Aspirin for primary prevention of coronary heart disease

Peter PR Jackson¹, Mohsen Aarabi², and Erica Wallis¹

¹Clinical Pharmacology and Therapeutics, Royal Hallamshire Hospital, Sheffield, UK

²Department of Epidemiology & Population, c/o Cochrane Heart Group, London, UK

Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effects, both harmful and beneficial of aspirin in the primary prevention of coronary heart disease.

Primary questions—Does aspirin prevent fatal and non-fatal CHD in people without symptomatic vascular disease?

Does aspirin reduce all-cause and cardiovascular mortality?

Secondary questions—Are the effects of aspirin, be they harmful or beneficial, affected by underlying risk of CHD?

Do the major adverse effects of Aspirin ever outweigh its benefit and is this balance affected by underlying CHD risk?

BACKGROUND

Because cardiovascular disease (CVD) is likely to become the number one worldwide killer in the 21st century, widespread deployment of affordable preventive strategies will be essential for both developed and developing countries (Murray 1996). Approximately 50

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Contact address: Peter PR Jackson, Clinical Pharmacology and Therapeutics, Royal Hallamshire Hospital, Division of Clinical Sciences (South), University of Sheffield, Room 119, Floor L, Glossop Road, Sheffield, South Yorkshire, S10 2JF, UK.
peter.r.jackson@sheffield.ac.uk.

Editorial group: Cochrane Heart Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

CONTRIBUTIONS OF AUTHORS

Dr Peter Jackson:

conceived the review and obtained funding; will help interpret data and provide a methodological, policy and clinical perspective on the data; in the case of disagreements arising in the selection of trials for inclusion, will arbitrate as to whether a paper should be included; will overview the writing of the review.

Dr Mohsen Aarabi:

prepared and designed the protocol and search strategy; and will coordinate the review process; run the search strategy, screen the results and organise the retrieval of papers; jointly appraise papers and extract data; and will be responsible for data entry and analysis.

Dr Erica Wallis:

Will assess the trials found according to the eligibility criteria for inclusion in the review; jointly appraise and extract the data; and will lead writing the review.

DECLARATIONS OF INTEREST

PRJ has received speakers fees and support to attend conferences from a range of pharmaceutical companies. EJW has received support to attend conferences from a range of pharmaceutical companies. The department performs industry sponsored research.

million people die from CVD in the world each year, which is 30% of all mortality worldwide; nine million of those deaths are in the developing countries (SoRelle 1999).

Cardiovascular disease is the main cause of death in the UK, accounting in 2000 for over 235 thousands deaths. More than one in three people die from CVD. About half of these deaths in the UK are from coronary heart disease (CHD) and about a quarter are from stroke (Petersen 2002). In the USA, CVD has been the dominant cause of death for at least 50 years, with heart disease ranking first and stroke ranking third as specific causes of death (Cooper 2000).

In view of the prevalence of CHD, preventing even a small proportion of cases would save lives and healthcare expenditures. The first trial of aspirin in CHD was published in 1953 by Dr Carven, a general practitioner working in California, (Carven 1953). At that time, nobody understood the effect of aspirin on platelets. Aspirin inhibits platelet aggregation by irreversibly inhibiting the enzyme cyclooxygenase. The balance between production of prostaglandin I₂ (an inhibitor of aggregation generated by vascular endothelium) and thromboxane (TX) (a stimulant of aggregation generated by platelets) is thus altered; endothelium can synthesise more cyclooxygenase enzyme but platelets cannot (Rang 2003). At the usual dosage of aspirin, the main adverse effect is gastric irritation and ulceration. The gastritis that occurs with aspirin may be due to irritation of the gastric mucosa by the undissolved tablet, to absorption in the stomach of non-ionized salicylate, or to inhibition of production of protective prostaglandins (Katzung 2001).

Recent meta-analysis demonstrates a clear reduction in mortality and non-fatal cardiovascular disease events among those with prior myocardial infarction (MI), stroke, bypass surgery, angioplasty, peripheral vascular surgery, or angina (ATC 1988; ATC 1994). In 1998, the US Food and Drug Administration extended indications for aspirin to acute evolving MI and to wider categories of secondary prevention (FDA 1998). Two meta-analyses showed that aspirin, used for primary prevention, significantly reduced all cardiovascular events by 13 to 15% (95% CI: 5 to 22%), and myocardial infarction by 30 to 32% (95% CI: 21 to 41%) (Hebert 2000; Sanmuganathan 2001).

In addition to its benefits, aspirin can have serious adverse effects. Aspirin may increase the incidence of gastrointestinal bleeding, and hemorrhagic strokes. As the benefit from aspirin is linked to the underlying risk of CHD, its use should be directed at those people at moderate or high risk (Sanmuganathan 2001).

Four British societies recommended aspirin, at a dose of 75 mg, in high risk men over the age of 50 years for primary prevention of CHD and other atherosclerotic diseases (Joint British 1998). The American Heart Association and the US Preventive Service Task Force agree that the data are still insufficient to recommend aspirin for the primary prevention of CVD in healthy individuals (USPSTF 1998). The European society of Cardiology recommends low-dose aspirin (75 mg) only for men at particularly high risk of CHD.

In this situation, a revised meta-analysis qualifying both the precise benefits and harms of aspirin in primary prevention is necessary.

OBJECTIVES

To determine the effects, both harmful and beneficial of aspirin in the primary prevention of coronary heart disease.

Primary questions

Does aspirin prevent fatal and non-fatal CHD in people without symptomatic vascular disease?

Does aspirin reduce all-cause and cardiovascular mortality?

Secondary questions

Are the effects of aspirin, be they harmful or beneficial, affected by underlying risk of CHD?

Do the major adverse effects of Aspirin ever outweigh its benefit and is this balance affected by underlying CHD risk?

METHODS

Criteria for considering studies for this review

Types of studies

1. Blinded studies or open, with blinded end point assessment, randomised controlled trials of aspirin versus no treatment or placebo;
2. Cluster randomised trial.

Types of participants—Adults, men, women without symptomatic occlusive vascular disease.

Any primary care setting or secondary care setting will be included. Both free living and people living in hospitals or residential accommodation will be included if the aspirin is given for primary prevention.

Types of interventions—Aspirin therapy, any dose, compared with placebo or no treatment control as a primary prevention at least for one year. Trials in which aspirin is given with other treatments will be included as long as the effects of aspirin can be determined without confounding. For the purposes of this analysis interactions will be ignored.

Types of outcome measures

1. Mortality (all cause, and due to CV events);
2. Myocardial Infarction (non-fatal and fatal) diagnosed by World Health Organisation criteria;

3. Stroke, non-fatal and fatal, (past experience shows studies do not separate ischaemic and haemorrhagic stroke, we include both of them as a measure of the benefit of aspirin.);
4. Transient ischaemic attack (TIA);
5. Angina pectoris (new onset), doctor diagnosis or validated questionnaire e.g. the Rose questionnaire;
6. Any other bleeding events, in GI tract or other parts of body, which need transfusion or surgery;
7. Quality of Life information;
8. Cost data.

Search methods for identification of studies

The search for relevant studies will be done by the reviewer (MA).

The following electronic data bases will be searched:

1. The Cochrane Controlled Trials Register (CCTR/CENTRAL) on the Cochrane Library;
2. The Database of Abstracts of Reviews of Effectiveness (DARE) 2003;
3. MEDLINE (1966 +), with the addition of an RCT filter (Dickersin 1994);
4. EMBASE (1980 +), the addition of an RCT filter (Lefebvre 1996);
5. Best Evidence until 2003;
6. Biological Abstracts to 2003;
7. Current Research in Britain (CRiB) until 2003;
8. National Research Register until 2003.

Further the reference lists of identified relevant studies and reviews will be checked; No language restrictions will be applied to this search strategy.

In case of incomplete information in published papers, authors will be contacted.

The following detailed strategy will be used to search MEDLINE:

1. aspirin/
2. aspirin.tw.
3. acetylsalicylic acid.tw.
4. salicylate\$.tw
5. salicylic\$.tw
6. or/1-3
7. exp Cardiovascular Diseases/

8. myocardial infarction.tw.
9. coronary.tw.
10. angina.tw.
11. stroke.tw.
12. cardiovascular.tw.
13. heart disease\$.tw.
14. or/5-11
15. prevent\$.tw.
16. prophyla\$.tw.
17. protect\$.tw.
18. exp Preventive Medicine/
19. or/13-16
20. 4 and 12 and 17

All the brand names of aspirin will be put in the search strategy as texts.

Data collection and analysis

Selecting studies for relevance to this review—Studies identified from the search will be assessed for eligibility for inclusion in the review. Two reviewers (MA and EW) will independently select trials identified using the search strategy for relevance and inclusion or exclusion by reading titles and abstracts of studies. The selected trials will be compared and any discrepancies will be resolved by discussion and consensus and if needed by recourse to a third reviewer (PJ).

Two reviewers, independently, will read the full text of retained studies and will include trials that meet the inclusion criteria. A pre-defined form will be used for this task. The form will be developed and piloted on five trials to refine it before use on all studies. Articles finally selected for the review will be checked to avoid including data published in duplicate. Records of this will be kept as advised in the “Quality of reporting of meta-analyses statement” or QUOROM statement (Moher 1999). A completed QUOROM statement will be prepared.

A consensus meeting will be used to deal with any disagreements arising in the selection of the articles. If no agreement can be reached a third investigator will decide whether the paper should be included.

Assessment of study quality—Scales have recently been recognised as potentially unhelpful in assessing quality of clinical trials (Juni 1999; Clarke 2003). However simple and effective methods to assess quality are available and we will follow the guidelines of the Cochrane Handbook for systematic reviews (Clarke 2003). Factors will be assessed are those related to applicability of findings, validity of individual studies, and certain design

characteristics that affect interpretation of results, such as double blinding and adherence, also four sources of bias will be checked: selection bias, performance bias, attrition bias, and detection bias. Two reviewers will independently assess methodological quality of selected studies, attending to adequacy of allocation concealment, which will be ranked as A (adequate), B (unclear) or C (inadequate). Any differences of opinion will be resolved by discussion and consensus and finally by discussion with a third reviewer.

Data extraction—From the trials included information will be collected regarding: the trial design, patient baseline characteristics, different dosage and duration of aspirin intervention, outcome measures of death, myocardial infarction (fatal and non-fatal), angina pectoris, cerebral infarction and haemorrhage (fatal and non-fatal), and any significant non-cerebral haemorrhage, GI bleeding and any other adverse events, Quality of Life and cost data. A form for this purpose will be used, and piloted on five trials to ensure its suitability. To assess baseline risk of CVD the following median/mean values will also be extracted: age, gender ratio, proportion of current (or stopped within last year) smokers, proportion of patients with diabetes, total cholesterol, HDL and LDL cholesterol, and blood pressure.

Contacting trialists—For unpublished studies or where data are incomplete in published papers, attempts will be made to contact authors or researchers to obtain further details.

Data analysis

Publication or other bias: A funnel plot will be carried out to test for the presence of publication bias based on the data for the primary outcome of all cause mortality. Publication bias is usually detected by asymmetry of the funnel plot. If asymmetry is seen, this will be discussed to consider reasons other than publication bias, for example selection bias, reporting bias, data irregularities, true heterogeneity and artefact (Sterne 2001). Subgroup analysis will be performed to determine whether benefit varies with aspirin dose.

Heterogeneity—Because trials found may not have been carried out according to a common protocol there will usually be variations in patient groups, clinical settings, concomitant care etc. Although some differences in treatment effect are to be expected, if it is greater than that expected by chance, it will be important to consider if it is still appropriate to pool data. Therefore we plan to assess homogeneity of trial data by using the Mantel-Haenszel chi-square test of heterogeneity. Trial data will be considered to be heterogeneous if $p < 0.10$. If significant heterogeneity is present, an attempt will be made to explain the differences based on the patient clinical characteristics and interventions of the included studies. In addition Relative risk will be calculated using the conservative, random effects method. If heterogeneity is removed using this method it will be considered safe to pool the data (Deeks 2001; Thompson 2001).

Dichotomous trials—For dichotomous variables (e.g. stroke or no stroke at follow-up), the relative risk difference will be calculated using RevMan 4.2 software and pooled relative risk calculated for all outcomes. We will use a fixed effect model (Mantel-Haenszel) if we have demonstrated the trial data to be homogeneous, see above. If heterogeneity is present

then we may still pool the data using a random effects model described by Der Simonian and Laird, if pooling is considered appropriate in face of heterogeneity.

If results for any outcome are significant, its will be also expressed as number needed to treat (NNT) or Number Needed to Harm (NNH). Caution will be advised in interpreting the NNT or NNH as both NNT and NNH vary with the underlying risk of the population and the values are generalisable across different populations only if their baseline risk is similar (Smeeth 1999; Ebrahim 2001).

Sensitivity analysis—Sensitivity analysis will be conducted to determine the impact of study quality on outcome. The default will be to include all studies identified. The effect of excluding category “C” studies will be investigated.

Meta regression—Differences in absolute event rates will be regressed against estimated absolute CHD risk (Anderson) weighted by estimated variance. Allowance for residual inter-trial variability will be accommodated using the method of Sharp and Thompson (Thompson 1999). If results provide insufficient data to estimate CHD risk then a meta-regression using observed placebo risk as a covariate with an MCMC Bayesian approach will be undertaken (Thompson 1997).

Acknowledgments

SOURCES OF SUPPORT

Internal sources

- Division of Clinical Sciences (South), Section of Clinical Pharmacology and Therapeutics, University of Sheffield, UK

External sources

- No sources of support supplied

WHAT'S NEW

Date	Event	Description
10 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2004

Additional references

- ATC 1988 . Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *BMJ*. 1988; 296:320–31. [PubMed: 3125883]
- ATC 1994 . Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994; 308:81–106. [PubMed: 8298418]

- Carven 1953 . Craven LL. Experience with aspirin (acetylsalicylic acid) in the non-specific prophylaxis of coronary thrombosis. *Mississippi Valley Med Journal*. 1953; 75:38–44.
- Clarke 2003 . Clarke, M.; Oxman, AD., editors. *Cochrane Reviewers' Handbook 4.2.0* [updated March 2003]. The Cochrane;
- Cooper 2000 . Cooper R, et al. Trends and disparities in coronary heart disease, stroke, and other cardiovascular disease in the United States, finding of the National conference on cardiovascular disease prevention. *Circulation*. 2000; 102:3137–47. [PubMed: 11120707]
- Deeks 2001 . Deeks, J. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger, M.; Davey Smith, G.; Altman, G., editors. *Systematic reviews in healthcare Meta-analysis in context*. 2nd Edition. BMJ publishing group; London: 2001. p. 285–312.
- Dickersin 1994 . Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ*. 1994; 309:1286–91. [PubMed: 7718048]
- Ebrahim 2001 . Ebrahim, S. Numbers needed to treat derived from meta-analyses: pitfalls and cautions. In: Egger, M.; Smith, G.; Altman, G., editors. *Systematic reviews in healthcare Meta-analysis in context*. 2nd Edition. BMJ publishing group; London: 2001. p. 386–99.
- FDA 1998 . Internal analgesic, antipyretic, and antirheumatic drug products for over the counter human use: final rule for professional labelling of aspirin, buffered aspirin, and aspirin in combination with antacid drug products. 1998. 63 Federal Register 568-0526817
- Hebert 2000 . Hebert PR, Hennekens CH. An overview of the 4 randomized trials of aspirin therapy in the primary prevention of vascular disease. *Archives of Internal Medicine*. 2000; 160(20): 3123–7. [PubMed: 11074741]
- Joint British 1998 . Wood D, Durrington P, McInnes G, Rees A, Wary R. Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart*. 1998; 80(Suppl 2):S1–S29.
- Juni 1999 . Juni P, Witschi A, et al. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA*. 1999; 282:1054–60. [PubMed: 10493204]
- Katzung 2001 . Katzung, BG. *Basic and Clinical Pharmacology*. 8th Edition. Lange Medical Books/McGraw - Hill; 2001.
- Lefebvre 1996 . Lefebvre, C.; McDonald, S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE; Paper presented at the Fourth 20-24 Oct 1996; Adelaide, Australia. *International Cochrane Colloquium*; 1996;
- Moher 1999 . Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of goal-analyses of randomised controlled trials: the QUOROM statement. *Quality of Reporting of Meta-analyses*. *Lancet*. 1999; 354:1896–1900. [PubMed: 10584742]
- Murray 1996 . Murray, CJL.; Lopez, AD. *The Global Burden of Disease*. Harvard School of Public Health; Cambridge, MA: 1996.
- Petersen 2002 . Petersen, S.; Rayner, M. *Coronary Heart Disease Statistics*. 2002 edition. British Heart Foundation Health Promotion Research Group, Department of Public Health, University of Oxford; Oxford: 2002.
- Rang 2003 . Rang, HP.; Dale, MM.; Ritter, JM.; Moore, PK. *Pharmacology*. 5th Edition. Churchill Livingstone: 2003.
- Sanmuganathan 2001 . Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart*. 2001; 85(3):265–71. [PubMed: 11179262]
- Smeeth 1999 . Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses - sometimes informative, usually misleading. *BMJ*. 1999; 318:1548–51. [PubMed: 10356018]
- SoRelle 1999 . SoRelle R. Global epidemic of cardiovascular disease expected by the year 2050. *Circulation*. 1999; 100:E101. [PubMed: 10562272]
- Sterne 2001 . Sterne, J.; Egger, M.; Davey Smith, G. Investigating and dealing with publication and other biases. In: Egger, M.; Davey Smith, G.; Altman, G., editors. *Systematic reviews in health care. Meta-analysis in context*. Vol. 2. BMJ Publishing Group; 2001. p. 189–208.

- Thompson 2001 . Thompson, SG. Why and how sources of heterogeneity should be investigated. In: Egger, M.; Smith, G.; Altman, G., editors. Systematic reviews in healthcare: meta-analysis in context. 2nd Edition. BMJ Publishing Group; London: 2001. p. 157-175.
- Thompson 1997 . Thompson SG, Smith TC, Sharp SJ. Investigating underlying risk as a source of heterogeneity in meta-analysis. *Statistics in Medicine*. 1997; 16:2741–58. [PubMed: 9421873]
- Thompson 1999 . Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Statistics in Medicine*. 1999; 18:2693–708. [PubMed: 10521860]
- USPSTF 1998 . US Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Annals of Internal Medicine*. 1998; 136(2): 157–60.

**Indicates the major publication for the study*