Supplementary Online Content

Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2018.20578

Supplement 1. Meta-analysis protocol

This supplementary material has been provided by the authors to give readers additional information about their work.

Meta-analysis protocol

Aim
To evaluate the cardiovascular efficacy and bleeding risk of aspirin in primary prevention populations using meta-analysis.

Population
Participants without cardiovascular disease

Intervention
Aspirin (acetylsalicylic acid) – any dose permitted

Comparison
Control: Placebo or no aspirin

Outcome
Primary cardiovascular outcome
- Composite cardiovascular outcome: cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke

Secondary cardiovascular outcome
- all-cause mortality
- cardiovascular mortality
- all myocardial infarction
- all stroke
- all ischaemic stroke

Primary bleeding safety outcome
- major bleeding

Secondary bleeding safety outcome
- intracranial haemorrhage
- major gastrointestinal bleeding

Exploratory cancer outcome
- Incident cancer
- Cancer mortality

Search strategy

The US Preventive Services Task Force conducted a meta-analysis in September 2015 investigating the cardiovascular efficacy of aspirin in primary prevention populations. Given that that review addressed a similar question to that set out in this current meta-analysis, we included studies identified in that review. The US Preventive Services Task Force undertook their literature search on January 6, 2015. Therefore we undertook an updated literature search from January 1, 2015 through to the search date.

Databases searched:

- MEDLINE, Embase and CENTRAL: via www.cochranelibrary.com
- From database inception through August 31, 2018

The initial search will be carried out by SLZ. All references will be collated on Endnote X7.

After removal of duplicates using the function on Endnote X7, the remaining articles will be subject to a screening and review steps:

1. Screening: Title and abstract will be screened with removal of obviously non-relevant studies. This step will be done by two authors (SLZ and AJR) without overlap i.e. the list of studies will be split evenly between SLZ and AJR and screened individually. Non-relevant studies will be decided at the reviewers' discretion and should be studies that are obviously not relevant to the study question. Specific reason for exclusion will not be recorded, and the reason will be given as "Non-relevant". Reviewers will be overly inclusive at this stage to reduce chance of omitting relevant articles.
2. Review: Remaining articles will be reviewed by SLZ and AJR in parallel and independently. The purpose at this stage is to more closely assess studies based on inclusion and exclusion criteria. Where necessary, full text will be reviewed. Reasons for exclusion will be recorded.

Additional systematic reviews and meta-analyses will be identified on MEDLINE by searching the drug class names and using pre-set systematic review and meta-analysis filters. These will then be hand screened for additional trials.

The search terms for each database are provided in the eMethods 1 (Detailed Statistical Methods).

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Study inclusion criteria

1. Randomised clinical trial
2. Enrolled participants without known pre-existing cardiovascular disease
3. Compared aspirin at any dose with placebo or no treatment
4. Follow-up of 12 months or longer
5. Enrolling >1000 participants
6. Provided information on any of the pre-specified cardiovascular and bleeding outcomes
7. English language

Note:
Can use data from secondary analyses of a trial if present data relevant to outcomes and the original trial meets entry inclusion criteria.

Data extraction

2 study authors (SLZ and AJR) will extract data in parallel and independently onto a dedicated spreadsheet. The spreadsheet will be prepared on Microsoft Excel and contain columns for all required extracted data. The spreadsheet will then be compared between two reviewers to ensure validity and accuracy of data extraction.

The following information will be extracted:

- Basic trial information:
    - First author, study acronym, year, journal of publication, trial NCT number
    - Study inclusion and exclusion criteria, specifically regarding whether participants were recruited or excluded based on cardiovascular risk factors or cardiovascular disease
    - Follow-up duration
    - Control treatment (placebo or no aspirin)
    - Patient demographics: age, % male/female, compliance, smoking status, BMI, % obese (BMI >=30) , % hypertensive, mean systolic blood pressure, % dyslipidaemic, mean cholesterol/LDL/HDL, % diabetes, % taking statin or proton-pump inhibitor
- For all cardiovascular (primary and secondary) and bleeding (primary and secondary) outcomes:
    - Event count in treatment and control (raw numbers)
    - Relative risk or hazard ratio where reported
    - Upper and lower 95% confidence intervals where reported
    - P value where reported

Statistical analysis

Statistical techniques

Bayesian hierarchical pairwise meta-analysis using GeMTC package on R (version 3.4.1). Fixed or random effects models will be selected based on the deviance information criterion, using the model with the smallest value. Analysis will be performed using Markov-chain Monte Carlo methods. Meta-analysis will be presented as hazard ratio (HR) with 95% credible intervals (CrI). For studies that do not report hazard ratios for outcomes, event counts, total number and follow-up duration will be incorporated using the Poisson likelihood and log link approach to generate HR estimates. Results will be presented graphically in forest plots comparing aspirin with no aspirin.

To calculate absolute risk differences, frequentist pairwise meta-analysis will be undertaken to generate risk ratio estimates for all cardiovascular and bleeding outcomes. Absolute risk differences will be calculated by multiplying the risk ratio and 95% confidence intervals by the placebo event rate, which is then subtracted from the placebo risk. Negative values will indicate outcomes favouring aspirin, and positive values will indicate outcomes favouring no aspirin.

Sensitivity analysis

Analysis will be repeated for all cardiovascular and bleeding outcomes excluding the following study types:

- Open label studies
- Studies randomizing to daily aspirin doses greater than 100mg
- Studies published before the year 2000

Additional analyses

Results (cardiovascular and bleeding outcomes) analysed using Frequentist meta-analysis will be provided in the Supplement. For Frequentist analysis, P-value cut-off of 0.05, two-sided.

Risk of bias assessment

Cochrane risk of bias assessment undertaken by two investigators (SLZ and AJR) independently (Chapter 8, Cochrane Handbook). Any discrepancy will be resolved through discussion, and if necessary a third reviewer. Risk of bias for individual trials will be presented in table format with an overall summary presented as Risk of bias graph.

For summarising risk of bias for a study across outcomes, Cochrane provides a framework that leaves the overall assessment at the discretion of the reviewers based on their own judgement on the relative importance of different domains (Table 8.7a, Cochrane Handbook).

As such, studies will be deemed to have overall high risk of bias if:

- High risk of bias in 1 or more of the following domains:
    - Allocation concealment
    - Blinding
- Unclear in 3 or more domains

Changes to Protocol

The following changes have been made to the original protocol and included in the final publication:

- An additional sensitivity analysis will be performed excluding trials enrolling patients with asymptomatic peripheral vascular disease as identified by ankle-brachial pressure index (ABPI), to account for an anticipated elevated cardiovascular risk in this population compared to unscreened individuals.
- An additional sensitivity analysis will be performed excluding the ASCEND trial from the primary cardiovascular outcome. The reason for this is because ASCEND defined stroke events in its primary outcome as exclusively ischaemic aetiology, whereas all other studies included in the primary cardiovascular outcome included ischaemic, haemorrhagic and unknown aetiologies.
- The search has been amended on request of peer-review and editorial advice to include all studies published from database inception to November 1, 2018. The search will be carried out by both authors in duplicate and independently.