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Rands G, Orrell M

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[Intervention Review]

Aspirin for vascular dementia

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ABSTRACT

Background

Aspirin is widely prescribed for patients with a diagnosis of vascular dementia. In a survey of UK geriatricians and psychiatrists 80% of patients with clinical diagnoses of vascular dementia were prescribed aspirin. However, a number of queries remain unanswered. Is there convincing evidence that aspirin benefits patients with vascular dementia? Does aspirin affect cognition and behaviour, or improve prognosis? Does the risk of cerebral or gastric haemorrhage outweigh any benefit?

Objectives

To assess the randomised trial evidence for efficacy and safety of aspirin in the treatment of vascular dementia.

Search methods

We searched ALOIS: the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 12 March 2012 using the terms: aspirin OR "acetylsalicylic acid". ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases, numerous trial registries and grey literature sources.

In addition, relevant websites were searched and some journals were handsearched. Specialists in the field were approached for unpublished material and any publications found were searched for additional references.

Selection criteria

Randomised controlled trials investigating the effect of aspirin for vascular dementia were eligible for inclusion.

Data collection and analysis

Retrieved studies were analysed independently by both review authors. Methodology and results were critically appraised and outcomes scanned included cognition, behavioural change, mortality and institutionalisation.

Main results

No trials were eligible for inclusion in this review.

Authors' conclusions

The most recent search for references to relevant research was carried out in March 2012. No trials were found for inclusion in this systematic review.

Low-dose aspirin is frequently used as 'treatment as normal' in control groups and as a baseline treatment in pharmacological trials.

There is still no good evidence that aspirin is effective in treating patients with a diagnosis of vascular dementia.

There is increasing concern that low-dose aspirin is associated with increased risk of haemorrhages.

Further research is needed to assess the effect of aspirin on cognition, and on other outcomes such as haemorrhages, mortality, institutionalisation and behaviour.

However, the feasibility of such research is limited by a number of factors, including the widespread use of low-dose aspirin for secondary prevention of cerebrovascular and cardiovascular conditions, and its low cost and lack of patent, which limit commercial interest in investing in these studies. In addition, there is increasing evidence of its potential to cause harm from haemorrhages, especially gastric and cerebral haemorrhages that can be fatal.

PLAIN LANGUAGE SUMMARY

There is no evidence that aspirin improves the symptoms of vascular dementia

Low-dose aspirin can improve the prognosis of heart disease and stroke, possibly by reducing clot formation within the blood vessels and helping to maintain or improve blood flow to the heart and brain. Many doctors assume that aspirin will also provide some benefit for people with vascular dementia.

This systematic review shows that there is no evidence to suggest that aspirin is useful for people with vascular dementia. It is possible that vascular dementia and stroke are caused by different pathological processes. Practitioners need to be aware of the risks of aspirin, such as haemorrhages, which can be fatal.

BACKGROUND

Description of the condition

Dementia is a syndrome consisting of a cluster of symptoms. The core feature is cognitive impairment, which may include deterioration in memory, verbal and non-verbal intellectual abilities, spatial orientation, attention, recognition and interpretation of perceptions. There may also be changes in personality, motivation, and regulation of emotions and behaviour. Each individual's symptom profile will depend on the areas of brain affected. The condition progresses and occurs in clear consciousness.

Vascular dementia is a subtype of dementia and "is the result of infarction of the brain owing to vascular disease, including hypertensive cerebrovascular disease. The infarcts are usually small but cumulative in their effect. Onset is usually in later life" (ICD 10 2010).

This term includes multi-infarct dementia, arteriosclerotic dementia, vascular dementia of acute onset, subcortical vascular dementia, mixed cortical and subcortical vascular dementia, leukoariosis and Binswanger's disease.

Description of the intervention

Aspirin is acetylsalicylic acid. It has analgesic, anti-pyretic, anti-inflammatory and anti-platelet clumping properties.

In the 5th century BC Hippocrates used the bitter powder from willow bark, which contains salicylic acid, as an anti-pyretic and analgesic. There are worldwide historical examples of its use, for instance by Native Americans, Middle Eastern civilisations and in medieval England.

In 1828 the French pharmacist Leroux isolated salicylic acid, which is also found in the wild flower, meadowsweet.

Hoffmann, working for Bayer, synthesised and sold aspirin as a powder and in 1899 this was patented. Eleven days later Bayer also patented the opiate heroin. In 1915 aspirin tablets were created and in 1917 the patent expired.

Aspirin tablets are available worldwide but the dosages vary. For instance, in the UK it is available as 75 mg and 300 mg tablets, and 300 mg suppositories. The standard tablet in the US is 325 mg, the baby aspirin tablet is 81 mg and in Europe aspirin is available as 100 mg tablet (cardioaspirin). The recommended analgesic dose is 300 to 900 mg every four to six hours, while the recommended dose for secondary prevention of thrombotic cerebrovascular and cardiovascular disease is 75 to 300 mg daily. Low-dose aspirin is generally defined as 75 to 300 mg/day.

How the intervention might work

Aspirin causes a non-competitive, irreversible inhibition of cyclo-oxygenase (COX) 1, 2 and 3. Its actions vary with the dose.

At low doses (75 to 300 mg/day) it irreversibly blocks COX 1, which is necessary for thromboxane A2 (TXA2) synthesis. Lowered thromboxane levels reduce platelet stickiness and reduce vasoconstriction. Hence, at low doses (300 mg/day or less) aspirin reduces the formation of intravascular clots and emboli and improves peripheral blood flow. Low-dose aspirin has little effect on prostaglandins.

Although aspirin is metabolised after a few hours, platelets are unable to synthesis more COX 1 so this effect lasts several days until more platelets are manufactured.

At high doses (1.2 to 3.6 g/day) aspirin acts predominantly on COX 2, which converts arachidonic acid to prostaglandins throughout the body. Thus at high doses, aspirin, like non-steroidal anti-inflammatory drugs, reduces prostaglandin synthesis and has anti-pyrexial, anti-inflammatory and analgesic properties, and can cause gastritis. The anti-inflammatory effects are mediated by vasoconstriction. There is little effect on platelet stickiness.

Thus, aspirin affects the balance between TXA2, which promotes aggregation of platelets and local vasoconstriction, and prostacyclin (PGI2), which inhibits aggregation. At low doses, aspirin decreases TXA2 synthesis without significantly reducing PGI2 synthesis, thus reducing platelet aggregation and promoting local vasodilation. By this mechanism or others, low-dose aspirin can improve outcomes for patients after a stroke or myocardial infarction.

Aspirin is widely prescribed for the management of stroke and myocardial infarction with a view to preventing further episodes. APT 1994 found that long-term anti-platelet treatment given to people who have suffered transient ischaemic attacks or mild ischaemic strokes reduced the proportional risk of non-fatal stroke by one third and fatal stroke by one fifth. It was also suggested that although there is some evidence that aspirin increases risk of intracranial haemorrhage, the overall stroke rate is still reduced.

Many clinicians assume that aspirin may benefit patients with vascular dementia by similar mechanisms and it is widely prescribed for these patients (Dennis 1998). In one study of practice by geriatricians and psychiatrists in the UK, more than 80% of patients with cognitive impairment and vascular risk factors were prescribed aspirin. In one survey of Canadian specialists in subcortical vascular dementia (Molnar 1998), 86% of respondents prescribed aspirin.

A retrospective case note analysis of patients with vascular dementia showed a statistically insignificant trend towards both increased life expectancy and time to institutionalisation in those regularly taking low-dose aspirin (Devine 2003).

Aspirin has complex pharmacological actions that could affect the progress of dementias.

If the aetiology of dementia is ischaemic, as proposed in vascular dementia, the pharmacological effects of low-dose aspirin predict a beneficial effect on symptoms and prognosis.

If the aetiology of any dementia is inflammatory then the mechanisms of aspirin treatment suggest that high-dose aspirin may be beneficial and improve prognosis.

However, the pharmacological effects of aspirin also predict a possible worsening of symptoms.

It is possible that aspirin causes small cerebral haemorrhages that could stimulate the amyloid cascade, a theoretical model for Alzheimer's disease.

There is increasing concern that aspirin is linked to cerebral haemorrhages that may be primary or secondary. Again these are predicted by its known actions on platelets and small blood vessels.

It is well known that aspirin can cause gastric haemorrhages, probably via its anti-prostaglandin actions, and that these can be fatal.

As aspirin has a range of pharmacological effects it is possible that it will be found to influence the progress of different dementias in different ways, either beneficially or adversely.

Why it is important to do this review

It is important to do this review to determine whether aspirin improves cognition or prognosis for patients with vascular dementia. This is important because it is a widely prescribed drug and has the potential risk of haemorrhage.

OBJECTIVES

To assess the randomised trial evidence for efficacy and safety of aspirin in the treatment of vascular dementia.

It primarily aims to assess cognitive, behavioural and global outcomes.

The secondary objective is to assess the effect of the aspirin on mortality, morbidity and institutionalisation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials of aspirin for the treatment of vascular dementia are eligible for inclusion.

Types of participants

Participants of any age with a diagnosis of vascular dementia, as defined in the description of the condition (i.e. this term includes multi-infarct dementia, arteriosclerotic dementia, vascular dementia of acute onset, subcortical vascular dementia, mixed cortical and subcortical vascular dementia, leukoariosis and Binswanger's disease).

Types of interventions

Trials assessing the effect of aspirin versus control (placebo or no placebo), with a minimum of six months' follow-up, were considered for inclusion, regardless of dosage.

Types of outcome measures

Primary outcomes of interest were:

- cognition, using validated scales;
- behaviour, using validated scales;
- global function.

Secondary outcomes were:

- institutionalisation;
- morbidity, for example, gastric and cerebral haemorrhage;
- mortality.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois - created in part using a grant from the American Alzheimer's Association) - the Cochrane Dementia and Cognitive Improvement Group's Specialised Register on 3 March 2012. The search terms used were: aspirin OR "acetylsalicylic acid".

ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies were identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and Lilacs;
2. monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the World Health Organization (WHO) portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
3. quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*);
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

The latest searches of July 2011 and March 2012, retrieved a total of 267 and 57 results respectively. After a first-assess and a de-duplication of these results the authors were left with 35 and 10 references from each search to assess further.

In addition, relevant websites and journals were searched for trials.

Searching other resources

Specialists in the field were approached for unpublished material and any publications found were searched for additional references.

Data collection and analysis

Selection of trials

Two review authors (GR, MO) independently considered the studies identified by the search against the inclusion criteria.

Data extraction

As there were no studies suitable for inclusion in this systematic review, data were not formally extracted.

RESULTS

Description of studies

See: Characteristics of excluded studies.
There were no studies eligible for the review.

Risk of bias in included studies

There were no included studies.

Effects of interventions

There were no studies eligible to be included, as updated in March 2012.

DISCUSSION

Low-dose aspirin has been widely prescribed for patients with a diagnosis of vascular dementia for many years. It is often assumed that because it has confirmed benefit in stroke, it will have benefit in vascular dementia. However, there is some evidence that the pathogenesis of these two conditions may differ. Furthermore, aspirin is often considered a safe treatment although evidence is accruing that it has significant risks of haemorrhage. Therefore both the advantages and disadvantages of prescribing low-dose aspirin for patients with vascular dementia must be considered.

There were no eligible studies that could be included in this review. The Meyer 1989 study was excluded on detailed inspection of its methodology. We had wished to assess cognitive, behavioural and global outcomes in addition to mortality, morbidity (specifically haemorrhages) and institutionalisation data, but this was not possible.

There are difficulties in assessing the effect of aspirin in vascular dementia. Vascular dementia is often diagnosed with reference to a history of stroke or myocardial infarction and such patients are likely to be taking aspirin already. This presents difficulty in constructing a placebo-controlled trial.

AUTHORS' CONCLUSIONS

Implications for practice

This review alerts the physician to the fact that despite the widespread prescription of aspirin in patients with vascular dementia, there is no empirical evidence to support this practice.

Implications for research

There is a case to be made for a multicentre randomised double-blind placebo-controlled trial assessing the effect of aspirin on cognition. In addition, the behavioural and global domains need to be assessed. Mortality, morbidity and institutionalisation data should also be measured.

However, the risk of potentially fatal haemorrhage associated with low-dose aspirin may make such a study unethical.

It would also be useful to research the mechanism underlying the effects of aspirin on the neurobiological bases of cognition, for instance blood flow studies, neuroimaging and detailed neuropsychological testing.

ACKNOWLEDGEMENTS

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Vittoria Lutje performed the 2008 update search.

Anna Noel-Storr performed the 2012 searches and Sue Marcus helped with the editorial process.

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AD 2000 *{published data only}*

AD2000 Collaborative Group, Bentham P, Gray R, Sellwood E, Hills R, Crome P, Raftery J. Aspirin in Alzheimer's disease (AD2000): a randomised open-label trial. *Lancet Neurology* 2008;**7**(1):41–9.

ASPREE 2008 *{published data only}*

Anon. Aspirin for the prevention of cognitive decline in the Elderly: a Neuro-Vascular Imaging Study (ENVISion), a sub-study of ASPirin in Reducing Events in the Elderly (ASPREE); [Official title] A multi-centre, randomised, double-blind, placebo controlled trial of the effects of 100mg enteric-coated aspirin on rate of increase of magnetic resonance imaging (MRI)-based white matter hyperintensity (WMH) and silent brain infarction (SBI), 2008. www.mrw.interscience.wiley.com/cochrane/clcentral/articles/617/CN-00724617/frame.html. (accessed 20 August 2012).

Broe 2000 *{published data only}*

Broe GA, Grayson DA, Creasey HM, Waite LM, Casey BJ, Bennett HP, et al.Anti-inflammatory drugs protect against Alzheimer's disease at low doses. *Archives of Neurology* 2000; **57**(11):1586–91.

Guekht 2011 *{published data only}*

Guekht AB, Moessler H, Novak PH, Gusev EI. Cerebrolysin in vascular dementia: Improvement of clinical outcome in a randomized, double-blind, placebo-controlled multicenter trial. *Journal of Stroke and Cerebrovascular Diseases* 2011;**20**(4):310–8.

Henderson 1997 *{published data only}*

Henderson AS, Jorm AF, Christensen H, Jacomb PA, Korten AE. Aspirin, Anti-inflammatory drugs and risk of dementia. *International Journal of Geriatric Psychiatry* 1997; **12**:926–30.

Meyer 1989 *{published data only}*

Meyer JS, Rogers RL, McClintic K, Mortel KF. Controlled clinical trial of daily aspirin therapy in multi-infarct dementia. *Stroke* 1988;**19**(1):148.

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Moretti 2004 *{published data only}*

Moretti R, Torre P, Antonello RM, Cazzato G, Griggio S, Ukmar M, et al.Rivastigmine superior to aspirin plus nimodipine in subcortical vascular dementia: an open 16 month, comparative study. *International Journal of Clinical Practice* 2004;**58**(4):346–53.

Price 2008 *{published data only}*

Price JF, Stewart MC, Deary IJ, Murray GD, Sandercock P, Butcher I, et al.Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial. *BMJ* 2008;**337**:a1198.

Richard 2010 *{published data only}*

Richard E, Gouw AA, Scheltens P, Van Gool WA. Vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of white matter lesions on MRI: the evaluation of vascular care in Alzheimer's disease (EVA) study. *Stroke* 2010;**41**(3):554–6.

Sturmer 1996 *{published data only}*

Sturmer T, Glynn RJ, Field TS, Taylor JO, Hennekens CH. Aspirin use and cognitive function in the elderly. *American Journal of Epidemiology* 1996;**143**(7):683–91.

Szekely 2008 *{published data only}*

Szekely CA, Breitner JC, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, et al.NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. *Neurology* 2008;**70**(1):17–24.

Teramoto 2010 *{published data only}*

Teramoto T, Shimada K, Uchiyama S, Sugawara M, Goto Y, Yamada N, et al.Rationale, design, and baseline data of the Japanese Primary Prevention Project (JPPP) - a randomized, open-label, controlled trial of aspirin versus no aspirin in patients with multiple risk factors for vascular events. *American Heart Journal* 2010;**159**(3):361–9.

Thoonsen 2010 *{published data only}*

Thoonsen H, Richard E, Bentham P, Gray R, De Haan RJ, Van Gool WA, et al.Aspirin in Alzheimer's disease: increased risk of intracerebral haemorrhage - cause for concern? Cerebrovascular Diseases. Proceedings of the 19th European Stroke Conference; 201 May 25-28; Barcelona. Basal: Karger, 2010.

Yining 2011 *{published data only}*

Yining H (principal investigator). Cilostazol versus aspirin for vascular dementia in poststroke patients with white matter lesions (CAVAD). clinicaltrials.gov/ct2/show/NCT00847860, 2011. (accessed 20 August 2012).

Zhai 2010 *{published data only}*

Zhai Q-J, Yue X-Y, Hong Z, Xu G-L, Liu X-F. Efficacy observation of batroxobin for treatment of vascular cognitive impairment. *Chinese Journal of Cerebrovascular Diseases* 2010;**7**(2):73–6.

Additional references

APT 1994

Antiplatelet Trialists' Collaboration. Collaborative Overview of trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994;**308**:81–106.

Dennis 1998

Dennis M, Boyle A. Management of cognitive impairment of vascular origin. *Psychiatric Bulletin: The Journal of Trends in Psychiatric Practice* 1998;**22**:285–7.

Devine 2003

Devine M, Rands G. Does aspirin affect outcome in vascular dementia? A retrospective case-notes analysis. *International Journal of Geriatric Psychiatry* 2003;**18**:425–31.

ICD 10 2010

World Health Organization. *International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010*. Geneva: World Health Organization, Division of Mental Health, 2010.

Molnar 1998

Molnar FJ, Man Song Hing M, St John P, Brymer C, Rockwood K, Hachinski V. Subcortical vascular dementia: survey of treatment patterns and research considerations. *Canadian Journal Of Neurological Sciences* 1998;**25**(4): 320–4.

References to other published versions of this review

Rands 2000

Rands G, Orrell M, Spector A. Aspirin for vascular dementia. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD001296]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AD 2000	This was a randomised open-label trial of low-dose aspirin in 310 community-resident patients with probable Alzheimer's dementia and was part of a trial of donepezil. There were no significant benefits in terms of cognition or functional abilities but the risk of haemorrhage was significantly greater in the treatment group (risk ratio 4. 4; 95% confidence interval 1.5 to 12.8; P = 0.007)
ASPREE 2008	A history of dementia was 1 of the key exclusion criteria in this protocol
Broe 2000	This was a community survey, not a treatment study 50 drugs or drug groups were categorised and their use by people with Alzheimer's and vascular dementias analysed
Guekht 2011	3 related papers found in search; all of them had aspirin as basic treatment for patients in control and treatment groups, with cerebrolysin as the trial drug (2008 to 2011)
Henderson 1997	This study was a community survey and was not specific for vascular dementia
Meyer 1989	The method of randomisation was alternate entry, with 4 cases who were intolerant of aspirin allocated to the next control group slot (personal communication described in this Cochrane review 1999)
Moretti 2004	The comparison was aspirin and nimodipine versus rivastigmine
Price 2008	At entry into the study the participants did not have dementia
Richard 2010	Excluded because aspirin is only 1 element of multicomponent vascular care intervention, and the outcome is radiological
Sturmer 1996	The study was a survey and not specific for vascular dementia
Szekely 2008	This was a large cohort study and people with vascular dementia were a very small group within it. Not a randomised controlled trial, natural controls only
Teramoto 2010	This study evaluated the primary prevention of aspirin in older Japanese people with risk factors for cerebrovascular and cardiovascular disease. Dementia and cognitive assessments were not included in their primary or secondary end points. The enrolment was completed in June 2007 and follow-up was an average of 4 years so results are imminent. Their results will be of interest in terms of risk of haemorrhages in the aspirin-treated group. So far only rationale, design and baseline data are available
Thoonsen 2010	Poster presentation of a systematic review of the 2 papers suggesting that the pooled risk ratio of intracranial haemorrhage in dementia patients using aspirin was 7.67 (95% confidence interval 1.73 to 34.1; P = 0.007)
Yining 2011	Excluded because aspirin was treatment as normal in both control and intervention groups

(*Continued*)

Zhai 2010	Aspirin was administered to all patients in both groups

DATA AND ANALYSES

Comparison 1. Aspirin versus no aspirin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognition	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Behaviour	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Global	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mortality	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 Aspirin related	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Other causes	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Morbidity	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Aspirin related	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Other causes	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

APPENDICES

Appendix 1. Update search: July 2011

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Keyword search: aspirin OR "acetylsalicylic acid"	38
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950 to present (Ovid SP)	1. Aspirin/ 2. aspirin.ti,ab. 3. "acetylsalicylic acid".ti,ab. 4. or/1-3 5. Dementia, Vascular/ 6. VaD.ti,ab. 7. "vascular cognitive impairment*".ti,ab. 8. VCI.ti,ab. 9. Dementia, Multi-Infarct/ 10. dementia*.ti,ab. 11. or/5-10 12. 4 and 11 13. (2008* or 2009* or 2010* or 2011*).ed. 14. 12 and 13	42

(*Continued*)

3. EMBASE 1980 to 2011 week 30 (Ovid SP)	1. Aspirin/ 2. aspirin.ti,ab. 3. "acetylsalicylic acid".ti,ab. 4. or/1-3 5. Dementia, Vascular/ 6. VaD.ti,ab. 7. "vascular cognitive impairment*".ti,ab. 8. VCI.ti,ab. 9. Dementia, Multi-Infarct/ 10. dementia*.ti,ab. 11. or/5-10 12. 4 and 11 13. (2008* or 2009* or 2010* or 2011*).em. 14. 12 and 13 15. randomly.ab. 16. randomi?ed.ti,ab. 17. trial.ti,ab. 18. placebo.ti,ab. 19. groups.ab. 20. or/15-19 21. 14 and 20	66
4. PsycINFO 1806 to July week 4 2011 (Ovid SP)	1. Aspirin/ 2. aspirin.ti,ab. 3. "acetylsalicylic acid".ti,ab. 4. or/1-3 5. VaD.ti,ab. 6. "vascular cognitive impairment*".ti,ab. 7. VCI.ti,ab. 8. Dementia, Multi-Infarct/ 9. dementia*.ti,ab. 10. exp Vascular Dementia/ 11. or/5-10 12. 4 and 11 13. (2008* or 2009* or 2010* or 2011*).up. 14. 12 and 13	14
5. CINAHL (EBSCOhost)	S1 (MH "Aspirin") S2 TX aspirin S3 TX "acetylsalicylic acid" S4 S1 or S2 or S3 S5 TX dementia* S6 (MH "Dementia, Vascular") OR (MH "Dementia, Multi-Infarct") S7 TX VaD S8 TX vascular cognitive impairment* S9 TX VCI	25

(*Continued*)

	S10 S5 or S6 or S7 or S8 or S9 S11 S4 and S10 S12 EM 2008 S13 EM 2009 S14 EM 2010 S15 EM 2011 S16 S12 or S13 or S14 or S15 S17 S11 and S16	
6. ISI Web of Knowledge - all databases [includes: Web of Science (1945 to present); BIOSIS Previews (1926 to present); MEDLINE (1950 to present); Journal Citation Reports]	Topic=(dement* OR VCI OR "vascular congitive impairment*" OR VaD) AND Topic=(aspirin OR "acetylsalicylic acid") AND Topic=(randomly OR placebo OR groups OR trial OR RCT OR randomized OR randomised) AND Year Published=(2008-2011)	43
7. LILACS (BIREME)	Aspirin AND dementia	6
8. CENTRAL (*The Cochrane Library*) (Issue 4, Oct 2010)	#1 MeSH descriptor Aspirin explode all trees #2 aspirin #3 "acetylsalicylic acid" #4 (#1 OR #2 OR #3) #5 dementia* #6 "vascular cognitive impairment*" #7 VCI OR VaD #8 (#5 OR #6 OR #7) #9 (#4 AND #8), from 2008 to 2011	21
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Interventional Studies | dementia | aspirin OR acetylsalicylic | received from 01/01/2008 to 07/30/2011	2
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	Interventional Studies | dementia OR VCI OR VaD | aspirin OR acetylsalicylic | received from 01/01/2008 to 07/30/2011	10
TOTAL before de-duplication		267

(*Continued*)

TOTAL after de-dupe and first-assess	35

FEEDBACK

Additional trials?

Summary

Peter Sandercock commented: "You don't mention the results of the thrombosis prevention trial (Richards M, Meade TW, Peart S, Brennan PJ, Mann AH (1997) Is there any evidence for a protective effect of antithrombotic medication on cognitive function in men at risk of cardiovascular disease? Some preliminary findings. J Neurol Neurosurg Psychiatry 62:269-72.). A further trial is planned as a substudy to the AAA trial - contact Prof Gerry Fowkes (Gerry.Fowkes@ed.ac.uk). It may also be that the Womens health study: (Buring J, Hennekens C, for the Womens Health Study Research Group (1992). Women's Health Study: study design. Journal of Myocardial Ischemia 4: 27-9) is looking prospectively at aspirin and cognitive function. There is also a small crossover study by Kellett, published as a letter to the BMJ some years ago, but never reported in full. I think it would be worth pursuing these and mentioning them in your next update." (29/08/1999)

Reply

The review author replied:
"Thank you. We are aware of the studies referred to. There is increasing evidence that low dose aspirin benefits people with angina, MIs, CVAs, and various cancers but to date there is no specific evidence that it benefits cognitive function in people with vascular dementia". (November 2003)

Contributors

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Gianetta Rands: grands@doctors.org.uk

WHAT'S NEW

Last assessed as up-to-date: 4 March 2012.

Date	Event	Description
17 September 2012	New search has been performed	An update search was performed for this review on 30 July 2011 and 4 March 2012. No studies were found for inclusion

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 2, 1999

Date	Event	Description
20 May 2008	New search has been performed	Update search of 5 January 2008 retrieved several studies for consideration by the author. Three studies have been added to the list of excluded studies; no studies have been included
20 July 2005	New search has been performed	July 2005: an update search was performed resulting in two new references to one study (Moretti 2002). There was however, no placebo group with which to compare, so it is not known whether aspirin reduced rate of decline over the period of the trial. Therefore the results and conclusions of the review remain unchanged
19 November 2003	New search has been performed	November 2003: An update search was done and no new studies were found. The reviewers dealt with the peer reviewers' and consumer editor's comments. Comments and criticisms were added
20 August 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

GR: clinical and research input to reviews, drafting updates, correspondence, selection and assessment of studies, co-drafting of review, summaries of reviewed papers.

MO: co-author and reviewer of evidence.

SW: all correspondence on original review, drafting of review, searches, selection and assessment of studies.

AS: support on previous review processes.

Contact editor: Gordon Wilcock.

Consumer editor: Owain Bennallack.

The review was peer reviewed (November 2003).

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHS R&D, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

November 2003: an update search was done and no new studies were found. The review authors dealt with the peer reviewers' and consumer editor's comments. Comments and criticisms have been added.

January 2008: updated search. No new studies to add. Excluded papers added.

March 2012: updated search. No new studies found. Excluded papers summarised and added. Increasing concerns about risks of low-dose aspirin noted.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Aspirin [*therapeutic use]; Cognition Disorders [drug therapy]; Dementia, Vascular [*drug therapy; mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans