

Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews

P Sutcliffe, M Connock, T Gurung, K Freeman, S Johnson, N-B Kandala, A Grove, B Gurung, S Morrow and A Clarke*

Warwick Evidence, Warwick Medical School, University of Warwick, Coventry, UK

*Corresponding author

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Scientific summary

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Background

Although there are guidelines and documented benefits for aspirin in secondary prevention of cardiovascular disease (CVD), and in vitro mechanisms and potential benefits have been elucidated, the overall benefits of use of aspirin in the primary prevention of either cancer or CVD are not yet clear. The potential for aspirin to improve health on a large scale is evident, because the diseases to be prevented are so common and serious. However, widespread use of aspirin for individuals who are as yet free of disease should be approached with caution, because of potential adverse events. No guidelines currently recommend the routine use of aspirin across the adult population for the primary prevention of either cancer or CVD. Recommended usage among higher-risk populations critically depends on definitions of 'higher' risk, and these vary considerably.

Aim

To investigate published evidence on the overall benefits and adverse events related to use of aspirin for the primary prevention of cancer and CVD.

Objectives

1. To identify randomised controlled trials (RCTs), systematic reviews and meta-analyses of the prophylactic use of aspirin in the primary prevention of CVD or cancer.
2. To undertake an overview and quality assessment of the identified systematic reviews and meta-analyses with particular reference to adverse events.
3. To undertake study-level meta-analysis to investigate the relative influence of individual studies on pooled estimates of benefits and risk of adverse events reported in identified systematic reviews and meta-analyses.
4. 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.
5. To undertake exploratory multivariable meta-regression of studies in identified systematic reviews and meta-analyses to investigate potential influence of study-level variables on reported pooled estimates of risk of adverse events (e.g. participant age and sex; follow-up duration; aspirin dose or dose frequency; level of or type of cardiovascular (CV) risk; year of investigation).
6. To summarise, synthesise and assess 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 1–5. To quantify relative and absolute risks and benefits, and, if appropriate, to make recommendations for further investigation.

Methods

Evidence was retrieved through searches during June 2012 in 13 electronic bibliographic databases, contact with experts, the scrutiny of references of included and excluded studies, checking of health services research-related resources, and recovery of citations of relevant referenced studies. The search strategy covered the concepts of aspirin and primary prevention. Searches aimed to identify RCTs,

meta-analysis and systematic reviews relating to adverse events from aspirin when taken by adults for the primary prevention of CVD or cancer.

Searches were performed (from 2008 to September 2012) in MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment databases [NHS Centre for Reviews and Dissemination (CRD)]; Science Citation Index (SCI) and Conference Proceedings (Web of Science); UK Clinical Research Network Portfolio Database; and ClinicalTrials.gov; and were limited to publications since 2008. Two reviewers independently applied inclusion and exclusion criteria. Data from included studies were tabulated and summarised. Studies were assessed using recognised quality checklists. We selected the most recent relevant comprehensive systematic reviews and meta-analyses for in-depth investigation. Meta-analyses, including cumulative meta-analysis, study-level meta-analysis and exploratory multivariable meta-regression were undertaken.

Results

We identified 2572 potentially relevant papers, of which 2545 were removed at title, abstract or full-paper sift, resulting in 27 papers that met the inclusion criteria. These studies comprised 22 systematic reviews and five RCTs. The systematic reviews examined the use of aspirin for primary prevention of CVD ($n = 9$) cancer ($n = 6$) and CVD in patients with diabetes ($n = 7$) while the RCTs assessed the use of aspirin for primary prevention of CVD ($n = 3$) and CVD in patients with diabetes ($n = 2$). Quality ratings were in general high. We found no primary studies in which aspirin use was for primary prevention of cancer. All identified cancer studies retrospectively assessed reduction in cancer incidence and mortality through re-analysis of RCTs of aspirin for primary prevention of CVD. Systematic reviews consistently reported on a core of nine RCTs, or a subset of the core nine, depending on the year that the review was undertaken. No completed RCTs that provided new information were identified post 2008.

Estimates of relative benefit [relative risk (RR) reduction] by aspirin from meta-analyses ranged from 6% risk reduction for all-cause mortality [RR 0.94, 95% confidence interval (CI) 0.88 to 1.00] to 10% for major CV events (MCEs) (RR 0.90, 95% CI 0.85 to 0.96), and 15% for total coronary heart disease (CHD) (RR 0.85, 95% CI 0.69 to 1.06). Larger risk reduction was reported for avoidance of cancer, but several potentially relevant large null effect studies were excluded from analyses. The 95% CIs for several benefits encompassed a null effect and cumulative meta-analyses for CVD outcomes indicated a tendency for diminishing benefit as more recent studies were included in analysis.

Absolute benefits of aspirin use, estimated using various methodologies, were relatively small compared with the total burden of the relevant diseases in the population. Fewer than 100 events were averted per 100,000 patient-years of follow-up. The number of unwanted events averted by aspirin use per 10,000 patients followed up for 10 years (100,000 patient-years) were as follows: 33–46 deaths (all-cause mortality), 60–84 MCEs, and 47–64 incidents of CHD. Retrospective analysis also indicated the possible avoidance of 34 deaths from colorectal cancer/100,000 person-years; however, in this analysis two large studies were excluded.

Potential harms of aspirin use include bleeding at various sites. Reported increased RRs from aspirin use were 37% for gastrointestinal (GI) bleeding (RR 1.37, 95% CI 1.15 to 1.62), between 54% (RR 1.54, 95% CI 1.30 to 1.82) and 62% (RR 1.62, 95% CI 1.31 to 2.00) for major bleeds, and between 32% (RR 1.32, 95% CI 1.00 to 1.74) and 38% (RR 1.38, 95% CI 1.01 to 1.82) for haemorrhagic stroke. The pooled estimates of increased RR for bleeding remained stable across trials conducted over several decades.

Absolute rates of harm from aspirin use, as with rates for benefit, were relatively small compared with the epidemiology of the diseases in the population. Estimates of the number of unwanted events incurred by

aspirin use per 100,000 patient-years of follow-up were 99–178 for non-trivial bleeds, 46–49 for major bleeds, 68–117 for GI bleeds, and 8–10 for haemorrhagic stroke.

For individuals with diabetes who had not experienced a CVD event, reported meta-analyses were underpowered for determining both adverse events and potential benefits of aspirin use. Subgroup analyses aimed at finding any differences in response according to sex were similarly inconclusive.

A New Zealand modelling study, based on individual patient data (IPD) from six RCTs, was undertaken to investigate the balance of potential benefit and harm from aspirin use for primary prevention of CVD. This study suggested that aspirin should be considered as a primary prevention measure for persons up to 80 years of age with a 5-year CVD risk $\geq 15\%$. This would encompass only about 13% of the primary prevention population, and for these we consider that alternative and more effective preventative strategies may currently be available.

Conclusions

Benefits of aspirin use for primary prevention of CVD are relatively small, in some instances remain statistically uncertain, and are an order of magnitude less than those observed in the secondary prevention of CVD. Harms (especially bleeding) occur at relatively higher frequency and are based on statistically stronger evidence. The balance of harms and benefits is not easy to judge, as it depends on the relative costs and values attached to unwanted events averted and incurred, but in the current context other interventions (lipid lowering, control of blood pressure, legislation to enhance smoking cessation and to reduce consumption of potentially harmful levels of dietary salt and fat) are likely to have greater beneficial effect in primary prevention of CVD.

Investigations that use a mix of IPD and study-level analyses of RCTs now point to a possible protection against several cancers (notably colon cancer) emanating after about 5 years of aspirin use. However, currently these studies should be viewed with some caution, as results, although promising, demonstrate only a small benefit and are dependent on retrospective analysis of CVD primary prevention trials for which cancer was not the primary outcome.

In such analyses undertaken to date, the two largest such trials that show no evidence of cancer protection by aspirin after ≥ 10 years' follow-up were excluded.

Absolute benefits and risks of aspirin use, estimated using various methodologies, are relatively rare (usually tens of events per 100,000 years of follow-up) compared with the total burden of the relevant diseases in the population and are finely balanced. It should be borne in mind that estimates, although based on the most complete available systematic review evidence, are associated with appreciable uncertainties. We recommend that policy decisions about the long-term use of aspirin for primary prevention of CVD or cancer in contemporary health care should be made on the basis of evidence becoming available from new trials. In the meantime, each individual doctor and patient should make their own decisions about the benefits and risk of aspirin in relation to CVD and cancer.

Research needs

There are several potentially relevant ongoing trials with expected completion dates between September 2013 and June 2019, including large RCTs of the potential benefits of aspirin in the prevention of cancer [e.g. ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events), May 2015; ASCEND (A Study of Cardiovascular Events in Diabetes), December 2016; ASPREE (Aspirin in Reducing Events in the Elderly), August 2016; ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial

in Diabetes), September 2013; CARING (Chronotherapy with Low-dose Aspirin for Primary Prevention), June 2019]. The following avenues of future research deserve consideration:

1. Investigation of the impact of different dose regimens on CV and cancer outcomes.
2. Further investigation in specific subgroups stratified according to reliable risk assessment tools.
3. Expanding the use of IPD meta-analysis of RCTs to the fullest extent possible by pooling data from variously publicly funded international investigations.

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