the timing of aspirin administration is much debated. For people with TIA and mild strokes, access to a specialist is often through the outpatient route. This increases the delay between symptom onset and specialist assessment, which results in the loss of critical time for the reduction and prevention of further damage to the brain.

Recently, there have been significant changes to service standards nationally, with an increased focus on delivering a 7-day service for people with TIA. However, current practice is to delay aspirin administration to people with TIA until detailed assessment takes place and delays in access to TIA clinics are known to occur. Therefore, this review seeks to examine the efficacy and safety of early aspirin administration, before expert assessment.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 16 with suspected TIA
Intervention	Aspirin (any dose) given before expert assessment
Comparisons	No aspirin or usual care (another antiplatelet or anticoagulant)
Outcomes	Critical Risk of stroke (stroke at 24, 72 hours and 14 days) Mortality Important Intra-cranial haemorrhage Major bleeding complications – e.g. gastrointestinal bleed Functional outcomes: • Modified Rankin scale (mRS) score Quality of life (both health- and social-related quality)
Study design	Randomised controlled trials Prospective cohort studies Systematic reviews and meta-analyses of the above

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[12] Methods specific to this review question are described in the review protocol in appendix A.

Risk of bias was assessed using the ROBIS checklist for systematic reviews, including individual patient data (IPD) meta-analyses. IPD analyses were included in the same way as

published systematic reviews, with the outcomes reported as described in the IPD analysis and risk of bias assessed for the IPD analysis per outcome.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy up to March 2018, and NICE's 2018 conflicts of interest policy from April 2018.

1.5 Clinical evidence

1.5.1 Included studies

One study was included in the review; [27] this is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 3).

This study is an individual patient data (IPD) analysis, consisting of eleven studies that compared aspirin to a placebo. It is noted that it combines stroke with TIA and, in the subgroup analysis reported here, includes people with aspirin administered up to 48 hours after the index event. For this reason the study has been downgraded for indirectness during the quality assessment.

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

1.5.2 Excluded studies

See the excluded studies list in appendix H.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Rothwell et al.[27] [subgroup analysis for those given aspirin within 48 hours of stroke onset from the Chinese Acute Stroke Trial and the International Stroke Trial]	Aspirin (n=15961); 160 mg or 300 mg (oral, nasogastric tube, rectal or intravenous) for 2-4 weeks. Vs Control (n=15883)	Adults aged 16 and over with acute stroke 10% received aspirin within the 3 days prior to randomisation Multiple countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, New Zealand, Norway, Poland, Portugal, Romania, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Sri Lanka, Switzerland, Turkey, UK, USA)	Risk of recurrent stroke	Data are presented separately for those who had received aspirin within the 3 days prior to randomisation

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Aspirin versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aspirin (95% CI)
Risk of Recurrent Stroke - 24 hours [excluding those who received aspirin prior to randomisation]	28552 (1 study) 24 hours	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	HR 0.94 (0.67-1.32)		Not available4
Risk of Recurrent Stroke - 3 days [excluding those who received aspirin prior to randomisation]	28552 (1 study) 72 hours	⨁⨁⊖⊖ VERY LOW1,2 due to risk of bias, indirectness	HR 0.31 (0.16 to 0.6)		Not available4

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aspirin (95% CI)
Risk of Recurrent Stroke - 7-14 days [excluding those who received aspirin prior to randomisation]	28552 (1 study) 14 days	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	HR 0.64 (0.45 to 0.91)		Not available4
Risk of recurrent ischaemic stroke at 14 days - Mild initial neurological deficit	8464 (2 studies)	⨁⨁⊖⊖ VERY LOW1,2 due to risk of bias, indirectness	RR 0.5 (0.33 to 0.76)	16 per 1000	8 fewer per 1000 (from 4 fewer to 11 fewer)
Risk of recurrent ischaemic stroke at 14 days - Moderate initial neurological deficit	23380 (2 studies)	⨁⊖⊖⊖ VERY LOW1,2,3,5 due to risk of bias, inconsistency, indirectness, imprecision	RR 0.61 (0.38 to 0.97)	22 per 1000	9 fewer per 1000 (from 1 fewer to 14 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, due to being a post-hoc sub group analysis and unclear review methodology (e.g. search strategy and data extraction).
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
4 Risk difference could not be calculated as only the summary statistics were reported.
5 Downgraded by 2 increments because of heterogeneity, with I^2=81%, p=0.02, unexplained by subgroup analysis

Table 4: Clinical evidence summary: Continued aspirin versus placebo (in those who received aspirin prior to randomisation)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aspirin (95% CI)
Risk of Recurrent Stroke at 24 hrs	3292 (1 study) 24 hours	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	HR 0.31 (0.11 to 0.87)		Not available4

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

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
4 Risk difference could not be calculated as only the summary statistics were reported.

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No relevant health economic studies were identified.

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

1.6.3 Unit costs

Table 5: UK costs of aspirin, other antiplatelets and anticoagulants

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per week (£)[b]	Source
Antiplatelets				
Aspirin 300mg tablets	300mg once daily until diagnosis established	£0.10	£0.10 - £0.73[c]	NHS Drug Tariff
Clopidogrel 75mg tablets	75mg once daily	£0.04	£0.29	NHS Drug Tariff
Ticagrelor 90mg tablets	180mg for 1 dose, then 90mg twice daily	£0.98	£14.63	NHS Drug Tariff
Dipyridamole 100mg tablets	200mg twice daily	£0.04	£1.20	NHS Drug Tariff
Anticoagulants				
Warfarin 3mg and 5 mg tablets	10mg on first day, then 9mg daily [5-10mg on first day, lower induction dose given over 3-4 weeks; maintenance 3-9mg daily]	£0.02[d]	£0.41	NHS Drug Tariff
Apixaban 5mg tablets	5mg twice daily	£0.95	£13.30	NHS Drug Tariff
Dabigatran etexilate 110mg capsules and 150mg capsules	110mg twice daily (aged 80+) - 110-150mg twice daily (aged 75-79) - 150mg twice daily (aged 18-74)	£0.85[d]	£11.90	NHS Drug Tariff
Edoxaban 30mg and 60mg tablets	30mg once daily (up to 61kg)- 60mg once daily (61kg and above)	£1.75[d]	£12.25	NHS Drug Tariff
Rivaroxaban 20mg tablets	20mg once daily	£1.80	£12.60	NHS Drug Tariff

(a) Dosages for adults
(b) Depending on number of units taken
(c) Range of costs per week depending on number of days taken to establish diagnosis: 1 day – 7 days
(d) Unit cost for all listed doses

Table 6: UK aspirin costs to people with TIA

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Antiplatelets				
Aspirin 300mg tablets	300mg once daily until diagnosis established	£0.02	£0.02 - £0.12[c]	Retail price from stockist[d]

(a) Dosages for adults
(b) Depending on number of units taken
(c) Range of costs per week depending on number of days taken to establish diagnosis: 1 day – 7 days
(d) Retail price obtained from www.boots.com

1.7 Resource costs

The recommendation made by the committee based on this review (see section **Error! Reference source not found.**) is not expected to have a substantial impact on resources.

1.8 Evidence statements

1.8.1 Clinical evidence statements

- Indirect evidence from individual patient data in 28552 people from 2 RCTs demonstrated a clinical benefit of aspirin compared to placebo early after stroke (including in subgroup analysis for those with mild ischaemic stroke; n=8464) for reducing the risk of recurrent stroke at 3 days, 7-14 days and 14 days among those who were not previously receiving aspirin (Very Low quality). However, no clinical difference was seen in risk of recurrent stroke at 24 hours after the index event (Very Low quality).
- Indirect evidence from individual patient data in 3292 people from 1 RCT demonstrated a clinical benefit of aspirin compared to placebo early after stroke for reducing the risk of recurrent stroke at 24 hours among those who were previously receiving aspirin (Very Low quality).

1.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The critical outcomes for this review were risk of stroke and mortality. Important outcomes were identified as intra-cranial haemorrhage, major bleeding complications, degree of disability or dependence in daily activities (modified Rankin scale [mRS]) and quality of life.

Evidence was only available for the 'risk of stroke' outcome.

1.9.1.2 The quality of the evidence

A post-hoc subgroup analysis from 1 study was included in the review. This study was a well-conducted individual patient data (IPD) meta-analysis, consisting of eleven studies that compared aspirin to a placebo. However, the population was indirect for this review because it included confirmed TIA and those with minor ischemic stroke and was based in secondary care, not when the patient had their first contact with healthcare professionals. The timing of the intervention is also indirect for this review as aspirin was given within 48 hours or as long as 1 month after diagnosis. Only one partially-applicable post-hoc subgroup analysis based on 2 large studies was included in the review in this guideline, as the majority of the evidence was too indirect to be considered. This included evidence for aspirin given within 48 hours of onset of acute ischaemic stroke, which is still an indirect population for first point of contact for suspected TIA. Some of the outcome data were imprecise, and there was unexplained heterogeneity for one outcome. Therefore, the evidence quality was rated as very low and the recommendations were largely based on consensus.

1.9.1.3 Benefits and harms

The indirect evidence strongly suggested a benefit of aspirin for reducing risk of recurrent stroke. This was 3.2 times less likely at 3 days following the event and 1.5 times less likely at 14 days among those treated with aspirin compared to placebo. However, the effect was not seen at the 24 hour time point, except among those who had received aspirin prior to randomisation. The committee agreed that it makes biological sense that the earlier aspirin can be administered, the better, as there is greater opportunity for prevention of recurrent thrombo-embolism due to aspirin's antiplatelet effect.

No other outcomes were reported for people given aspirin very early after the index event, and so no further evidence was available.

The committee agreed that once a diagnosis of TIA has been suspected by a healthcare professional, it should be safe to give aspirin without significantly increasing the risk of haemorrhage. Aspirin should not be self-administered for suspected TIA without first seeking professional medical advice, which could include NHS 111, paramedics, a GP, nurse, pharmacist or emergency department (ED) physician. The committee discussed the potential risk of giving aspirin to people with suspected TIA who actually have undiagnosed intracerebral haemorrhage. It was noted that the baseline risk of haemorrhage is greater with stroke than TIA, but that even in mild stroke (The National Institutes of Health Stroke Scale [NIHSS] <3) the risk of haemorrhage is <5%, as discussed in the included study. It was also recognised that intracerebral haemorrhage (including intracerebral haemorrhage or convexity subarachnoid haemorrhage) can cause transient focal neurological symptoms that can mimic TIA. The suspected TIA group are likely to have a much lower risk of intracerebral haemorrhage than patients with minor stroke, and therefore aspirin is more likely to be safe. The committee were also aware of some retrospective data suggesting that even when aspirin is given in cases of intracerebral haemorrhage, the clinical condition does not deteriorate. Therefore, taking all of these factors into account the risk of haemorrhage was agreed to be low. Other risks associated with administering aspirin in this group were discussed to be an aspirin allergy or GI bleed (particularly in people already taking anticoagulants) in common with aspirin use in any population, but it was agreed that a single 300 mg dose is likely to carry a low risk of causing or aggravating bleeding.

The committee also considered that patients should be seen in a TIA clinic within 24 hours thus limiting the time period during which an adverse event might occur.

Overall, the committee agreed that there was evidence for a benefit of aspirin in the early management of TIA or suspected TIA but that its use needs to be regulated to minimise any possible harm. Therefore, based on indirect evidence and on consensus they recommended that a healthcare professional contacted, whether this is in person or on the telephone, should offer aspirin immediately once TIA is suspected. Urgent expert assessment, for example in a TIA clinic or other secondary care setting, should also be arranged for a definitive diagnosis and, if appropriate, a management plan put in place including continuation of aspirin.

Please see evidence review B on risk scoring systems for people with TIA for a discussion on urgent expert assessment within 24 hours.

1.9.2 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of aspirin for people with suspected TIA prior to assessment in a TIA clinic.

In the absence of economic evidence, the committee considered the unit cost of aspirin; currently £0.10. The clinical evidence, in an indirect population, described a reduced risk of stroke when aspirin is given early after minor stroke or confirmed TIA. In considering the cost

effectiveness of aspirin for people with suspected TIA, the committee discussed the expected cost savings produced by preventing strokes following TIA and the expected costs of adverse events resulting from inappropriate aspirin use.

The committee noted that there might be harms and costs associated with treating those given aspirin inappropriately. However, they thought that at a population level, these risks would most likely be offset by the benefits of giving aspirin quickly to those with suspected TIA.

The committee stressed that all people with TIA are at a high risk of stroke and so all those with suspected TIA should be assessed within 24 hours in a TIA clinic. Please see evidence review B on 'risk scoring systems for TIA' for a discussion of the cost effectiveness of assessing people with suspected TIA within 24 hours in a TIA clinic.

In conclusion, the committee chose to recommend that aspirin is offered immediately if a healthcare professional suspects TIA. The unit cost of aspirin is very low; currently £0.10. The committee agreed that the small unit cost of aspirin, coupled with both the reduced risk of stroke and low risk of adverse effects, would render aspirin cost effective.

1.9.3 Other factors the committee took into account

It was noted that a large proportion (30--50%) of cases referred to a TIA clinic may ultimately not be diagnosed with a TIA. Common TIA mimics to be excluded were discussed, including migraine aura, seizure, and syncope.

A less common, but important TIA mimic was noted to be convexity subarachnoid haemorrhage (transient focal neurological episodes [TFNE] or 'amyloid spells', often presenting with recurrent, stereotyped attacks of a "positive" (tingling or "pins and needles") sensory disturbance of spreading onset), which might have a high risk of more severe intracerebral haemorrhage if aspirin was administered. Convexity subarachnoid haemorrhage can be detected by both CT and MRI after specialist TIA assessment.

The committee discussed their experience that people with a TIA may delay seeking medical attention and may not get treatment in time even once TIA is suspected. It did not want the recommendation to give aspirin immediately to lessen the urgency for accessing a TIA clinic or to lead to prolonged aspirin use without specialist assessment.

The impact of prescribing aspirin was discussed. The recommendation requires that first-line healthcare professionals (e.g. paramedics, NHS 111, community pharmacists, GPs, nurses, ED physicians) advise people with a suspected TIA to take aspirin. General practices will need to ensure they have adequate supplies of aspirin to enable immediate administration.

The committee considered the option of proposing a research recommendation but agreed that it was unlikely that randomised trial in this area would ever be carried out. The committee believed that given the indirect evidence available and taking into account their experience, the interests of people with suspected TIA would be best served by making an active recommendation.

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Appendices

Appendix A: Review protocols

Table 6: Review protocol: Aspirin

Field	Content
Review question	Should people with a suspected TIA be advised to take aspirin prior to assessment in a TIA clinic?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine whether aspirin for secondary prevention is safe and effective for early use in people with suspected TIA.
Eligibility criteria – population / disease / condition / issue / domain	People aged over 16 with suspected TIA
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Aspirin (any dose) given before expert assessment
Eligibility criteria – comparator(s) / control or reference (gold) standard	No aspirin or usual care (another antiplatelet or anticoagulant)
Outcomes and prioritisation	<u>Critical</u> Risk of stroke (stroke at 24, 72 hours and 14 days) Mortality <u>Important</u> Intra-cranial Haemorrhage Major bleeding complications – e.g. GI bleed Degree of disability or dependence in daily activities: • mRS score Quality of life (both health- and social-related quality)
Eligibility criteria – study design	Randomised controlled trials Prospective cohort studies Systematic reviews and meta-analyses of the above
Other inclusion exclusion criteria	Inclusion Language: Restrict to English only Settings: Emergency department, Other non-stroke unit/hospital wards in secondary care, Pre-hospital setting (paramedic / ambulance), General practice/walk in centres/primary care, Community pharmacies and NHS 111/999

Proposed sensitivity / subgroup analysis, or meta-regression	Strata Previous intra-cranial haemorrhage People already taking anticoagulants/antiplatelets Subgroups No subgroups
Selection process – duplicate screening / selection / analysis	Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• EndNote will be used for reference management, sifting, citations and bibliographies. • EviBASE will be used for data extraction and quality assessment for clinical studies. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Databases: Medline, Embase, Cochrane Library, Language: Restrict to English only Date restriction: none Key papers 1. Rothwell PM, Giles MF, Chandratheva A et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370(9596):1432–1442. 2. Lavallee PC, Meseguer E, Abboud H et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurology 2007;6(11):953–960. 3. Rothwell PM, Algra A, Chen Z et al. (18-5-2016) Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet .
Identify if an update	Recommendations made on TIA in CG68, but no specific question on early aspirin use. **Recommendations from CG68** 1.1.2.2 People who have had a suspected TIA who are at high risk of stroke (that is, with an ABCD2 score of 4 or above) should have: • aspirin (300 mg daily) started immediately • specialist assessment[10] and investigation within 24 hours of onset of symptoms • measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors. 1.1.2.4 People who have had a suspected TIA who are at lower risk of stroke (that is, an ABCD2 score of 3 or below) should have: • aspirin (300 mg daily) started immediately • specialist assessment[10] and investigation as soon as possible, but definitely within 1 week of onset of symptoms • measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10071

Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ [Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.]
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.

Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 7: Health economic review protocol

Review question	All questions – health economic evidence
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 – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. 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 (2014).[24] **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 make a decision 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 on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix H. 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 2002 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 (including any such studies included in the previous guideline) 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

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 09 February 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 09 February 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 2 of 12 CENTRAL to 2018 Issue 1 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	exp Brain Ischemia/
3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	Ischemic Attack, Transient/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
29.	27 not 28
30.	exp Aspirin/
31.	(aspirin or caprin or disprin or aspro or acetylsaliclyic acid or 2-acetoxybenzoic acid or acetylsalicylate or solprin).ti,ab.
32.	ASA.ti,ab.
33.	or/30-32
34.	29 and 33
35.	trial.ab.
36.	clinical trials as topic.sh.
37.	trial.ti.
38.	Meta-Analysis/
39.	Meta-Analysis as Topic/
40.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
41.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.

42.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
43.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
44.	(search* adj4 literature).ab.
45.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
46.	cochrane.jw.
47.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
48.	or/38-47
49.	Epidemiologic studies/
50.	Observational study/
51.	exp Cohort studies/
52.	(cohort adj (study or studies or analys* or data)).ti,ab.
53.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
54.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
55.	Controlled Before-After Studies/
56.	Historically Controlled Study/
57.	Interrupted Time Series Analysis/
58.	(before adj2 after adj2 (study or studies or data)).ti,ab.
59.	or/49-58
60.	exp case control study/
61.	case control*.ti,ab.
62.	or/60-61
63.	59 or 62
64.	Cross-sectional studies/
65.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
66.	or/64-65
67.	59 or 66
68.	59 or 62 or 66
69.	randomized controlled trial.pt.
70.	controlled clinical trial.pt.
71.	randomi#ed.ab.
72.	placebo.ab.
73.	randomly.ab.
74.	clinical trials as topic.sh.
75.	trial.ti.
76.	or/69-75
77.	59 or 68 or 76
78.	34 and 77

Embase (Ovid) search terms

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	*brain ischemia/ or *hypoxic ischemic encephalopathy/

3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	*Transient ischemic attack/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
27.	25 not 26
28.	exp Aspirin/
29.	(aspirin or caprin or disprin or aspro or acetylsaliclyic acid or 2-acetoxybenzoic acid or acetylsalicylate or solprin).ti,ab.
30.	ASA.ti,ab.
31.	28 or 30
32.	27 and 31
33.	systematic review/
34.	Meta-Analysis/
35.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
36.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
37.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39.	(search* adj4 literature).ab.
40.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
41.	cochrane.jw.
42.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
43.	or/33-42

44.	Epidemiologic studies/
45.	Observational study/
46.	exp Cohort studies/
47.	(cohort adj (study or studies or analys* or data)).ti,ab.
48.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
49.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
50.	Controlled Before-After Studies/
51.	Historically Controlled Study/
52.	Interrupted Time Series Analysis/
53.	(before adj2 after adj2 (study or studies or data)).ti,ab.
54.	or/44-53
55.	exp case control study/
56.	case control*.ti,ab.
57.	or/55-56
58.	54 or 57
59.	Cross-sectional studies/
60.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
61.	or/59-60
62.	54 or 61
63.	54 or 57 or 61
64.	random*.ti,ab.
65.	factorial*.ti,ab.
66.	(crossover* or cross over*).ti,ab.
67.	((doubl* or singl*) adj blind*).ti,ab.
68.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
69.	crossover procedure/
70.	single blind procedure/
71.	randomized controlled trial/
72.	double blind procedure/
73.	or/64-72
74.	43 or 58 or 73
75.	32 and 74

Cochrane Library (Wiley) search terms

#1.	(mini or minor or mild or acute) near/2 (stroke or strokes):ti,ab
#2.	MeSH descriptor: [Brain Ischemia] explode all trees
#3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#4.	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#5.	(isch?emi* near/2 attack*):ti,ab
#6.	TIA*:ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Aspirin] explode all trees

#9.	(aspirin or caprin or disprin or aspro or acetylsaliclyic acid or 2-acetoxybenzoic acid or acetylsalicylate solprin):ti,ab
#10.	ASA:ti,ab
#11.	#8 or #9 or #10
#12.	#7 and #11

B.2 Health Economics literature search strategy

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

Table 9: Database data parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Embase	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 01 January 2007 – 10 November 2017 NHSEED - 01 January 2007 – March 2015	None

Medline (Ovid) search terms

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/

14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to english language
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	economics/
40.	value of life/
41.	exp "costs and cost analysis"/
42.	exp Economics, Hospital/
43.	exp Economics, medical/
44.	Economics, nursing/
45.	economics, pharmaceutical/
46.	exp "Fees and Charges"/
47.	exp budgets/
48.	budget*.ti,ab.
49.	cost*.ti.
50.	(economic* or pharmaco?economic*).ti.
51.	(price* or pricing*).ti,ab.
52.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
53.	(financ* or fee or fees).ti,ab.
54.	(value adj2 (money or monetary)).ti,ab.
55.	or/39-54
56.	38 and 55

Embase (Ovid) search terms

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
35.	33 not 34

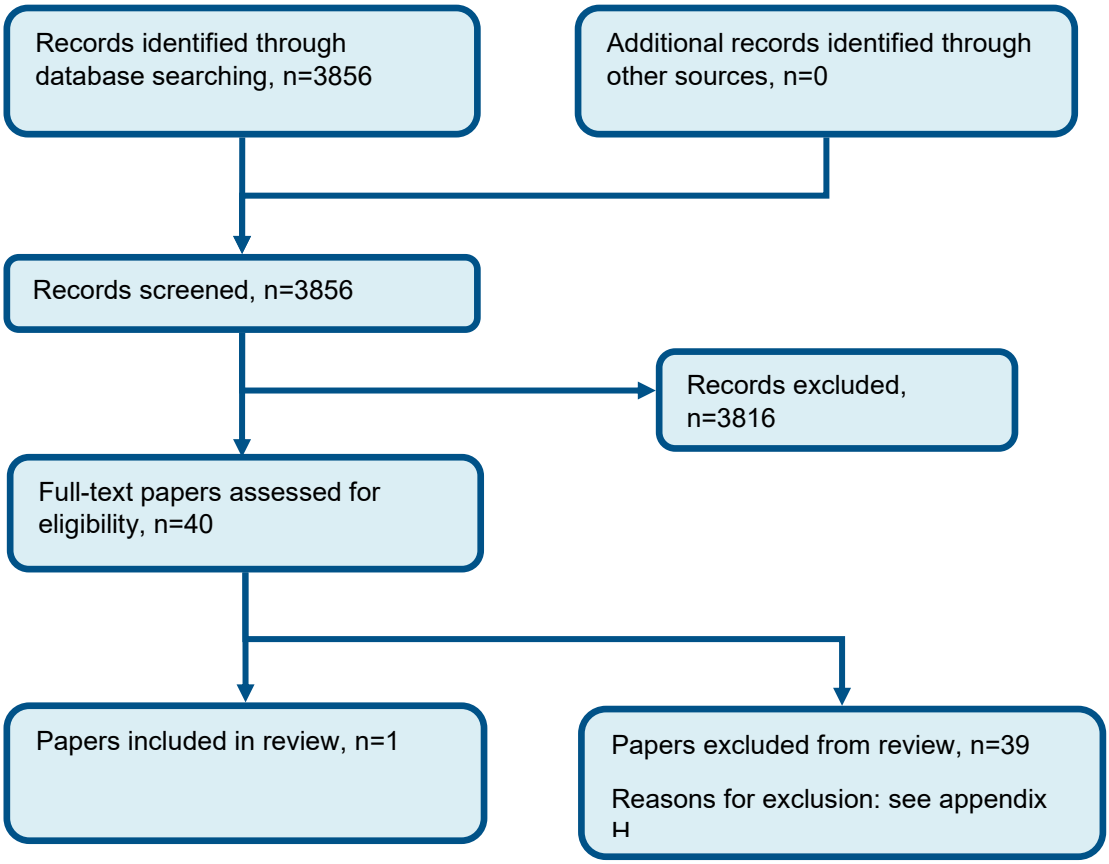
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(finance* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Stroke EXPLODE 1 2
#2.	((stroke or strokes))
#3.	(((cerebro* or cerebral*) adj2 (accident* or apoplexy)))
#4.	((CVA or poststroke or poststrokes))
#5.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#6.	((brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)))
#7.	(((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)))
#8.	MeSH DESCRIPTOR Brain Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES
#10.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)))
#11.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#12.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*))
#13.	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES
#14.	((isch?emi* adj2 attack*))
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of aspirin



Appendix D: Clinical evidence tables

Study	Rothwell 2016[27]
Study type	Systematic Review
Number of studies (number of participants)	12 (n=15 778)
Countries and setting	Conducted in Multiple countries; Setting: Various -
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Trials were eligible if they randomised the following: patients with TIA or ischaemic stroke to regular aspirin (any dose; in the presence or absence of another antiplatelet drug) versus no antiplatelet or anticoagulant in the secondary prevention of stroke and other vascular events; patients with acute ischaemic stroke to regular aspirin (any dose) versus no aspirin, in the presence or absence of another antithrombotic treatment, for acute treatment and prevention of early recurrence; or patients with TIA or ischaemic stroke to regular dipyridamole (any dose) versus no dipyridamole (in the presence or absence of another antiplatelet drug) in the secondary prevention of stroke and other vascular events. With searches done up to Jan 31, 2016, PMR identified trials through searches of the Antithrombotic Trialists' (ATT) Collaboration,13,23 subsequent systematic reviews, and the Cochrane Collaboration.24,25 In view of the historical nature of the trials, no additional searches were made for ongoing trials or abstracts presented at meetings. For all eligible trials of aspirin or dipyridamole in secondary prevention after TIA or stroke, we sought to obtain individual patient data.
Exclusion criteria	N/A
Recruitment/selection of patients	For all eligible trials of aspirin or dipyridamole in secondary prevention after TIA or stroke, we sought to obtain individual patient data.
Age, gender and ethnicity	Age - Mean (SD): 62.18 (9.63). Gender (M:F): N/A. Ethnicity: N/A
Further population details	-
Extra comments	-
Indirectness of population	Very serious indirectness: Population, objective, timing of outcome

Study	Rothwell 2016[27]
Interventions	(n=5213) Intervention 1: Aspirin (any dose) - Aspirin. Any dose. Duration 2-4 weeks. Concurrent medication/care: N/A. Indirectness: Serious indirectness (n=4422) Intervention 2: Control. Duration 2-4 weeks. Concurrent medication/care: N/A. Indirectness: Serious indirectness
Funding	Academic or government funding (Wellcome Trust, the National Institute of Health Research (NIHR) Biomedical Research Centre, Oxford)
Protocol outcomes not reported by the study	Mortality at 24hrs, 72hrs & 14 days; Intra-cranial Haemorrhage at 24hrs, 72hrs & 14 days; Major bleeding at 24hrs, 72hrs & 14 days; Degree of disability or dependence in daily activities at 24hrs, 72hrs & 14 days; Quality of life at 24hrs, 72hrs & 14 days

Appendix E: Forest plots

E.1 Aspirin vs placebo

Figure 2: Risk of recurrent stroke (hazard ratios)

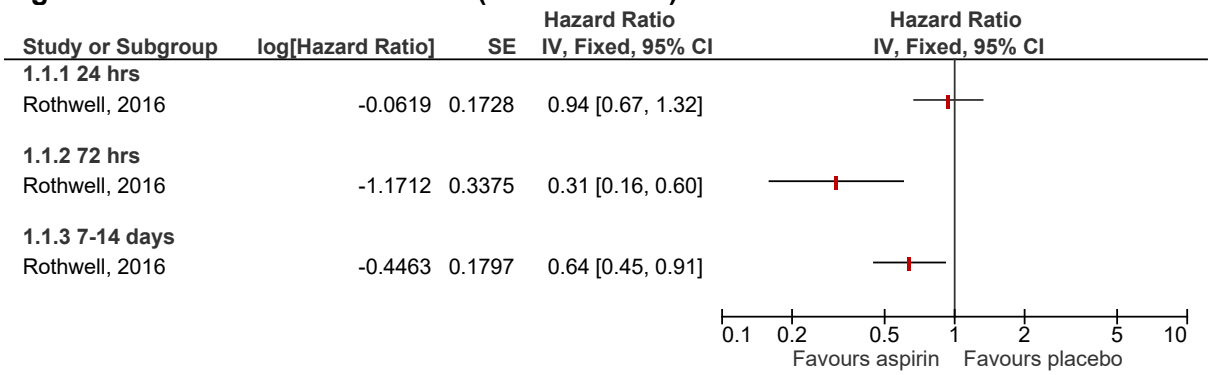


Figure 3: Risk of recurrent stroke at 14 days – mild initial neurological deficit

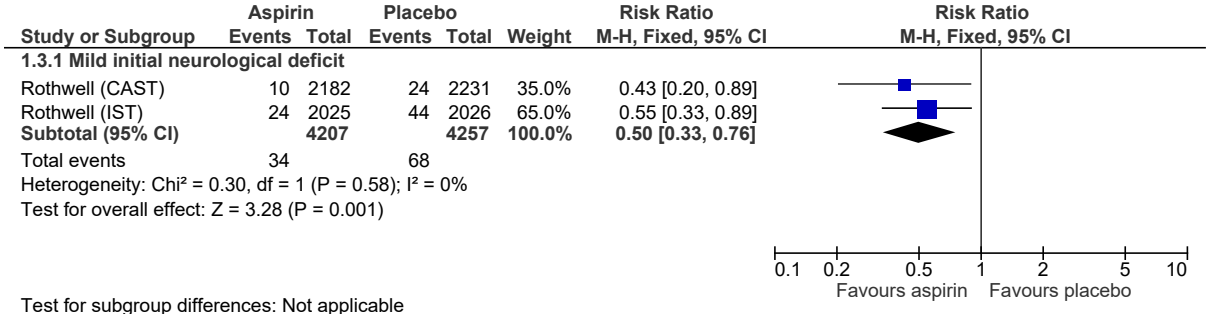
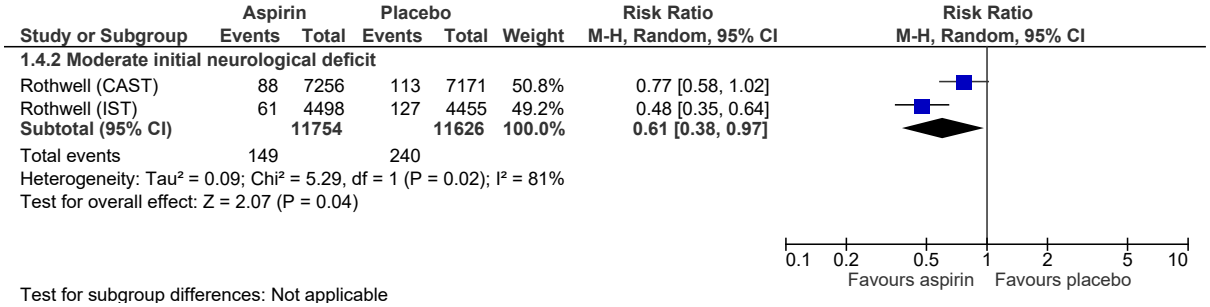
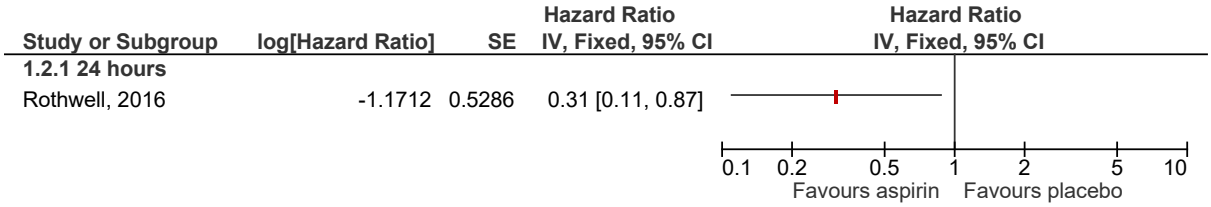


Figure 4: Risk of recurrent stroke at 14 days – moderate initial neurological deficit



E.2 Continued aspirin vs placebo in those with prior aspirin use

Figure 5: Risk of Recurrent Stroke (hazard ratios)



Appendix F: GRADE tables

Table 10: Clinical evidence profile: Aspirin versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute		
Risk of Recurrent Stroke - 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	15961	15883	HR 0.94 (0.67 to 1.32)		⊕OOO VERY LOW	CRITICAL
Risk of Recurrent Stroke - 3 days												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	15961	15883	HR 0.31 (0.16 to 0.6)		⊕OOO VERY LOW	CRITICAL
Risk of Recurrent Stroke - 7-14 days												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	15961	15883	HR 0.64 (0.45 to 0.91)		⊕OOO VERY LOW	CRITICAL
14-day risk of recurrent ischaemic stroke - Mild initial neurological deficit												
2	randomised trials	serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	34/4207 (0.81%)	1.6%	RR 0.5 (0.33 to 0.76)	8 fewer per 1000 (from 4 fewer to 11 fewer)	⊕OOO VERY LOW	CRITICAL
14-day risk of recurrent ischaemic stroke - Moderate initial neurological deficit												
2	randomised trials	serious[1]	very serious[4]	very serious[2]	serious[3]	none	149/11754 (1.3%)	2.2%	RR 0.61 (0.38 to 0.97)	9 fewer per 1000 (from 1 fewer to 14 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 2 increments because of heterogeneity, with I2=81%, p=0.02, unexplained by subgroup analysis

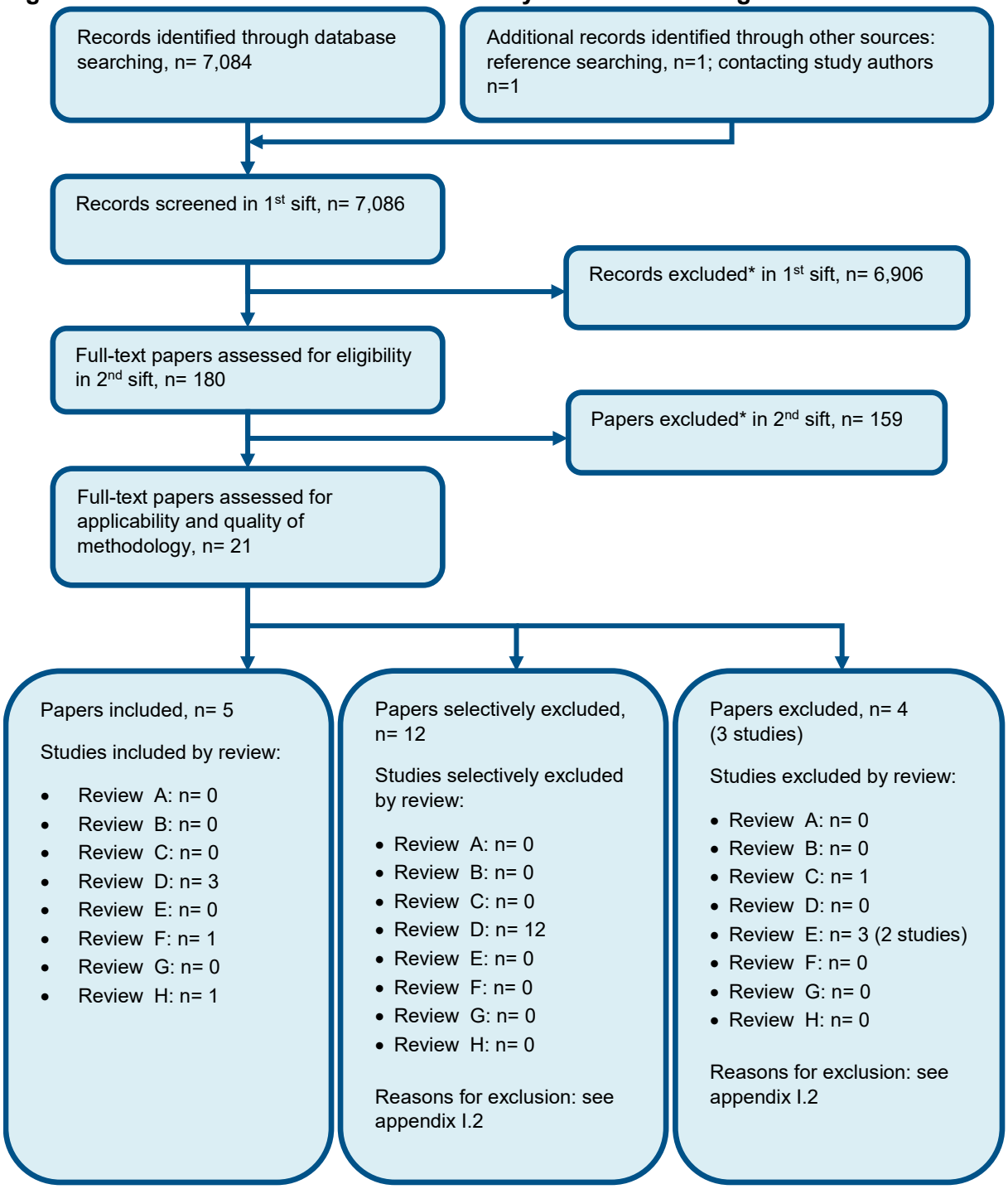
Table 11: Clinical evidence profile: Continued aspirin versus placebo in those with prior aspirin use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute		
Risk of Recurrent Stroke at 24 hrs (prior aspirin) (follow-up 24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none			HR 0.31 (0.11 to 0.87)	-	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 6: Flow chart of health economic study selection for the guideline



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

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 12: Studies excluded from the clinical review

Study	Exclusion reason
Aglua 2017[1]	Systematic review; results are unclear
Amarenco 2017[2]	Not review population or time point
Amarenco 2017[3]	Not review population or time point
Anon 1978[25]	Not review population or time point
Anon 1991[38]	Not review population or time point
Anon 1991[33]	Not review population or time point
Anon 1996[32]	Not review population or time point
Biller 1989[4]	Not review population or time point
Bousser 1983[6]	Not review population or time point
Bousser 2011[5]	Not review population or time point
Boysen 1988[7]	Not review population or time point
Britton 1987[8]	Not review population or time point
Candelise 1982[9]	Inappropriate comparison
Chen 1997[11]	Included in Rothwell IPD meta-analysis. Abstract only
Chen 2000[10]	Not review population or time point
De Schryver 2012[13]	Incorrect interventions. Inappropriate comparison
Diener 1996[14]	Not review population or time point
Easton 2017[15]	Not review population or time point
ESPS Group 1997[16]	Not review population. Included in Rothwell IPD meta-analysis
Fields 1977[17]	Not review population. Included in Rothwell IPD meta-analysis
Huang 2017[18]	Not review population or time point
Johnston 2015[21]	Not review population or time point
Johnston 2016[20]	Not review population or time point
Johnston 2016[19]	Abstract only
Lavallee 2007[22]	Incorrect interventions
Murakami 1983[23]	Not in the English language
Redman 2001[26]	Systematic review is not relevant to review question or unclear PICO
Rothwell 2007[28]	Not review population or time point
Sandercock 2014[29]	Systematic review is not relevant to review question or unclear PICO
Sorensen 1983[30]	Not review population. Included in Rothwell IPD meta-analysis
Stachenko 1991[31]	Systematic review is not relevant to review question or unclear PICO
Sze 1988[34]	Systematic review is not relevant to review question or unclear PICO
Takahashi 2014[35]	Not review population or time point

Study	Exclusion reason
Thijs 2008[36]	Systematic review is not relevant to review question or unclear PICO
Tohgi 1987[37]	Not review population or time point
Wa 2017[39]	Systematic review is not relevant to review question or unclear PICO
Wang 2016[40]	Systematic review is not relevant to review question or unclear PICO. Not review population
Wang 2017[41]	Not review population or time point
Weinberger 2005[42]	Not review population or time point