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Protocol NIHR HTA Programme project number 11/130/02

1. Research question

What is the risk of adverse events from aspirin, taken for prophylactic use for the primary prevention of cardiovascular disease or cancer? Analysis using randomised controlled trials (RCTs), systematic reviews and meta-analyses from RCTs.

2. Name of TAR team and project 'lead'

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Date Completed:	31 August 2012

3. Plain English Summary

Taken in appropriate dosage, long term use of aspirin is thought to protect people from future heart problems and cancer. However, for some individuals, taking aspirin has unwanted side effects such as bleeding and stomach pain. Therefore, potential benefit of protection must be balanced against possible harm from side effects. This balance may be different for different

people and it is particularly important to know the risk of side effects from preventative aspirin for those people as yet free from, but at risk of, developing cardiovascular disease or cancer. This report aims to find the current scientific evidence about this and to summarise this literature by looking in detail at systematic reviews and meta-analyses on the occurrence of side effects from the preventative use of aspirin in people free of cardiovascular disease and cancer.

4. Decision problem

Objectives

i. To identify RCTs, systematic reviews and meta-analyses of RCTs of the prophylactic use of aspirin in the primary prevention of cardiovascular disease or cancer.

ii. With particular reference to adverse events, undertake an overview and quality assessment of the identified systematic reviews and meta-analyses.

iii. To undertake study level meta-analysis to investigate the relative influence of individual studies on pooled estimates of risk of adverse events reported in identified systematic reviews and meta-analyses.

iv. To undertake cumulative meta-analysis on time of study initiation or study publication to investigate influence on pooled estimates of risk of adverse events reported in identified systematic reviews and meta-analyses.

v. To undertake exploratory multivariable meta-regression of studies in identified systematic reviews and meta-analyses to investigate the potential influence of study level variables on reported pooled estimates of risk of adverse events (e.g. participant age and gender; follow up duration; aspirin dose or dose frequency; level of or type of cardiovascular risk; year of investigation). (Whilst we are aware that it is recommended that each study level variable requires approximately 8 studies, we will emphasise the exploratory nature of the analyses should variables exceed this ratio).

vi. To summarise, synthesise and assess the recommendations provided in the systematic reviews and meta-analyses reporting on adverse events resulting from prophylactic use of aspirin in primary prevention in the light of objectives i-v and if appropriate to make recommendations for further investigation

4.1 Background

Aspirin (acetylsalicylic acid) is a widely used antiplatelet drug for primary and secondary prevention of cardiovascular events.[1] Typical doses employed range from75 to 325 mg daily or

every other day. Some authors[2] have defined low dose, medium and high doses of aspirin, but such classification is somewhat arbitrary and subjective.

The regular use of even low dose aspirin appears to increase the risk of death from GI bleeding, cerebrovascular bleeding[3,4] and may exaggerate the severity of asthma attacks.[5] Some evidence suggests that relative to higher doses, lower doses may be protective while resulting in fewer adverse effects.[6] Aspirin related GI bleeding may be more common in older patients (>70 years) and in those with a past history of peptic ulcer.[7] Discontinuation of long term use has been linked to increased risk of non-fatal myocardial infarction compared to those who continued treatment.[8]

Several guidelines exist that consider the prophylactic use of aspirin; these are based on an assessment of the balance between cardiovascular benefits (e.g. reduced MI and stroke) and various harms (especially bleeding); some recommend widespread employment of aspirin for individuals at increased risk of CVD.[9,10] Recently, opinion and evidence appear to have shifted. Firstly, benefits in primary prevention of CVD are now generally viewed as relatively modest, remain statistically uncertain, and are an order of magnitude less than that observed in secondary prevention with aspirin, while harms (especially bleeding) occur at relatively high frequency (very high frequency in some populations). Secondly, investigations that use a mix of individual patient data (IPD) and study level meta-analyses of randomised controlled trials (RCTs) and of observational studies, now point to a possible protection against several cancers[11] (notably colon cancer). Apparent protection emanates after about five years of aspirin use, and there is also evidence for protection against cancer metastasis. These latter studies have been viewed with caution by some because data from the two largest CVD primary prevention trials were excluded.[12,13]

4.2 Scoping searches

In November 2011 Warwick Evidence carried out search of current relevant research related to potential harms from aspirin given in low dose (taken as <300mg) for any indication. The aim of the scoping searches was to generate a rapid overview of evidence on the potential harms from prophylactic aspirin (<300mg) for any indication, and to gauge the current status of policy concerning aspirin prophylaxis in primary prevention. Details are provided in *Appendix 1*

Amore recent scoping search (April 2012) undertaken in response to correspondence with NIHR HTA focused on the use of aspirin for primary prevention. This revealed that evidence relating to

benefits and risks of prophylactic aspirin is currently a very active area of systematic review and meta-analysis. There are already several recent systematic reviews of prophylactic aspirin for the primary prevention of cardiovascular events,[14-16] each of which have meta-analysed the same basic core of nine randomised controlled trials of primary prevention.[17-25] These RCTs have included over 100,000 patients.

Similarly, scoping has indicated the existence of a growing number of reviews and meta-analyses that focus on the possible protection of long term aspirin against cancers and cancer metastasis. Primary prevention RCTs, secondary prevention studies,[26] and observational studies have featured in these analyses and, in some, IPD meta-analyses[11] have been conducted. In general it appears that adverse events (e.g. bleeding) are rarely reported in these cancer protection studies, except where studies have been included from amongst the core nine RCTs of long term aspirin for primary prevention cardiovascular disease.

In summary: The RCT evidence-base to address the protocol research questions does not appear to have grown since the publication of the AAA trial in 2011[19] (several unreported on-going trials have been identified in scoping). This evidence has been subject to intense systematic review and meta-analysis including many study level meta-analytic investigations and a landmark IPD meta-analysis published in 2009.[1] In general the published meta-analyses appear to be well conducted and current according to the time they were undertaken; however inferences and conclusions appear to differ from study to study. Thus far it appears that no overview of these meta-analyses and reviews has been undertaken or published.

We therefore plan:
A] With particular reference to the occurrence of adverse events, to undertake an overview of the systematic reviews and meta-analyses of RCTs which have investigated the long-term use of aspirin for primary prevention of CVD or cancer.

B] So as to identify changes through time, undertake cumulative meta-analysis of these RCTs.

C] So as to investigate the relative influence of individual RCTs on pooled estimates, undertake study level meta-analysis of the RCTs.

D] So as to identify study level variable that influence the occurrence of adverse events undertake exploratory multi variable meta-regression of the RCTs.

These options are relatively straightforward to undertake. Option A] is justified on the grounds that although a plethora of meta-analytic studies have been generated, no overview has yet been published that compares them, particularly with regard to adverse events, or sets them in context. Options B] to D] are justified since they can address how aspirin use in the primary prevention of CVD or cancer has evolved since clinical trials in the 1980s, and the introduction of guidelines on the use of aspirin in primary prevention from trials published up to 2010. Moreover, trials' conditions and patients' characteristics have also evolved over time and there is considerable heterogeneity among randomized trials. In the meanwhile, preventative treatments for CVD have greatly changed (introduction of statins and anti-hypertensive drugs), and there are observed differences in the outcomes from the trials. Therefore, early results cannot be easily compared with later studies, a limitation that prior meta-analyses accounted for only partially or not at all.

Alternative avenues of investigation have been considered but not judged viable on reviewer's advice, and on the basis of the project's time scale and remit from NIHR HTA. These are as follows: (i) to expand the analysis so as to include observational studies. Since RCTs account for over 100,000 patients and the ratio of RCTs to cohort studies in a previous meta-analysis that was restricted to patients with diabetes was about 4:1, including the results from such studies may not add significant value to knowledge already accumulated; (ii) to perform IPD meta-analysis of RCTs, by expanding on the six primary prevention RCTs previously analysed by Baigent et al 2009[1] Negotiating agreement for access to RCT data would be difficult and time consuming and possibly unsuccessful since it is very likely Baigent et al. requested IPD for these studies but were unable to obtain it. Because of the low probably of obtaining IPD and the time required to obtain and analyse it, this option was not judged viable within the project time scale and remit. (iii) Expand the analysis to include IPD from the THIN registry (a UK NHS general practice registry that holds data on 3 million patients, about 2,000 of whom were prescribed low dose aspirin). An industry sponsored analysis of GI bleeding resulting from use of low dose aspirin has already been published using data in the THIN registry. Analysis of intracranial bleeding would probably be hampered by lack of discrimination between types of stroke entered into the registry. Furthermore the larger number of participants in the available RCTs brings into question the added value from such an undertaking.

5. Report methods for synthesis of clinical evidence

With particular reference to adverse events an overview will be undertaken of RCTs, systematic reviews and meta-analyses of RCTs of the prophylactic use of aspirin for the primary prevention of cardiovascular disease or cancer published since 2008. The general principles recommended by NHS Centre for Reviews and Dissemination (CRD) will be applied.[27]

5.1 Identification and selection of studies

Scoping searches were undertaken to assess the volume and type of literature relating to the assessment question. A search strategy will be developed which focuses the searches to meet the inclusion and exclusion criteria (see below). All searches will be undertaken in September2012.

5.1.1 Search strategy for clinical effectiveness

An iterative procedure will be used to inform the development of the search strategy, with input from clinical advisors and previous HTA and systematic reviews (e.g. Bartlolucci et al. 2011,[14] Berger et al. 2011,[16] Rothwell et al. 2012[11]). Copies of search strategies to be used in the major databases are provided in

Appendix 2. These draft search strategies developed for MEDLINE will be adapted as appropriate for other databases. The strategies cover the concepts of aspirin, prevention and control,[1] and selected publication types (systematic reviews, meta-analyses and randomised controlled trials).

The search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases
- Contact with experts in the field
- Scrutiny of references of included studies

Databases will include:
MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews; CENTRAL; DARE, NHS EED, HTA databases (NHS-CRD); Science Citation Index and Conference Proceedings (Web of Science); UKCRN Portfolio Database; Clinical Trials.gov.

In addition, the reference lists of relevant articles will be checked and various health services research related resources will be consulted via the Internet. These are likely to include HTA organisations, including the NIHR and the National Research Register (NRR) Archive, guideline producing bodies, generic research and trials registers:

- Medicines and Healthcare products Regulatory Authority (MHRA)
- US Food and Drug Administration
- The Aspirin Foundation
- The British Cardiovascular Society
- European Society of Cardiology
- American Heart Association
- Cancer Research UK
- Institute of Cancer Research
- American Association for Cancer Research

5.1.2 Inclusion of relevant studies

[1]MeSH floating sub-heading pc.fs which will be used in MEDLINE and EMBASE. An alternative will be considered for other databases.

Study design:
RCTs, systematic reviews and meta-analyses of RCTs on the use of aspirin in the primary prevention of CVD or cancer.

Studies will be defined as primary prevention if participants with previous ischaemic vascular events or relevant cancers have been excluded (or are separately identified and can be excluded) or represent <20% of included participants.

To be included, systematic reviews needed to report data from studies separately with a minimum of 50% of studies being eligible RCTs.

Population:
Adults aged over 18 years without clinical cardiovascular disease (established or symptomatic), or adults aged over 18 years without cancer (established or symptomatic).

Intervention:
Aspirin (any dosage) taken prophylactically for primary prevention of cancer or cardiovascular disease.
Aspirin combination therapy (e.g. Aspirin combined with a second antithrombotic agent) will only be included if there are separate placebo and aspirin-only treatment groups, in which case the data from these groups only will be included.

Comparator:
Placebo, no aspirin or no other treatment.

Outcomes:
The primary outcome of interest is the risk of adverse events from prophylactic aspirin for primary prevention, compared to placebo, no aspirin or no other treatment.

Other outcomes reported in the included reviews and meta-analyses will be recorded.

5.1.3 Exclusion criteria

- All study designs other than RCTs, systematic reviews or meta-analyses
- Systematic reviews or meta-analyses that only include secondary prevention studies

- Systematic reviews or meta-analyses that only include observational studies
- Studies not in English

5.2 Review methods

A record of all papers rejected at full text stage and reasons for exclusion will be documented. Titles and abstracts of retrieved studies will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus.

5.3 Data extraction strategy

The full data will be extracted by one reviewer and checked by a second. Extraction forms for systematic reviews have been developed (see Appendix 3). Any disagreements will be resolved by discussion. Further discrepancies will be resolved with involvement of a third reviewer when necessary. Summary tables will detail information about study design, participant, intervention, comparator and outcomes. In addition we will provide a summary of the findings and authors conclusions.

Data will be extracted to allow quality assessment of the included studies (see below).

5.4 Quality assessment strategy

Quality criteria will be applied independently by two reviewers, with any disagreements resolved by independent assessment by a third reviewer. Included systematic reviews will be quality assessed using the NHS CRD[27] checklist for systematic reviews and the Cochrane Risk of Bias tool[28] for RCTs (See Appendix 4).

5.5 Methods of analysis/synthesis

A narrative overview and analysis of included systematic reviews and meta-analyses will be undertaken and supplemented with further meta-analysis.

Data from the included studies will be tabulated and summarised. Meta-analyses will be undertaken using random effects models using STATA software (StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA). Following the scoping searches it is considered that a random effects model is likely to be the primary analysis due to the likely differences in patient characteristics and aspirin doses. Particular attention will be focused on the reporting of adverse events (outcome statistic), the range of adverse event definitions employed in the primary studies,

and how discrepant event definitions have been handled when data has been synthesised by meta-analysts.

We anticipate conducting meta-analyses including cumulative meta-analysis of studies to identify changes through time; study level meta-analysis to investigate the relative influence of individual RCTs and exploratory multi variable meta-regression (we are aware that it is recommended that each variable requires approximately 8 RCTs, however we will emphasise the exploratory nature of the analysis should the variables exceed this ratio). Because of clinical heterogeneity a random effects model will be the method of choice, and tau squared will be recorded. We will explore publication bias using methods in the Cochrane handbook (recommended methods for testing funnel plot asymmetry): and statistical heterogeneity beyond that expected through chance would be investigated using I^2.

6. Expertise in this TAR team

Warwick Evidence is a technology assessment group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. The team planned for the work includes: Dr Paul Sutcliffe and Dr Tara Gurung, who are experienced systematic reviewers; Mrs Samantha Johnson, information specialist; Professor Aileen Clarke, Dr Kandala Ngianga-Bakwin provide epidemiological and statistical expertise; Professor Peter Elwood, University of Cardiff, and Professor Martin Underwood and Dr Saverio Stranges, University of Warwick and Dr Wendy Gregory, Clinical Consultant Gastroenterologist will provide methodological and clinical advice; Ms Amy Grove and Ms Sarah morrow will provide project management and reviewing support.

7. Competing interests of authors and advisors

None of the authors have any competing interests.

8. Timetable/milestones

Draft protocol finalised	TBC
Commissioning decision	TBC
Anticipated start date	17th September 2012
Draft Final report	30th November 2012

10. Team members' contributions

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10.1 Methodological advisors

Professor Peter Elwood, Honorary Professor of Epidemiology, University of Cardiff
Ms Sarah Morrow, Green Templeton College, University of Oxford

Contribution of methodological advisor: previous experience of modelling in this area, multistate models, general evidence synthesis, statistics issues in health economic modelling, application of statistical methods to cardiothoracic medicine and surgery.

10.2 Clinical Advisors

Professor Martin Underwood, University of Warwick

Dr Saverio Stranges, University of Warwick

Dr Wendy Gregory, Clinical Consultant Gastroenterologist

Contribution of clinical advisors: protocol development, help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness and review of report drafts.

11. References

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12. Appendices

Appendix 1

Scoping search November 2011

Warwick Evidence carried out an overview of current relevant UK research related to potential harms from aspirin given in low dose (<300mgs) for any indication. We conducted a scoping search in November 2011 on harms of aspirin given in low doses and contacted UK and international expert in the field. The aim of the scoping searches was to present a short overview of the current status of policy and research in the UK and internationally concerning the potential harms from aspirin given in low dose (<300mgs) for any indication. This has informed the development of the current search strategy.

The following databases were searched: Medline (1948 to November 2011), Embase (1974 to November 2011), Cochrane (all sections), HTA (www.HTA.ac.uk), DARE were searched (until November 2011). No language filters were applied. Full search strategies are available on request from the authors. RCT and SR filters were applied to Medline, Embase as detailed in the search strategies. Combined searches produced 3064 references; de-duplicating the database resulted in a final set of 2981 references. Economics searches were undertaken in Medline (1948 to December 2011), EMBASE (1974 to December 2011) and NHS-EED. A search of the Current Controlled Trials Database (http://www.controlled-trials.com/mrct/) produced 629 results, of which, 44 were considered to be potentially relevant.

Five[3,29-32] reviews were identified on the adverse events of low dose aspirin. The most recent review[3] entitled "Low Doses of Acetylsalicylic Acid (ASA) Increase Risk of Gastrointestinal Bleeding in a Meta-Analysis" centred exclusively on risk of GI bleeding related to low dose aspirin (75-325 mg/d). The review included any randomised controlled studies that evaluated low-dose ASA, alone or in combination with anticoagulant, clopidogrel or proton pump inhibitors (PPIs). A total of 61 trials were included in the review. Thirty-five RCTs included analysis of ASA alone, and three RCTs included analysis of ASA plus proton pump inhibitors. The study reported all-cause mortality, fatal bleeding, and fatal GI bleeding, major bleeding, any bleeds (including cerebral bleed) and dyspepsia as their outcome.

Economic evidence was limited in comparison to clinical and public health evidence in this area. We did not identify any comprehensive reviews of cost or cost effectiveness on the topic and

therefore a further analysis of cost-effectiveness or primary economic research will not be undertaken within the current work.

Appendix 2. Search strategy for Medline via OVID interface

Searched on 19/09/2012

1	exp *Aspirin/
2	(aspirin or acetylsalicyl* or "acetyl-salicyl*" or "acetyl salicyl*").tw.
3	1 or 2
4	(prevent* or prophyla*).tw.
5	exp Primary Prevention/
6	4 or 5
7	randomized controlled trial.pt.
8	(random* or controlled trial* or clinical trial* or rct).tw.
9	meta-analysis.pt.
10	("meta-analysis" or "meta analysis" or metaanalysis or "systematic review*").tw.
11	7 or 8 or 9 or 10
12	3 and 6 and 11
13	limit 12 to (english language and humans)
14	limit 13 to yr="2008 -Current"

Appendix 3. Data extraction form

a) Data extraction form for systematic reviews

Name of the reviewer:

Study details
Study ID (Ref man):
First author surname:
Year of publication:
Country:
Funding:
Aim of the study:
Methods
Databases searched:
Last date of search:
Inclusion criteria:
Participants:
Interventions:
Comparators:
Outcome measures:
Types of studies included:
Quality assessment criteria used:
Application of methods:
Methods of analysis:
1. narrative, 2. meta-analysis, 3. indirect comparison, 4. others
Results
Quantity and quality of included studies:
Treatment effect:
Economic evaluation:
Conclusions:
Implications of the review:
Methodological comments
Search strategy:

Participants: Inclusion/exclusion criteria: Quality assessment of studies: Method of synthesis:
General comment
Generalisability: Funding:
Authors conclusion
Reviewer's conclusion

b) Data extraction form for studies for primary prevention of cardiovascular events or cancers

Name of the reviewer:

Study details
Study ID (Ref man):
First author surname:
Year of publication:
Country:
Study design:
Study setting:
Number of centres:
Duration of study:
Follow up period:
Funding:
Aim of the study:
Participants
Total number of participants:
Sample attrition/drop out:
Inclusion criteria:
Exclusion criteria:
Characteristics of participants:
Mean age:
Mean sex:
Race:
Date of diagnosis:
Diagnosis:
Diabetes (%):
Smokers (%):
Site/type of cancer to be prevented:
Annual risk of cardiovascular events (%):
Intervention
Indication for treatment:

Aspirin dose: Any comparison: Duration of treatment: Compliance: Other interventions used:		
Outcomes		
Primary outcomes: Secondary outcomes: Method of assessing outcomes: Timing of assessment: Study end point: Survival analysis: Yes/No Mortality: Yes/No Adverse event: Yes/No Health related quality of life: Yes/No Length of follow up:		
Number of participants	**Intervention**	**Comparator**
Screened		
Randomised/Included		
Excluded		
Missing participants		
Withdrawals		
Patient's baseline characteristics	**Intervention**	**Comparator**
Insert baseline characteristics table here		
Survival data	**Intervention**	**Comparator**
Actuarial survival		
Overall survival		
Kaplan-Meier estimates		
Survival by era (at 5 year intervals)		
Adverse events	**Intervention**	**Comparator**
Bleeding/haemorrhagic end points		
Stroke		
Upper GI bleeding		

Peptic ulcer		
Rashes		
Wheezing/asthma • Episodes • Mortality		
Quality of life	**Intervention**	**Comparator**
Authors conclusion		
Reviewer's conclusion		

Appendix 4. Quality assessment forms

Quality assessment criteria for systematic reviews:
Based on NHS Centre for Reviews and Dissemination (CRD)[27]

Question	Score
1. Are any inclusion/exclusion criteria reported to the primary studies which address the review question?	Yes or No
2. Is there evidence of a substantial effort to search for all relevant research?	Yes or No
3. Is the validity of included studies adequately assessed?	Yes or No
4. Is sufficient detail of the individual studies presented?	Yes or No
5. Are the primary studies summarised appropriately?	Yes or No

Quality assessment criteria for RCTs:
Based on the Cochrane Risk of Bias tool[28]

Question	Rating
1. Adequate sequence generation	
2. Adequate allocation concealment	
3. Blinding (especially outcome assessment)	
4. Incomplete outcome data addressed	
5. Free of selective reporting	
6. Free of other bias (e.g. similarity at baseline, power assessment, conflict of interest)	

Rating (by criteria fulfilled, i.e. 'yes' response): 0 to 2 low quality, 3 to 4 medium quality, 5 to 6 high quality